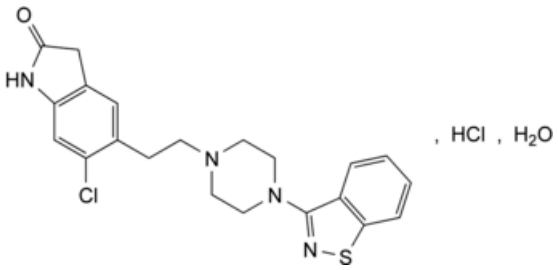
Edition: BP 2025 (Ph. Eur. 11.6 update)

Ziprasidone Hydrochloride Monohydrate

General Notices

(Ph. Eur. monograph 2421)



$C_{21}H_{22}Cl_2N_4OS,H_2O$ 467.4 *138982-67-9*

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ 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 hydrochloride monohydrate.

Content

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

CHARACTERS

Appearance

White or slightly pink powder.

Solubility

Practically insoluble in water, slightly soluble in methanol and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *ziprasidone hydrochloride monohydrate 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.

B. Suspend 30 mg in 2 mL of *water R*, acidify with 0.15 mL of *dilute nitric acid R* and filter. The clear filtrate gives reaction (a) of chlorides (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and prepare the solutions immediately before use.*

Solvent mixture A *water R*, *methanol R* (40:60 *V/V*).

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

Test solution (a) Dissolve 23 mg of the substance to be examined in solvent mixture A and dilute to 100.0 mL with solvent mixture A.

Test solution (b) Dissolve 23 mg of the substance to be examined in solvent mixture B and dilute to 50.0 mL with solvent mixture B.

Reference solution (a) Dissolve 2.5 mg of *ziprasidone for system suitability 1 CRS* (containing impurities A, B and C) in solvent mixture A and dilute to 10.0 mL with solvent mixture A.

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

Reference solution (c) Dissolve the contents of a vial of *ziprasidone for system suitability 2 CRS* (containing impurities D and E) in 1.0 mL of solvent mixture B.

A. *Column*:
- — *size*: *l* = 0.15 m, Ø = 4.6 mm;
- — *stationary phase*: spherical *octylsilyl silica gel for chromatography R* (5 µm);
- — *temperature*: 40 °C.

Mobile phase:
- — *mobile phase A*: mix 40 volumes of *methanol R* and 60 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.5 with *phosphoric acid R*;
- — *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	100	0
20 - 21	100 → 0	0 → 100
21 - 24	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 229 nm.

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

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

Relative retention With reference to ziprasidone (retention time = about 7 min): impurity A = about 0.4; impurity B = about 0.8; impurity C = about 0.9.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 1.2, where H_p = height above the baseline of 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.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 0.7;

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

— *impurity A in test solution (b)*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *impurity C in test solution (a)*: not more than 0.75 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

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

— *disregard limit in test solution (b)*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard the peak due to impurity C and any peak with a retention time greater than 20 min.

B. *Column*:
— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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

— *temperature*: 35 °C.

Mobile phase Mix 5 volumes of *methanol R*, 40 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 6.0 with a 280 g/L solution of *potassium hydroxide R*, and 55 volumes of *acetonitrile R1*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 229 nm.

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

Run time 11 times the retention time of ziprasidone.

Identification of impurities Use the chromatogram supplied with *ziprasidone for system suitability 2 CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities D and E.

Relative retention With reference to ziprasidone (retention time = about 4.5 min): impurity D = about 2.0; impurity E = about 3.0.

System suitability Reference solution (c):

— *resolution*: minimum 6.0 between the peaks due to ziprasidone and impurity D.

Limits:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity D = 1.4; impurity E = 0.5;

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

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

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak eluting before the peak due to ziprasidone.

Limit:

— *total for tests A and B*: maximum 0.5 per cent.

Water (*2.5.12*)

3.7 per cent to 5.0 per cent, determined on 0.250 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*). *Carry out the test protected from light and prepare the solutions immediately before use*.

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

Test solution Dissolve 23.0 mg of the substance to be examined in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Reference solution Dissolve 23.0 mg of *ziprasidone hydrochloride monohydrate CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, *Ø* = 4.6 mm;

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

— *temperature*: 40 °C.

Mobile phase Mix 40 volumes of *methanol R* and 60 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 229 nm.

Injection 20 µL.

Run time Twice the retention time of ziprasidone.

Retention time Ziprasidone = about 7 min.

System suitability Reference solution:

— *symmetry factor*: maximum 2.0 for the peak due to ziprasidone.

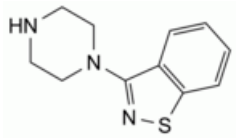
Calculate the percentage content of $C_{21}H_{22}Cl_2N_4OS$ from the declared content of *ziprasidone hydrochloride monohydrate CRS*.

STORAGE

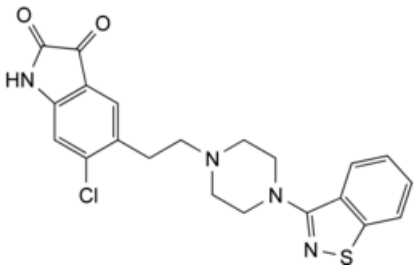
Protected from light.

IMPURITIES

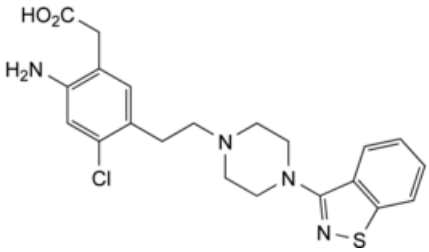
Specified impurities *A, B, C, D, E.*



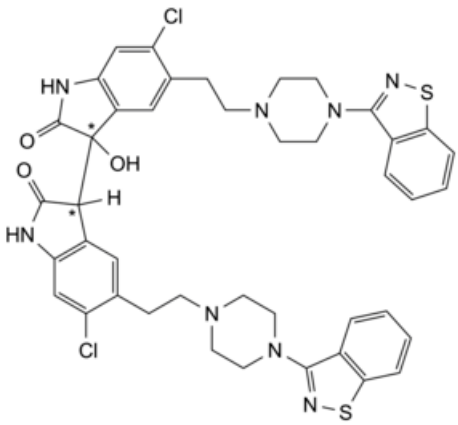
A. 3-piperazin-1-yl-1,2-benzisothiazole,



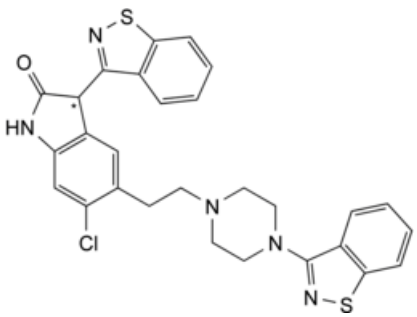
B. 5-[2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]ethyl]-6-chloro-1*H*-indole-2,3-dione,



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.