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

Olanzapine Orodispersible Tablets

General Notices

Orodispersible Olanzapine Tablets

Action and use

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

DEFINITION

Olanzapine Orodispersible Tablets contain Olanzapine in a suitable orodispersible basis.

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

Content of Olanzapine, $C_{17}H_{20}N_4S$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 60 mg of Olanzapine with 20 mL of *methanol*, filter and evaporate the filtrate to dryness. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of olanzapine (*RS 477*).

TESTS

Dissolution

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

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.
(b) Use 900 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the dissolution medium.

PROCEDURE

(1) After 15 minutes withdraw a sample of the medium, filter and dilute with the dissolution medium, if necessary, to produce a solution expected to contain 0.00028% w/v of Olanzapine. Measure the *absorbance* of this solution in a 4-cm cell, at 260 nm, Appendix II B using dissolution medium in the reference cell.
(2) 0.00028% w/v solution of *olanzapine BPCRS* in the dissolution medium. Measure the *absorbance* in a 4-cm cell, at 260 nm, Appendix II B using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of olanzapine, $C_{17}H_{20}N_4S$, in the medium from the absorbances obtained and using the declared content of $C_{17}H_{20}N_4S$ in *olanzapine BPCRS*.

LIMITS

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

Related substances

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

(1) Disperse a quantity of powdered tablets containing 25 mg of Olanzapine in 5 mL of *water*. Add 40 mL of *acetonitrile*, mix with the aid of ultrasound, add 40 mL of *water* and shake for 20 minutes, add sufficient *water* to produce 100 mL and filter through a 0.45-µm PTFE filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*. Dilute 1 volume of the resulting solution to 5 volumes with the same solvent mixture.
(3) 0.025% w/v of *olanzapine for system suitability EPCRS* with a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Inertsil ODS-3 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 250 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 45 volumes of a mixture of equal volumes of *acetonitrile* and *methanol* and 55 volumes of a 0.345% w/v buffer solution of *sodium dihydrogen orthophosphate monohydrate* adjusted to pH 6.8 with *dilute sodium hydroxide*.

Mobile phase B 25 volumes of the buffer solution described under Mobile phase A and 75 volumes of a mixture of equal volumes of *acetonitrile* and *methanol*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100	0	isocratic
2-7	100→60	0→40	linear gradient
7-13	60	40	isocratic
13-17	60→0	40→100	linear gradient
17-30	0	100	isocratic
30-31	0→100	100→0	linear gradient
31-34	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention times relative to olanzapine (retention time about 15 minutes) are; impurity 2, about 0.13; impurity 3, about 0.34; impurity C, about 0.37; impurity D, about 0.40; impurity B, about 0.6 and impurity 1, about 0.61.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and impurity D is at least 6.0.

LIMITS

Identify any peaks in the chromatogram obtained with solution (1) corresponding to impurities B and D using solution (3) and multiply the areas of these peaks by the corresponding correction factors; impurity B, 0.63, impurity D, 1.52.

In the chromatogram obtained with solution (1):

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

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

the area of any peak due to impurity 1 is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak due to impurity 3 is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

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

the sum of the areas of all the *secondary peaks* is not greater than 7.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

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

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, protected from light.

(1) Disperse a quantity of powdered tablets containing 25 mg of Olanzapine in 5 mL of *water*. Add 40 mL of *acetonitrile* and mix with the aid of ultrasound. Add 40 mL of *water* and shake for 20 minutes, dilute to 100 mL and filter through a 0.45-µm PTFE filter. Discard the first 2 mL of the filtrate.
(2) 0.025% w/v of *olanzapine BPCRS* in a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*.
(3) 0.025% w/v of *olanzapine for system suitability EPCRS* with a mixture of 4 volumes of *acetonitrile* and 6 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel* (5 µm) (Inertsil ODS-3 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 250 nm.
(f) Inject 10 µL of each solution.

MOBILE PHASE

25 volumes of a 0.345% w/v solution of *sodium dihydrogen orthophosphate monohydrate* previously adjusted to pH 6.8 with *dilute sodium hydroxide* and 75 volumes of a mixture of equal volumes of *acetonitrile* and *methanol*.

SYSTEM SUITABILITY

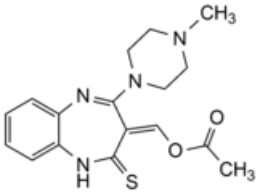
The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity D and olanzapine is at least 8.0.

DETERMINATION OF CONTENT

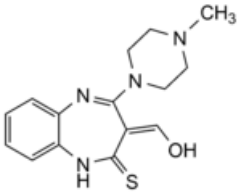
Calculate the content of $C_{17}H_{20}N_4S$ in the tablets using the declared content of $C_{17}H_{20}N_4S$ in *olanzapine BPCRS*.

IMPURITIES

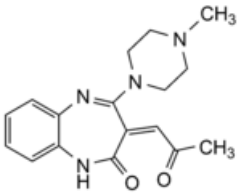
The impurities limited by the requirements of this monograph include those listed under Olanzapine and:



1. [4-(4-methylpiperazin-1-yl)-2-thioxo-2,3-dihydro-1*H*-1,4-benzodiazopin-3-ylidene]ethen-1-yl acetate; acetoxymethylidene thione;



2. 1-[(3*Z*)-4-(4-methylpiperazin-1-yl)-2-thioxo-2,3-dihydro-1*H*-1,4-benzodiazopin-3-ylidene]propan-2-one;



3. 4-(4-methylpiperazin-1-yl)-3-(2-oxopropylidene)-1*H*-1,4-benzodiazopin-2(3*H*)-one.