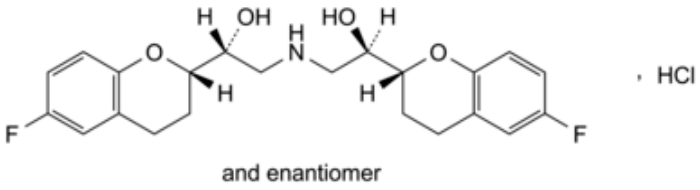
Edition: BP 2025 (Ph. Eur. 11.6 update)

Nebivolol Hydrochloride

General Notices

(Ph. Eur. monograph 2775)



and enantiomer

$C_{22}H_{26}ClF_2NO_4$ 441.9 *152520-56-4*

Action and use

Beta-adrenoceptor antagonist.

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DEFINITION

(1*RS*)-1-[(2*RS*)-6-Fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-[[(2*RS*)-2-[(2*SR*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]amino]ethan-1-ol hydrochloride.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white crystalline powder.

Solubility

Very slightly soluble in water, sparingly soluble in methanol, very slightly soluble in heptane.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison nebivolol hydrochloride CRS.

B. Dissolve 20 mg in 20 mL of methanol R and add 1 mL of silver nitrate solution R1. Shake and allow to stand. A curdled, white precipitate is formed. Remove the supernatant and suspend the precipitate in 5 mL dilute nitric acid R. The precipitate does not dissolve. Add 20 mL of ammonia R and shake well. The precipitate dissolves easily with the possible exception of a few large particles which dissolve slowly.

TESTS

Impurity D

Liquid chromatography (2.2.29).

Test solution Dissolve 20.0 mg of the substance to be examined in methanol R and dilute to 5.0 mL with the same solvent.

Reference solution (a) Dilute 3.0 mL of the test solution to 100.0 mL with methanol R. Dilute 1.0 mL of this solution to 20.0 mL with methanol R.

Reference solution (b) Dissolve the contents of a vial of nebivolol impurity D CRS in 1 mL of the test solution.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: amylose derivative of silica gel for chiral separation R (5 µm);

— *temperature*: 40 °C.

Mobile phase diethylamine R, ethanol (96 per cent) R (0.1:99.9 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 20 µL.

Run time 3 times the retention time of nebivolol isomer 1.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurity D.

Relative retention With reference to nebivolol isomer 1 (retention time = about 14 min): nebivolol isomer 2 = about 1.3; impurity D (isomer 1) = about 1.9; impurity D (isomer 2) = about 2.8.

System suitability Reference solution (b):

— resolution: minimum 2.0 between the peaks due to impurity D (isomer 1) and impurity D (isomer 2).

Calculation of percentage content:

— use the concentration of nebivolol hydrochloride (both isomers) in reference solution (a).

Limit:

— *impurity D*: maximum 0.3 per cent for the sum of the 2 isomers.

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Test solution (a) Dissolve 20.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with the solvent mixture.

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

Reference solution (b) Dissolve 10.0 mg of nebivolol hydrochloride CRS in the solvent mixture and dilute 50.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of nebivolol for peak identification CRS (containing impurity A) in 1 mL of the solvent mixture.

Reference solution (d) Dissolve the contents of a vial of nebivolol impurity B CRS in 1 mL of reference solution (a).

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated end-capped phenylsilyl silica gel for chromatography R (5 µm);

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, 3.4 g/L solution of tetrabutylammonium hydrogen sulfate R (5:95 *V/V*

— *mobile phase B*: water for chromatography R, acetonitrile R (5:95 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 18	76	24
18 - 30	76 → 65	24 → 35
30 - 45	65	35

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 280 nm.

Injection 10 µL of test solution (a) and reference solutions (a), (c) and (d).

Identification of impurities Use the chromatogram supplied with nebivolol for peak identification CRS and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity B.

Relative retention With reference to nebivolol (retention time = about 19 min): impurity A = about 0.8; impurity B = about 1.1.

System suitability Reference solution (d):

— *resolution*: minimum 2.0 between the peaks due to nebivolol and impurity B.

Calculation of percentage content:

— for each impurity, use the concentration of nebivolol hydrochloride in reference solution (a).

Limits:

— *impurities A, B*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 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 for 3 h.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase:

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	74	26
15 - 20	74 → 30	26 → 70
20 - 25	30	70

Flow rate 1.2 mL/min.

Injection 20 µL of test solution (b) and reference solution (b).

Retention time Nebivolol = about 12 minutes.

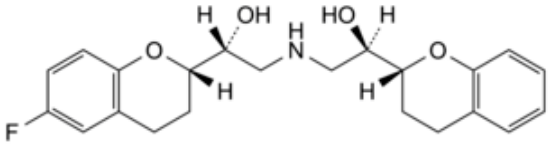
Calculate the percentage content of $C_{22}H_{26}ClF_2NO_4$ taking into account the assigned content of *nebivolol hydrochloride CRS*.

IMPURITIES

Specified impurities *A, B, D.*

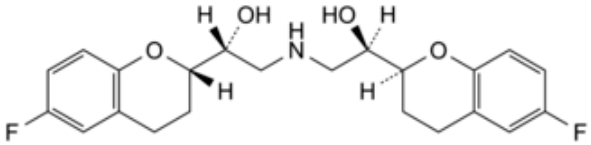
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for

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) C.



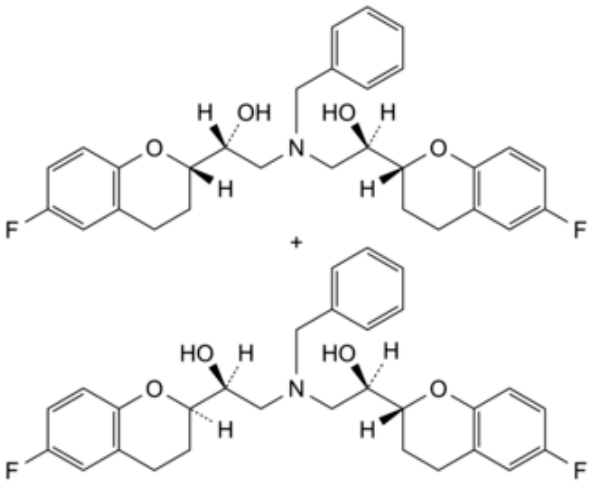
and enantiomer

A. (1*RS*)-1-[(2*RS*)-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-[[(2*RS*)-2-[(2*SR*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]amino]ethan-1-ol,



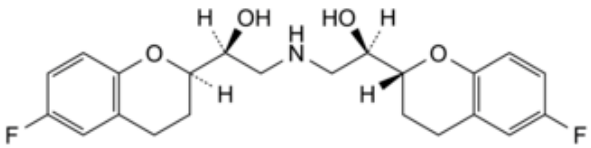
and enantiomer

B. (1*RS*,1′*RS*)-2,2′-azanediylbis[1-[(2*SR*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]ethan-1-ol],



and their enantiomers

C. (1*RS*)-2-[benzyl[(2*RS*)-2-[(2*RS*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]amino]-1-[(2*SR*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]ethan-1-ol and (1*RS*)-2-[benzyl[(2*SR*)-2-[(2*RS*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]amino]-1-[(2*RS*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]ethan-1-ol,



and enantiomer

D. (1*RS*)-1-[(2*RS*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-[[(2*SR*)-2-[(2*RS*)-6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl]-2-hydroxyethyl]amino]ethan-1-ol.

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