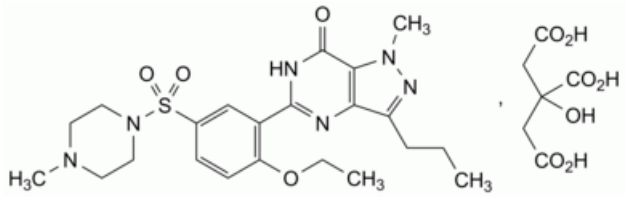
Edition: BP 2025 (Ph. Eur. 11.6 update)

Sildenafil Citrate

General Notices

(Ph. Eur. monograph 2270)



$C_{28}H_{38}N_6O_{11}S$ 667 *171599-83-0*

Action and use

Selective inhibitor of cyclic GMP-specific phosphodiesterase (Type V) with vasodilator action; treatment of erectile dysfunction.

Preparations

Sildenafil Tablets

Sildenafil Chewable Tablets

Sildenafil Orodispersible Tablets

Sildenafil Orodispersible Films

Sildenafil Powder for Oral Suspension

Sildenafil Injection

Ph Eur

DEFINITION

5-[2-Ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one dihydrogen 2-hydroxypropane-1,2,3-tricarboxylate.

Content

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

CHARACTERS

Appearance

White or almost white, slightly hygroscopic, crystalline powder.

Solubility

Slightly soluble in water and in methanol, practically insoluble in hexane.

IDENTIFICATION

First identification: A.

Second identification: B, C.

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *sildenafil citrate CRS*.

B. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution Dissolve 10 mg of *sildenafil citrate CRS* in *methanol R* and dilute to 5.0 mL with the same solvent.

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

Mobile phase *concentrated ammonia R*, *methanol R*, *methylene chloride R* (1:14:85 *V/V*).

Application 5 µL.

Development Over 3/4 of the plate.

Drying In air.

Detection A Examine in ultraviolet light at 254 nm.

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

Detection B Treat with *dilute potassium iodobismuthate solution R*; examine the chromatogram in daylight.

Results B The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

C. To 0.1 g of the substance to be examined, add 10 mL of *water R* and 0.1 mL of *concentrated ammonia R*. Allow to stand for 5 min with gentle swirling. Filtrate through a paper filter. To the filtrate add 1 mL of *calcium chloride solution R*; the solution is clear. Boil the solution in a water bath and rub the inside of the test-tube with a glass rod. A white precipitate is formed.

TESTS

Impurity E

Thin-layer chromatography (2.2.27).

Solvent mixture *concentrated ammonia R*, *water R*, *methanol R* (5:25:75 *V/V/V*).

Test solution Dissolve 35.0 mg of the substance to be examined in 2.0 mL of the solvent mixture, with the aid of ultrasound if necessary.

Reference solution (a) Dissolve 7.0 mg of *imidazole CRS* (impurity E) in the solvent mixture and dilute to 20.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dilute 5.0 mL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Mix 1 mL of the test solution and 1 mL of reference solution (a).

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

Mobile phase concentrated ammonia R, ethanol (96 per cent) R, ethyl acetate R, methylene chloride R (1:20:30:50 *V/V/V/V*).

Application 10 µL of the test solution and reference solutions (b) and (c) as bands of 6 mm.

Development Over 2/3 of the plate.

Drying At 100 °C for about 15 min.

Detection Expose to iodine vapour until the plate is light brown and examine under ultraviolet light at 254 nm.

Retardation factors Citrate = about 0; impurity E = about 0.25; sildenafil = about 0.4.

System suitability Reference solution (c):

— the chromatogram shows 2 clearly separated zones.

Limit:

— *impurity E*: any zone due to impurity E is not more intense than the principal zone in the chromatogram obtained with reference solution (b) (0.1 per cent).

Related substances

Liquid chromatography (2.2.29).

Buffer solution Dissolve 2.72 g of potassium dihydrogen phosphate R in 900 mL of water for chromatography R and adjust to pH 6.5 with a 120 g/L solution of potassium hydroxide R in water for chromatography R. Dilute to 1.0 L with water for chromatography R.

Solvent mixture acetonitrile for chromatography R, mobile phase A (10:90 *V/V*).

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

Test solution (b) Dilute 2.0 mL of test solution (a) to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 2 mg of sildenafil impurity A CRS in test solution (a) and dilute to 10.0 mL with test solution (a). Dilute 1.0 mL of the solution to 20.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of sildenafil for peak identification CRS (containing impurity D) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

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.

Reference solution (d) Dissolve 25.0 mg of sildenafil citrate CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 2.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

Mobile phase:

— *mobile phase A*: acetonitrile for chromatography R, buffer solution (20:80 *V/V*);

— *mobile phase B*: buffer solution, methanol R1, acetonitrile for chromatography R (20:20:60 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	75	25
3 - 26	75 → 30	25 → 70
26 - 38	30	70

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 230 nm.

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

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *sildenafil for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity D.

Relative retention With reference to sildenafil (retention time = about 16 min): citrate = about 0.1; impurity D = about 0.15; impurity A = about 1.25.

System suitability Reference solution (a):

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

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity D by 0.7;

— for each impurity, use the concentration of sildenafil citrate in reference solution (c).

Limits:

— *impurities A, D*: for each impurity, maximum 0.15 per cent;

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

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to citrate.

Water (*2.5.12*)

Maximum 2.5 per cent, determined on 0.200 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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

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

Calculate the percentage content of $C_{28}H_{38}N_6O_{11}S$ taking into account the assigned content of *sildenafil citrate CRS*.

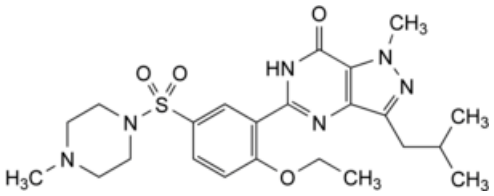
STORAGE

In airtight container.

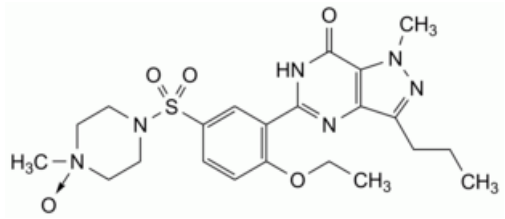
IMPURITIES

Specified impurities *A, D, E*.

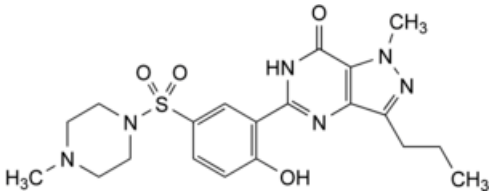
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



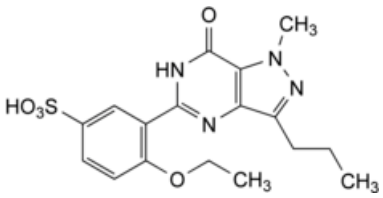
A. 5-[2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-methyl-3-(2-methylpropyl)-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one,



B. 1-methyl-4-[4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzene-1-sulfonyl]piperazine 1-oxide,

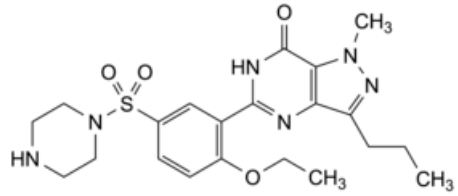


C. 5-[2-hydroxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one,

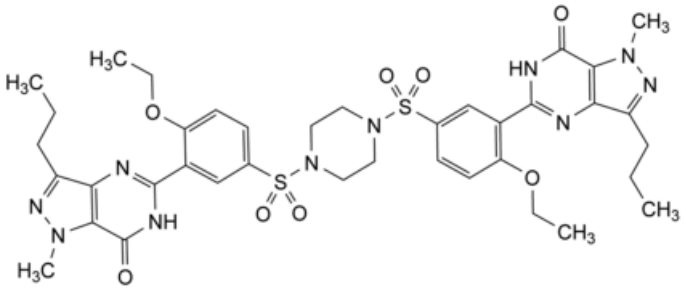


D. 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzene-1-sulfonic acid,

E. 1*H*-imidazole,



F. 5-[2-ethoxy-5-(piperazine-1-sulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one,



G. 2^{6},6^{4}-diethoxy-1^{3},7^{3}-dipropyl-$1^{1}H$,$7^{1}H$-3,5-dithia-1,7(5)-bis(pyrazolo[4,3-*d*]pyrimidina)-4(1,4)-piperazina-2,6(1,3)-dibenzenaheptaphan-1^{7},3,3,5,5,7^{7}-hexaone.

Ph Eur