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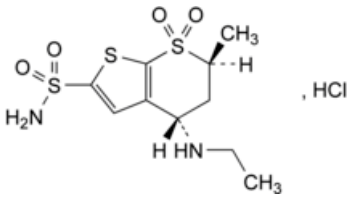
Edition: BP 2025 (Ph. Eur. 11.6 update)

Dorzolamide Hydrochloride

General Notices

(Ph. Eur. monograph 2359)



$C_{10}H_{17}ClN_2O_4S_3$ 360.9 *130693-82-2*

Action and use

Carbonic anhydrase inhibitor; treatment of glaucoma and ocular hypertension.

Preparations

Dorzolamide Eye Drops

Dorzolamide and Timolol Eye Drops

Ph Eur

DEFINITION

(4*S*,6*S*)-4-(Ethylamino)-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride.

Content

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

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Soluble in water, slightly soluble in methanol, very slightly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

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IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison dorzolamide hydrochloride CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

B. It complies with the test for impurity A (see Tests).
C. It gives reaction (a) of chlorides (2.3.1).

TESTS

Impurity A

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, glacial acetic acid R, 1,1-dimethylethyl methyl ether R (3:10:87 *V/V/V*).

Test solution In a centrifuge tube, dissolve 20.0 mg of the substance to be examined in 4 mL of dilute ammonia R4, add 4 mL of ethyl acetate R, and mix. Separate the organic layer and transfer it to a separate centrifuge tube. Add 4 mL of ethyl acetate R to the aqueous layer, mix, separate the organic layer, and combine it with the 1st extract. Evaporate the combined organic layers to dryness in a water-bath at 50 °C under a stream of nitrogen R. Dissolve the residue in 3 mL of acetonitrile R, add 0.06 mL of (*S*)-(-)-α-methylbenzyl isocyanate R, and heat in a water-bath at 50 °C for 5 min. Evaporate to dryness in a water-bath at 50 °C under a stream of nitrogen R. Dissolve the residue in 10 mL of the solvent mixture.

Reference solution In a centrifuge tube, dissolve 18.0 mg of dorzolamide hydrochloride CRS and 2.0 mg of dorzolamide impurity A CRS in 4 mL of dilute ammonia R4, and proceed as indicated for the test solution beginning with “add 4 mL of ethyl acetate R, and mix”.

Column:

— *size*: *l* = 0.25 m, *Ø* = 4.6 mm;

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

Mobile phase water R, acetonitrile R, heptane R, 1,1-dimethylethyl methyl ether R (0.2:2:35:63 *V/V/V/V*).

Flow rate 2 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 3 times the retention time of dorzolamide.

Relative retention With reference to dorzolamide (retention time = about 10 min): impurity A = about 1.4.

System suitability Reference solution:

— resolution: minimum 4.0 between the peaks due to dorzolamide and impurity A.

Calculate the percentage content of impurity A using the following expression:

$$\frac{A}{B}$$

A	=	area of the peak due to impurity A in the chromatogram obtained with the test solution;
B	=	area of the peak due to dorzolamide in the chromatogram obtained with the test solution.

Limit:

— *impurity A*: maximum 0.5 per cent.

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Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 30.0 mg of the substance to be examined in mobile phase A and dilute to 50.0 mL with mobile phase A.

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

Reference solution (b) Dissolve 2 mg of *dorzolamide for system suitability CRS* (containing impurity C) in 2 mL of mobile phase A.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

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

— *temperature*: 35 °C.

Mobile phase:

— *mobile phase A*: mix 65 mL of *acetonitrile R* and 935 mL of a 3.7 g/L solution of *potassium dihydrogen phosphate R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 30	100 → 50	0 → 50
30 - 37	50 → 100	50 → 0
37 - 44	100	0

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Identification of impurities Use the chromatogram supplied with *dorzolamide for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to dorzolamide (retention time = about 11 min): impurity C = about 0.9.

System suitability Reference solution (b):

— *resolution*: minimum 2.0 between the peaks due to impurity C and dorzolamide.

Limits:

— *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 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 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).

Loss on drying (2.2.32)

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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

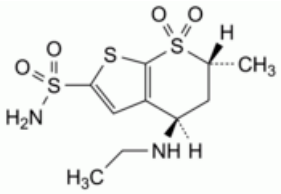
Dissolve 0.150 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*, using sonication if necessary. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 1st and the 3rd points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.05 mg of $C_{10}H_{17}N_2O_4S_3Cl$.

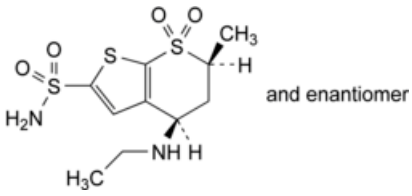
IMPURITIES

Specified impurities A, C.

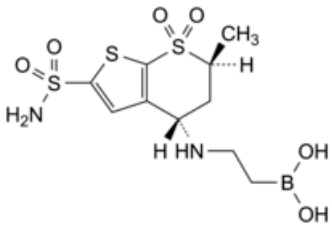
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



A. (4*R*,6*R*)-4-(ethylamino)-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide,



B. (4*RS*,6*SR*)-4-(ethylamino)-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide,



C. [2-[[(4*S*,6*S*)-6-methyl-7,7-dioxo-2-sulfamoyl-4,5,6,7-tetrahydro-7λ^6-thieno[2,3-*b*]thiopyran-4-yl]amino]ethyl]boronic acid,

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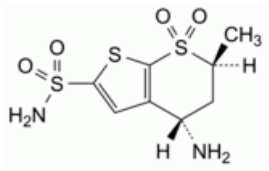

D. (4*S*,6*S*)-4-amino-6-methyl-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide.

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