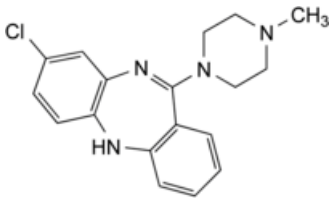
Edition: BP 2025 (Ph. Eur. 11.6 update)

Clozapine

General Notices

(Ph. Eur. monograph 1191)



$C_{18}H_{19}ClN_4$ 326.8 *5786-21-0*

Action and use

Dopamine D_4 receptor antagonist; neuroleptic.

Preparation

Clozapine Oral Suspension

Ph Eur

DEFINITION

8-Chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine.

Content

99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance

Yellow, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, soluble in ethanol (96 per cent). It dissolves in dilute acetic acid.

IDENTIFICATION

A. Melting point (2.2.14): 182 °C to 186 °C.
B. Infrared absorption spectrophotometry (2.2.24).

Comparison clozapine CRS.

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture water R, methanol R2 (20:80 *V/V*).

Solution A Dissolve 2.04 g of potassium dihydrogen phosphate R in 1000 mL of water R and adjust to pH 2.4 ± 0.05 with dilute phosphoric acid R.

Test solution Dissolve 75 mg of the substance to be examined in 80 mL of methanol R2 and dilute to 100 mL with water R.

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

Reference solution (b) Dissolve the contents of a vial of clozapine for peak identification CRS (containing impurities A, B, C and D) in 1.0 mL of the solvent mixture.

Column:

— *size*: *l* = 0.125 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, methanol R2, solution A (1:1:8 *V/V/V*);

— *mobile phase B*: acetonitrile for chromatography R, methanol R2, solution A (4:4:2 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	100	0
4 - 24	100 → 0	0 → 100
24 - 29	0	100

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 257 nm.

Injection 20 µL.

Identification of impurities Use the chromatogram supplied with clozapine for peak identification CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B, C and D.

Relative retention With reference to clozapine (retention time = about 11 min): impurity C = about 0.9; impurity D = about 1.1; impurity A = about 1.6; impurity B = about 1.7.

System suitability Reference solution (b):

— resolution: minimum 2.5 between the peaks due to impurity C and clozapine;

— the chromatogram obtained with reference solution (b) is similar to the chromatogram supplied with clozapine for peak identification CRS.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity D by 2.7;

— *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurities B, D*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *impurity C*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 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 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 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).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

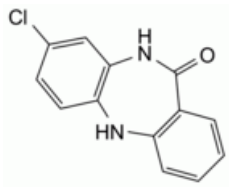
ASSAY

Dissolve 0.100 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

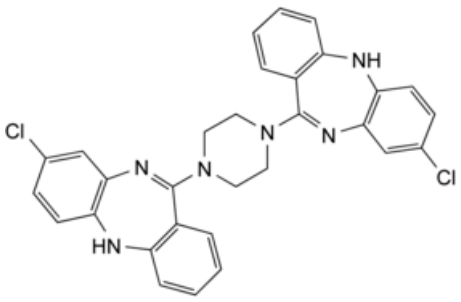
1 mL of *0.1 M perchloric acid* is equivalent to 16.34 mg of $C_{18}H_{19}ClN_4$.

IMPURITIES

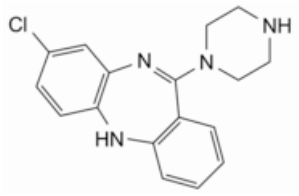
Specified impurities *A, B, C, D.*



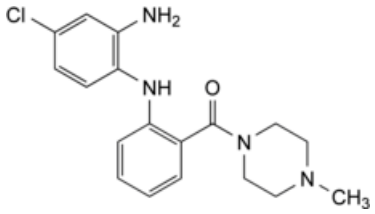
A. 8-chloro-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one,



B. 11,11′-(piperazine-1,4-diyl)bis(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepine),



C. 8-chloro-11-(piperazin-1-yl)-5*H*-dibenzo[*b*,*e*][1,4]diazepine,



D. 1-[2-[(2-amino-4-chlorophenyl)amino]benzoyl]-4-methylpiperazine.

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