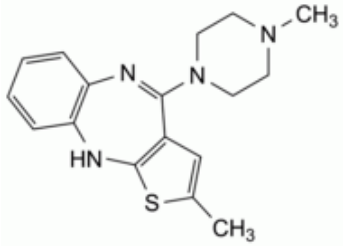
Edition: BP 2025 (Ph. Eur. 11.6 update)

Olanzapine

General Notices

(Ph. Eur. monograph 2258)



$C_{17}H_{20}N_4S$ 312.4 *132539-06-1*

Action and use

Dopamine D_2 receptor antagonist; serotonin $5HT_2$ receptor antagonist; neuroleptic.

Preparation

Olanzapine Orodispersible Tablets

Ph Eur

DEFINITION

2-Methyl-4-(4-methylpiperazin-1-yl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine.

Content

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

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, slightly soluble in ethanol (96 per cent).

It shows polymorphism (5.9).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison olanzapine CRS.

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

TESTS

Related substances

Liquid chromatography (2.2.29). *Prepare the test and reference solutions immediately before use or keep them refrigerated and inject within 20 h of preparation.*

Solution A Dissolve 13 g of sodium dodecyl sulfate R in about 1450 mL of water R, add 5 mL of phosphoric acid R and adjust to pH 2.5 by slowly adding strong sodium hydroxide solution R. If a precipitate is formed, this precipitate has to be re-dissolved prior to final pH adjustment. Dilute to 1500 mL with water R.

Solvent mixture Mix 4 volumes of acetonitrile R1 with 6 volumes of a 37 mg/L solution of sodium edetate R in solution A.

Test solution Dissolve 10 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Reference solution (a) 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.

Reference solution (b) Dissolve 4 mg of olanzapine for system suitability CRS (containing impurities B, C and D) in 10.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R1, solution A (48:52 *V/V*);

— *mobile phase B*: solution A, acetonitrile R1 (30:70 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	100	0
10 - 20	100 → 0	0 → 100
20 - 25	0	100

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 20 µL.

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

Relative retention With reference to olanzapine (retention time = about 13 min): impurity B = about 0.3; impurity D = about 0.9; impurity C = about 1.2.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurity D and olanzapine.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity B by 0.4;

— *impurities B, C, D*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (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 (a) (0.10 per cent);

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

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

Water (*2.5.12*)

Maximum 1.0 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*).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (a) Dissolve 50.0 mg of *olanzapine CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 2.0 mL of the solution to 10.0 mL with the mobile phase.

Reference solution (b) Dissolve 10 mg of the substance to be examined and 1 mg of *olanzapine impurity A CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

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

Mobile phase Mix 1 volume of *acetonitrile R* with 1 volume of a 6.9 g/L solution of *sodium dihydrogen phosphate monohydrate R* adjusted to pH 2.5 with *phosphoric acid R* and containing 12 g/L of *sodium dodecyl sulfate R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 260 nm.

Injection 20 µL.

Run time 1.2 times the retention time of olanzapine.

Relative retention With reference to olanzapine (retention time = about 7 min): impurity A = about 0.8.

System suitability Reference solution (b):

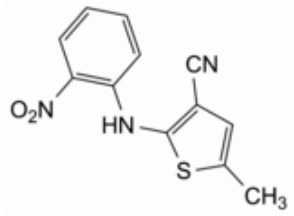
— *resolution*: minimum 2.0 between the peaks due to impurity A and olanzapine.

Calculate the percentage content of $C_{17}H_{20}N_4S$ using the chromatogram obtained with reference solution (a) and the declared content of *olanzapine CRS*.

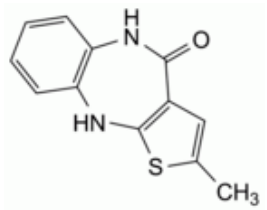
IMPURITIES

Specified impurities *B, C, D.*

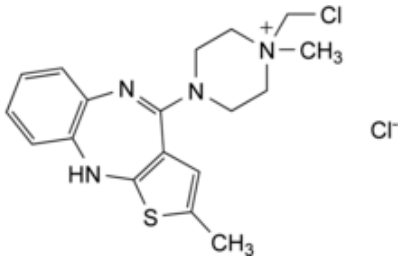
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



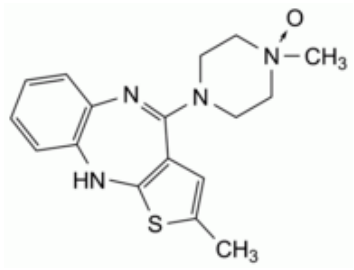
A. 5-methyl-2-[(2-nitrophenyl)amino]thiophene-3-carbonitrile,



B. 2-methyl-5,10-dihydro-4*H*-thieno[2,3-*b*][1,5]benzodiazepin-4-one,



C. 1-(chloromethyl)-1-methyl-4-(2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepin-4-yl)piperazin-1-ium chloride,



D. 1-methyl-4-(2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepin-4-yl)piperazin-1-oxide.

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