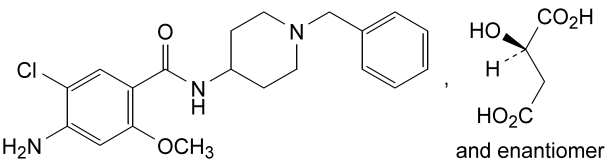
01/2005:1303

CLEBOPRIDE MALATE

Clebopridi malas



and enantiomer

$C_{24}H_{30}ClN_3O_7$ M_r 508.0

DEFINITION

Clebopride malate contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of 4-amino-*N*-(1-benzylpiperidin-4-yl)-5-chloro-2-methoxybenzamide acid (*RS*)-2-hydroxybutanedioate, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, sparingly soluble in water and in methanol, slightly soluble in ethanol, practically insoluble in methylene chloride.

It melts at about 164 °C, with decomposition.

IDENTIFICATION

First identification: B, C.

Second identification: A, C, D.

A. 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*. Examined between 230 nm and 350 nm (*2.2.25*), the solution shows two absorption maxima, at 270 nm and 307 nm. The specific absorbances at the maxima are 252 to 278 and 204 to 226, respectively.

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *clebopride malate CRS*. Examine the substances prepared as discs.

C. Dissolve 20 mg in 1 ml of *sulphuric acid R*, add 1 ml of *β-naphthol solution R1* and mix. The solution examined in daylight has a yellow colour with blue fluorescence.

D. Examine by thin-layer chromatography (*2.2.27*), using as the coating substance a suitable silica gel with a fluorescent indicator having an optimal intensity at 254 nm.

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

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

Apply to the plate as bands 10 mm by 3 mm, 5 µl of each solution. Develop over a path of 15 cm using a mixture of 2 volumes of *concentrated ammonia R*, 14 volumes of *acetone R*, 14 volumes of *methanol R* and 70 volumes of *toluene R*. Allow the plate to dry in air and examine in ultraviolet light at 254 nm. The principal band in the chromatogram obtained with the test solution is similar in position and size to the principal band in the chromatogram obtained with the reference solution (a). The identification is not valid unless the chromatogram obtained with reference solution (b) shows two clearly separated bands.

TESTS

Solution S. Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 100.0 ml with the same solvent.

Appearance of solution. Examined immediately after preparation, solution S is clear (*2.2.1*) and colourless (*2.2.2, Method I*).

pH (*2.2.3*). The pH of solution S is 3.8 to 4.2.

Related substances. Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.10 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 10.0 mg of *clebopride malate CRS* and 10.0 mg of *metoclopramide hydrochloride CRS* in the mobile phase and dilute to 100.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

The chromatographic procedure may be carried out using:

– a stainless steel column 0.12 m long and 4.0 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (5 µm),

– as mobile phase at a flow rate of 1 ml/min a mixture of 20 volumes of *acetonitrile R* and 80 volumes of a 1 g/l solution of *heptane sulphonate sodium R* adjusted to pH 2.5 with *phosphoric acid R*,

– as detector a spectrophotometer set at 215 nm.

Equilibrate the column with the mobile phase for 30 min. Inject 20 µl of reference solution (b). Adjust the sensitivity of the system so that the heights of the peaks in the chromatogram obtained are at least 30 per cent of the full scale of the recorder. The test is not valid unless the retention time of the second peak (clebopride) is about 15 min and the relative retention time of the first peak is about 0.45. Inject 20 µl of the test solution and 20 µl of reference solution (a). Continue the chromatography of the test solution for twice the retention time of the principal peak. In the chromatogram obtained with the test solution: the area of any peak, apart from the principal peak and the two peaks eluting within 2 min, is not greater than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent); the sum of the areas of all peaks, apart from the principal peak and the two peaks eluting within 2 min, is not greater than three times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent). Disregard any peak with an area less than 0.25 times that of the principal peak in the chromatogram obtained with reference solution (a).

Chlorides. *Prepare the solutions at the same time.*

Test solution. Dissolve 0.530 g of the substance to be examined 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 separately both solutions recently prepared to 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 (100 ppm).

Sulphates. *Prepare the solutions at the same time.*

Test solution. Dissolve 3.00 g of the substance to be examined 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 *sulphate standard solution (10 ppm SO_4) R1*, add 6 ml of *glacial acetic acid R*.

Into two test tubes introduce 1.5 ml of *sulphate 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 one 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 containing the reference solution (100 ppm).

Heavy metals (*2.4.8*). 1.0 g complies with limit test D for heavy metals (20 ppm). Prepare the standard using 2 ml of *lead standard solution (10 ppm Pb) R*.

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying in an oven at 100 °C to 105 °C.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

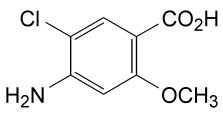
Dissolve 0.400 g in 50 ml of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

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

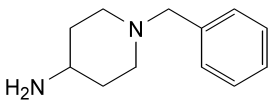
STORAGE

Store protected from light.

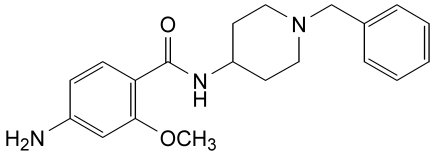
IMPURITIES



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



B. 1-benzylpiperidin-4-amine,

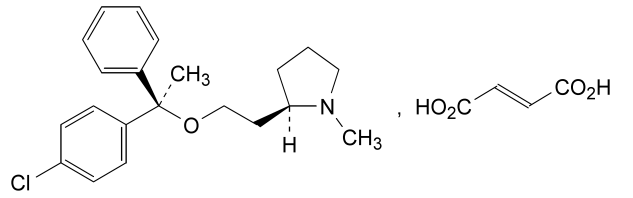


C. 4-amino-*N*-(1-benzylpiperidin-4-yl)-2-methoxybenzamide.

01/2005:1190

CLEMASTINE FUMARATE

Clemastini fumaras



$C_{25}H_{30}ClNO_5$ M_r 460.0

DEFINITION

Clemastine fumarate contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (2*R*)-2-[2-[(*R*)-1-(4-chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine (*E*)-butenedioate, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, very slightly soluble in water, sparingly soluble in alcohol (70 per cent *V/V*), slightly soluble in alcohol (50 per cent *V/V*) and in methanol.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. It complies with the test for specific optical rotation (see Tests).

B. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *clemastine fumarate CRS*.

C. Examine the chromatograms obtained in the test for related substances (see Tests). The principal spot in the chromatogram obtained with test solution (b) is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

D. Examine by thin-layer chromatography (*2.2.27*), using *silica gel G R* as the coating substance.

Test solution. Dissolve 40 mg of the substance to be examined in *methanol R* and dilute to 2 ml with the same solvent.

Reference solution. Dissolve 50 mg of *fumaric acid CRS* in *alcohol R* and dilute to 10 ml with the same solvent.

Apply separately to the plate 5 µl of each solution. Develop over a path of 15 cm using a mixture of 5 volumes of *water R*, 25 volumes of *anhydrous formic acid R* and 70 volumes of *di-isopropyl ether R*. Dry the plate at 100 °C to 105 °C for 30 min, allow to cool and spray with a 16 g/l solution of *potassium permanganate R*. Examine in daylight. In the chromatogram obtained with test solution the spot with the highest R_f value is similar in position, colour and size to the spot in the chromatogram obtained with the reference solution.

TESTS

Solution S. Dissolve 0.500 g of substance to be examined in *methanol R* and dilute to 50.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).