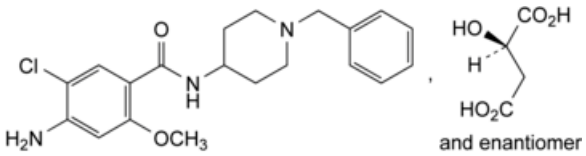
Edition: BP 2025 (Ph. Eur. 11.6 update)

Clebopride Malate

General Notices

(Ph. Eur. monograph 1303)



$C_{24}H_{30}ClN_3O_7$ 508.0 *57645-91-7*

Action and use

Dopamine receptor antagonist; antiprotozoal (veterinary).

Ph Eur

DEFINITION

4-Amino-*N*-(1-benzylpiperidin-4-yl)-5-chloro-2-methoxybenzamide acid (*RS*)-2-hydroxybutanedioate.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Sparingly soluble in water and in methanol, slightly soluble in anhydrous ethanol, practically insoluble in methylene chloride.

mp

About 164 °C, with decomposition.

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (2.2.25).

Test solution Dissolve 20.0 mg in *water R* and dilute to 100.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *water R*.

Spectral range 230-350 nm.

Absorption maxima At 270 nm and 307 nm.

Specific absorbance at the absorption maxima:

— at 270 nm: 252 to 278;

— at 307 nm: 204 to 226.

B. Infrared absorption spectrophotometry (2.2.24).

Comparison *clebopride malate CRS*.

C. Dissolve 20 mg in 1 mL of *sulfuric acid R*, add 1 mL of *β-naphthol solution R1* and mix. The solution examined in daylight is yellow with blue fluorescence.

D. Thin-layer chromatography (2.2.27).

Test solution Dissolve 5 mg of the substance to be examined in *anhydrous ethanol R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *clebopride malate CRS* in *anhydrous ethanol R* and dilute to 10 mL with the same solvent.

Reference solution (b) Dissolve 5 mg of *clebopride malate CRS* and 5 mg of *metoclopramide hydrochloride CRS* in *anhydrous ethanol R* and dilute to 10 mL with the same solvent.

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

Mobile phase *concentrated ammonia R*, *acetone R*, *methanol R*, *toluene R* (2:14:14:70 *V/V/V/V*).

Application 5 µL as bands of 10 mm by 3 mm.

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated zones.

Results The principal zone in the chromatogram obtained with the test solution is similar in position and size to the principal zone in the chromatogram obtained with reference solution (a).

TESTS

Solution S

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S, examined immediately after preparation, is clear (2.2.1) and colourless (2.2.2, *Method I*).

pH (2.2.3)

3.8 to 4.2 for solution S.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

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

Reference solution (b) Dissolve 10 mg of the substance to be examined and 10 mg of *metoclopramide hydrochloride CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 10.0 mL with the mobile phase.

Column:

— *size*: *l* = 0.12 m, Ø = 4.0 mm;

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

Mobile phase Mix 20 volumes of *acetonitrile R1* and 80 volumes of a 1 g/L solution of *sodium heptanesulfonate R* adjusted to pH 2.5 with *phosphoric acid R*.

Flow rate 1 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time Twice the retention time of clebopride.

Relative retention With reference to clebopride (retention time = about 15 min): metoclopramide = about 0.45.

System suitability Reference solution (b):

— *resolution*: minimum 5.0 between the peaks due to metoclopramide and clebopride.

Limits:

— *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 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 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); disregard the 2 peaks eluting within the first 2 min.

Chlorides

Maximum 100 ppm.

Prepare the solutions at the same time.

Test solution Dissolve 0.530 g in 20.0 mL of *anhydrous acetic acid R*, add 6 mL of *dilute nitric acid R* and dilute to 50.0 mL with *water R*.

Reference solution To 1.5 mL of *0.001 M hydrochloric acid* add 20.0 mL of *anhydrous acetic acid R* and 6 mL of *dilute nitric acid R* and dilute to 50.0 mL with *water R*.

Transfer both freshly prepared solutions to separate test-tubes. Add to each tube 1 mL of *silver nitrate solution R2*. Allow to stand for 5 min protected from light. Examine the tubes laterally against a black background. Any opalescence in the test solution is not more intense than that in the reference solution.

Sulfates

Maximum 100 ppm.

Prepare the solutions at the same time.

Test solution Dissolve 3.00 g in 20.0 mL of *glacial acetic acid R*, heating gently if necessary. Allow to cool and dilute to 50.0 mL with *water R*.

Reference solution To 9 mL of *sulfate standard solution (10 ppm SO_4) R1* add 6 mL of *glacial acetic acid R*.

Into 2 test-tubes introduce 1.5 mL of *sulfate standard solution (10 ppm SO_4) R1* and add 1 mL of a 250 g/L solution of *barium chloride R*. Shake and allow to stand for 1 min. To one of the tubes add 15 mL of the test solution and to the other add 15 mL of the reference solution. After 5 min, any opalescence in the tube containing the test solution is not more intense than that in the tube containing the reference solution.

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

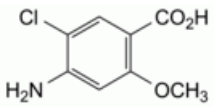
1 mL of *0.1 M perchloric acid* is equivalent to 50.80 mg of $C_{24}H_{30}ClN_3O_7$.

STORAGE

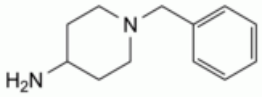
Protected from light.

IMPURITIES

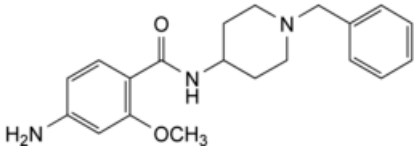
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



A. 4-amino-5-chloro-2-methoxybenzoic acid,



B. 1-benzylpiperidin-4-amine,



C. 4-amino-*N*-(1-benzylpiperidin-4-yl)-2-methoxybenzamide.

Ph Eur