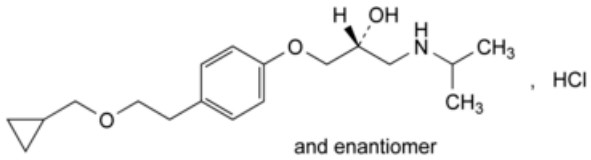
Edition: BP 2025 (Ph. Eur. 11.6 update)

Betaxolol Hydrochloride

General Notices

(Ph. Eur. monograph 1072)



$C_{18}H_{30}ClNO_3$ 343.9 *63659-19-8*

Action and use

Beta-adrenoceptor antagonist.

Preparations

Betaxolol Eye Drops, Solution

Betaxolol Eye Drops, Suspension

Ph Eur

DEFINITION

(2*RS*)-1-[4-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]propan-2-ol hydrochloride.

Content

98.5 per cent to 101.5 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent), soluble in methylene chloride.

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 113 °C to 117 °C.
B. Infrared absorption spectrophotometry (2.2.24).

Comparison betaxolol hydrochloride CRS.

C. Thin-layer chromatography (2.2.27).

Test solution Dissolve 10 mg of the substance to be examined in 1 mL of methanol R.

Reference solution (a) Dissolve 20 mg of betaxolol hydrochloride CRS in 2 mL of methanol R.

Reference solution (b) Dissolve 10 mg of oxprenolol hydrochloride CRS in 1 mL of reference solution (a).

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

Mobile phase perchloric acid R, methanol R, water R (0.5:50:50 *V/V/V*).

Application 2 µL.

Development Over a path of 10 cm.

Drying In air.

System suitability Reference solution (b):

— the chromatogram shows 2 clearly separated spots.

Detection A Examine in ultraviolet light at 254 nm.

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

Detection B Spray with a 50 g/L solution of vanillin R in a mixture of 5 volumes of sulfuric acid R, 10 volumes of glacial acetic acid R and 85 volumes of methanol R, heat at 100-105 °C until the colour of the spots reaches maximum intensity (10-15 min), and examine in daylight.

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

D. It gives reaction (a) of chlorides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and colourless (2.2.2, Method II).

Dissolve 0.5 g in water R and dilute to 25 mL with the same solvent.

Acidity or alkalinity

Dissolve 0.20 g in carbon dioxide-free water R and dilute to 20 mL with the same solvent. Add 0.2 mL of methyl red solution R and 0.2 mL of 0.01 M hydrochloric acid. The solution is red. Add 0.4 mL of 0.01 M sodium hydroxide. The solution is yellow.

Related substances

Liquid chromatography (2.2.29). *Prepare reference solutions (c) and (d) immediately before use.*

Test solution Dissolve 10 mg of the substance to be examined in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution (a) Dissolve 8 mg of the substance to be examined and 4 mg of *betaxolol impurity A CRS* in 20.0 mL of the mobile phase.

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

Reference solution (c) Dissolve 2 mg of *betaxolol impurity C CRS* in 50 mL of the mobile phase. Dilute 5 mL of the solution to 20 mL with the mobile phase.

Reference solution (d) Dissolve 10 mg of *betaxolol for peak identification CRS* (containing impurities B, D and E) in 5 mL of reference solution (c).

Column:

— *size*: *l* = 0.25 m, *Ø* = 4 mm;

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

Mobile phase Mix 175 mL of *acetonitrile R* and 175 mL of *methanol R* and dilute to 1 L with a 3.4 g/L solution of *potassium dihydrogen phosphate R*, previously adjusted to pH 3.0 with *phosphoric acid R*.

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 273 nm.

Injection 20 µL of the test solution and reference solutions (a), (b) and (d).

Run time 4.5 the retention time of betaxolol.

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram supplied with *betaxolol for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities B, C, D and E.

Relative retention With reference to betaxolol (retention time = about 8 min): impurity B = about 0.3; impurity A = about 0.8; impurity D = about 1.5; impurity E = about 2.2; impurity C = about 4.1.

System suitability Reference solution (a):

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

Limits:

— *impurities A, B, C, D, E*: for each impurity, not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *unspecified impurities*: for each impurity, not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (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 0.300 g in a mixture of 10.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

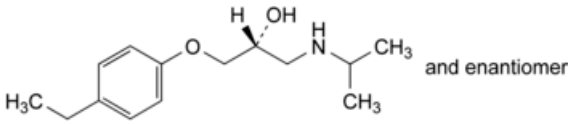
1 mL of *0.1 M sodium hydroxide* is equivalent to 34.39 mg of $C_{18}H_{30}ClNO_3$.

STORAGE

Protected from light.

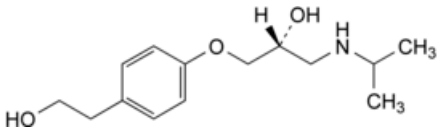
IMPURITIES

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



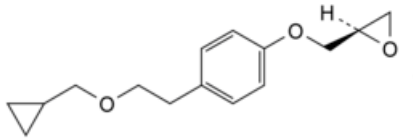
and enantiomer

A. (2*RS*)-1-(4-ethylphenoxy)-3-[(1-methylethyl)amino]propan-2-ol,



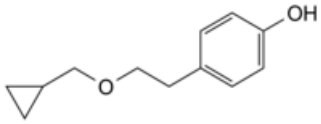
and enantiomer

B. (2*RS*)-1-[4-(2-hydroxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol,

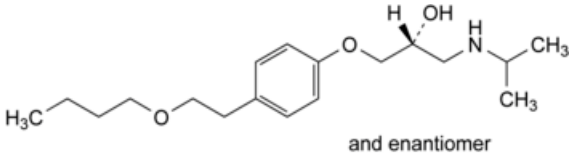


and enantiomer

C. (2*RS*)-2-[[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]methyl]oxirane,



D. 4-[2-(cyclopropylmethoxy)ethyl]phenol,



and enantiomer

E. (2*RS*)-1-[4-(2-butoxyethyl)phenoxy]-3-[(1-methylethyl)amino]propan-2-ol.

Ph Eur