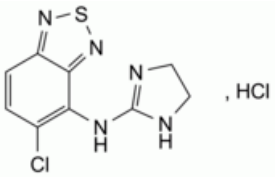
Edition: BP 2025 (Ph. Eur. 11.6 update)

Tizanidine Hydrochloride

General Notices

(Ph. Eur. monograph 2578)



$C_9H_9Cl_2N_5S$ 290.2 *64461-82-1*

Action and use

Alpha$_2$-adrenoceptor agonist; skeletal muscle relaxant.

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DEFINITION

5-Chloro-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine hydrochloride.

Content

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

CHARACTERS

Appearance

White or yellowish-white, crystalline powder.

Solubility

Soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison *tizanidine hydrochloride CRS*.

B. Solution S (see Tests) gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

pH (2.2.3)

3.7 to 5.0 for solution S.

Impurity H

Thin-layer chromatography (2.2.27).

Test solution Dissolve 0.200 g of the substance to be examined in *methanol R* and dilute to 5.0 mL with the same solvent.

Reference solution Dissolve 8.0 mg of *ethylenediamine R* (impurity H) in *methanol R* and dilute to 100.0 mL with the same solvent.

Plate *TLC cellulose plate R*.

Mobile phase *glacial acetic acid R*, *water R*, *methanol R* (1:25:75 *V/V/V*).

Application 5 µL.

Development Over 1/2 of the plate.

Drying In a current of cold air.

Detection Spray with a mixture of 15 volumes of a 20 g/L solution of *ninhydrin R* in *glacial acetic acid R* and 85 volumes of *butanol R*, then heat at 100 °C for 5 min.

Relative retention with reference to tizanidine (R_F = about 0.8): impurity H = about 0.3.

Limit:

— *impurity H*: any spot due to impurity H is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (0.2 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 30.0 mg of the substance to be examined in mobile phase A, using sonication if necessary, and dilute to 25.0 mL with mobile phase A. Dilute 5.0 mL of the solution to 50.0 mL with mobile phase A.

Reference solution (a) Dissolve 3 mg of *tizanidine impurity B CRS* in mobile phase A and dilute to 25.0 mL with mobile phase A. Dilute 1.0 mL of the solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with the test solution.

Reference solution (b) Dilute 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 (c) Dissolve 30.0 mg of *tizanidine hydrochloride CRS* in mobile phase A, using sonication if necessary, and dilute to 25.0 mL with mobile phase A. Dilute 5.0 mL of the solution to 50.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 18 volumes of *acetonitrile R1* and 82 volumes of a 3.86 g/L solution of *sodium pentanesulfonate monohydrate R* previously adjusted to pH 3.0 with *phosphoric acid R*;

— *mobile phase B*: mix 20 volumes of a 3.86 g/L solution of *sodium pentanesulfonate monohydrate R* previously adjusted to pH 3.0 with *phosphoric acid R* and 80 volumes of *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0
15 - 25	100 → 0	0 → 100
25 - 27	0	100

Flow rate 0.6 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 10 µL of the test solution and reference solutions (a) and (b).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity B.

Relative retention With reference to tizanidine (retention time = about 6 min): impurity B = about 1.3.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to tizanidine and impurity B.

Calculation of percentage contents:

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

Limits:

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

— *total*: maximum 0.2 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.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

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

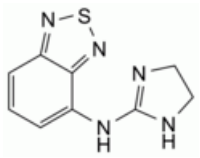
Injection Test solution and reference solution (c).

Calculate the percentage content of $C_9H_9Cl_2N_5S$ taking into account the assigned content of *tizanidine hydrochloride CRS*.

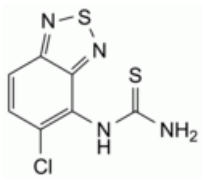
IMPURITIES

Specified impurities *H*.

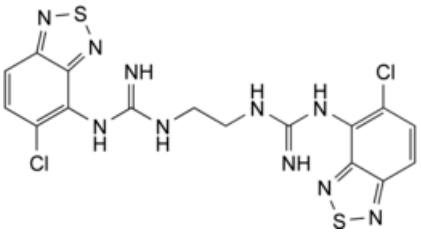
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



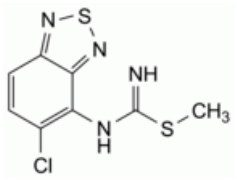
A. *N*-(4,5-dihydro-1*H*-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine,



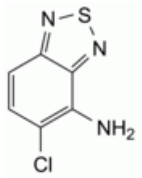
B. *N*-(5-chloro-2,1,3-benzothiadiazol-4-yl)thiourea,



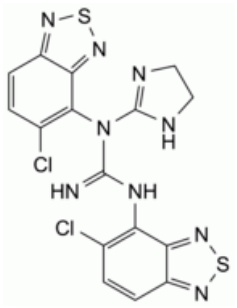
C. 1,1′-ethane-1,2-diylbis[3-(5-chloro-2,1,3-benzothiadiazol-4-yl)guanidine],



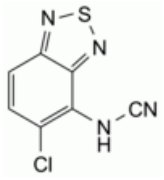
D. methyl *N*-(5-chloro-2,1,3-benzothiadiazol-4-yl)carbamimidothioate,



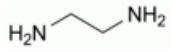
E. 5-chloro-2,1,3-benzothiadiazol-4-amine,



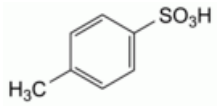
F. 1,3-bis(5-chloro-2,1,3-benzothiadiazol-4-yl)-1-(4,5-dihydro-1*H*-imidazol-2-yl)guanidine,



G. (5-chloro-2,1,3-benzothiadiazol-4-yl)cyanamide,



H. ethane-1,2-diamine (ethylenediamine),



I. 4-methylbenzenesulfonic acid (*p*-toluenesulfonic acid).

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