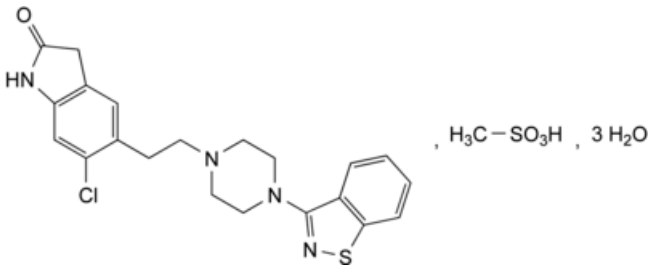
Edition: BP 2025 (Ph. Eur. 11.6 update)

Ziprasidone Mesilate Trihydrate

General Notices

(Ph. Eur. monograph 2649)



$C_{22}H_{25}ClN_4O_4S_2,3H_2O$ 563.1 *199191-69-0*

Action and use

Dopamine D_2 receptor antagonist; serotonin 5HT2 receptor antagonist; neuroleptic.

Ph Eur

DEFINITION

5-[2-[4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one methanesulfonate trihydrate.

Content

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

PRODUCTION

It is considered that alkyl methanesulfonate esters are genotoxic and are potential impurities in ziprasidone mesilate trihydrate. The manufacturing process should be developed taking into consideration the principles of quality risk management, together with considerations of the quality of starting materials, process capability and validation. The general methods 2.5.37. *Methyl, ethyl and isopropyl methanesulfonate in methanesulfonic acid*, 2.5.38. *Methyl, ethyl and isopropyl methanesulfonate in active substances* and 2.5.39. *Methanesulfonyl chloride in methanesulfonic acid* are available to assist manufacturers.

CHARACTERS

Appearance

White or almost white powder.

Solubility

Very slightly soluble in water, slightly soluble in methanol, practically insoluble in acetonitrile.

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *ziprasidone mesilate trihydrate CRS*.

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

TESTS

Related substances

Carry out the tests protected from light and prepare the solutions immediately before use.

A. Liquid chromatography (2.2.29).

Solvent mixture *hydrochloric acid R*, *water R*, *methanol R* (0.04:40:60 *V/V/V*).

Test solution (a) Dissolve 27.0 mg of the substance to be examined in 35 mL of the solvent mixture, sonicate for about 2 min and shake. Dilute to 50.0 mL with the solvent mixture.

Test solution (b) Dilute 2.0 mL of test solution (a) to 20.0 mL with the solvent mixture.

Reference solution (a) Dissolve 27.0 mg of *ziprasidone hydrochloride monohydrate CRS* in 35 mL of the solvent mixture, sonicate for about 2 min and shake. Dilute to 50.0 mL with the solvent mixture. Dilute 2.0 mL of the solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve 2.5 mg of *ziprasidone for system suitability 1 CRS* (containing impurities B and C) in a mixture of 40 volumes of *water R* and 60 volumes of *methanol R* and dilute to 10 mL with the same mixture of solvents.

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

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

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

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: mix 40 volumes of *methanol R1* and 60 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: *methanol R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 40	100	0
40 - 41	100 → 0	0 → 100
41 - 50	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 229 nm.

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

Identification of impurities Use the chromatogram supplied with *ziprasidone for system suitability 1 CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B and C.

Relative retention With reference to ziprasidone (retention time = about 6 min): impurity B = about 0.8; impurity C = about 0.9.

System suitability Reference solution (b):

— *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline for the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity B; minimum 2.0, where H_p = height above the baseline for the peak due to impurity C and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to ziprasidone.

Calculation of percentage contents:

— for each impurity, use the concentration of ziprasidone mesilate trihydrate in reference solution (c).

Limits:

— *impurity B*: maximum 0.15 per cent;

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

— *reporting threshold*: 0.05 per cent; disregard any peak with a retention time greater than 40 min.

B. Liquid chromatography (*2.2.29*).

Solvent mixture *hydrochloric acid R*, *water R*, *methanol R* (0.04:20:80 *V/V/V*).

Test solution Dissolve 27 mg of the substance to be examined in 35 mL of the solvent mixture, sonicate for about 2 min and shake. Dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *ziprasidone for system suitability 2 CRS* (containing impurities D and E) in 1 mL of the solvent mixture.

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

Column:

— *size*: *l* = 0.15 m, Ø = 3.9 mm;

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

— *temperature*: 35 °C.

Mobile phase Mix 8 volumes of *methanol R1*, 42 volumes of *acetonitrile for chromatography R* and 50 volumes of a solution prepared as follows: dissolve 3.4 g of *potassium dihydrogen phosphate R* and 21.6 g of *sodium octanesulfonate R* in 900 mL of *water for chromatography R*, adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 229 nm.

Injection 20 µL.

Run time 15 times the retention time of ziprasidone.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peaks due to impurities D and E.

Relative retention With reference to ziprasidone (retention time = about 3 min): impurity E = about 2.6; impurity D = about 7.8.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurities E and D.

Calculation of percentage contents:

— for each impurity, use the concentration of ziprasidone mesilate trihydrate in reference solution (b).

Limits:

— *impurity D*: maximum 0.15 per cent;

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

— *reporting threshold*: 0.05 per cent; disregard any peak eluting before the peak due to ziprasidone.

Limit:

— *total for tests A and B*: maximum 0.2 per cent.

Water (*2.5.12*)

8.5 per cent to 10.1 per cent, determined on 0.050 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*)

Less than 17.5 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

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

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

Calculate the percentage content of $C_{22}H_{25}ClN_4O_4S_2$ taking into account the assigned content of *ziprasidone hydrochloride monohydrate CRS* and a conversion factor of 1.133.

STORAGE

Protected from light. If the substance is sterile, store in a sterile, airtight, tamper-evident container.

IMPURITIES

Test A for related substances

A, B, C.

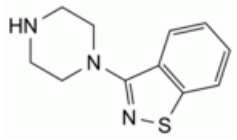
Test B for related substances

D, E.

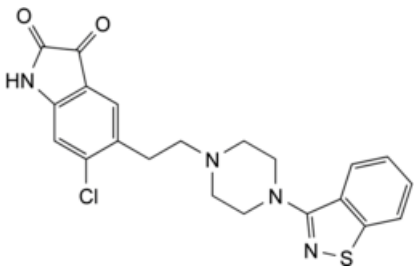
Specified impurities *B, D*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by

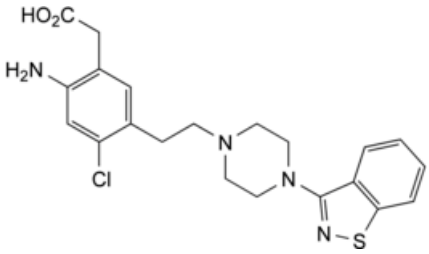
the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, C, E*.



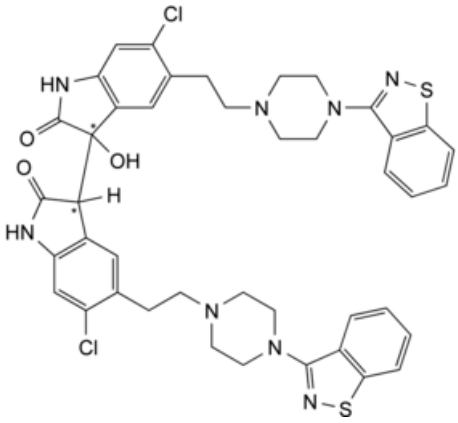
A. 3-piperazin-1-yl-1,2-benzisothiazole,



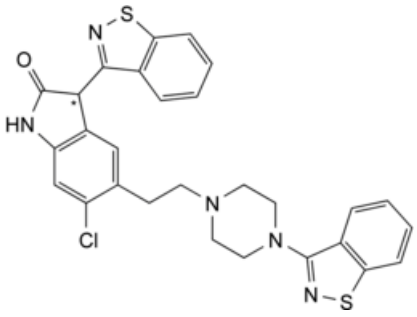
B. 5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1*H*-indole-2,3-dione,



C. 2-[2-amino-5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-4-chlorophenyl]acetic acid,



D. 5,5′-bis[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6,6′-dichloro-3-hydroxy-1,1′,3,3′-tetrahydro-2*H*,2′*H*-3,3′-biindole-2,2′-dione,



E. 3-(1,2-benzisothiazol-3-yl)-5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1,3-dihydro-2*H*-indol-2-one.

Ph Eur