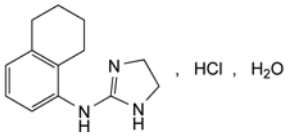
01/2008:1597

TRAMAZOLINE HYDROCHLORIDE MONOHYDRATE

Tramazolini hydrochloridum monohydricum



$C_{13}H_{18}ClN_3,H_2O$ M_r 269.8
[74195-73-6]

DEFINITION

N-(5,6,7,8-Tetrahydronaphthalen-1-yl)-4,5-dihydro-1*H*-imidazol-2-amine hydrochloride monohydrate.

Content: 98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: soluble in water and in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *tramazoline hydrochloride monohydrate CRS*.

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

pH (*2.2.3*): 4.9 to 6.3 for solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in a mixture of 50 volumes of *acetonitrile R* and 50 volumes of *water R* and dilute to 50.0 mL with the same mixture of solvents.

Reference solution (a). Dissolve 5.0 mg of *tramazoline impurity A CRS* and 5.0 mg of *tramazoline impurity B CRS* in 5 mL of a mixture of 50 volumes of *acetonitrile R* and 50 volumes of *water R* and add 5 mL of the test solution.

Reference solution (b). Dilute 0.2 mL of reference solution (a) to 100 mL with a mixture of 50 volumes of *acetonitrile R* and 50 volumes of *water R*.

Column:
- *size*: *l* = 0.125 m, Ø = 4 mm,
- *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: 2.0 g/L solution of *sodium dodecyl sulfate R* in a mixture of 6 volumes of *2-propanol R*, 42 volumes of *acetonitrile R* and 52 volumes of *water R*.

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 5 µL.

Run time: 3 times the retention time of tramazoline.

Relative retention with reference to tramazoline (retention time = about 6.5 min): impurity A = about 0.71; impurity B = about 0.86.

System suitability: reference solution (a):
- the chromatogram obtained shows 3 clearly separated peaks,
- *resolution*: minimum 1.5 between tramazoline and impurity B.

Limits:
- *impurity A*: not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent),
- *impurity B*: not more than 3 times the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.3 per cent),
- *any other impurity*: not more than the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.1 per cent),
- *sum of other impurities*: not more than twice the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.2 per cent),
- *disregard limit*: 0.2 times the area of the peak due to impurity B in the chromatogram obtained with reference solution (b) (0.02 per cent).

Water (*2.5.12*): 6.2 per cent to 7.2 per cent, determined on 0.500 g.

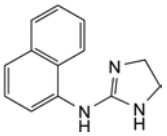
Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

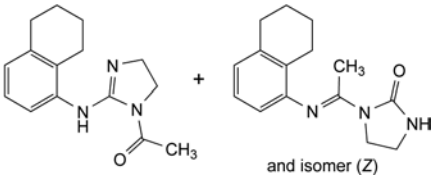
Dissolve 2.000 g in a mixture of 5 mL of *0.1 M hydrochloric acid* and 75 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*) using *1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *1 M sodium hydroxide* is equivalent to 251.8 mg of $C_{13}H_{18}ClN_3$.

IMPURITIES



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

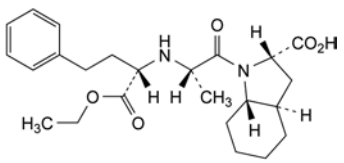


B. mixture of 1-acetyl-*N*-(5,6,7,8-tetrahydronaphthalen-1-yl)-4,5-dihydro-1*H*-imidazol-2-amine and 1-[(*EZ*)-1-[(5,6,7,8-tetrahydronaphthalen-1-yl)imino]ethyl]imidazolidin-2-one.

01/2008:2245
corrected 7.0

TRANDOLAPRIL

Trandolaprilum



$C_{24}H_{34}N_2O_5$ M_r 430.5
[87679-37-6]

DEFINITION

(2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in anhydrous ethanol.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *trandolapril CRS*.

TESTS

Appearance of solution. The solution is not more intensely coloured than reference solution Y_7 (*2.2.2, Method II*).

Dissolve 1.0 g in *methanol R* and dilute to 10 mL with the same solvent.

Specific optical rotation (*2.2.7*): – 16.5 to – 18.5 (anhydrous substance).

Dissolve 1.0 g in *anhydrous ethanol R* and dilute to 50.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in mobile phase A and dilute to 10.0 mL with mobile phase A.

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

Reference solution (b). Dissolve 5 mg of *trandolapril impurity C CRS* and 5 mg of *trandolapril impurity D CRS* in mobile phase A and dilute to 5 mL with mobile phase A. Dilute 1 mL of this solution to 20 mL with mobile phase A.

Column:

– *size*: *l* = 0.15 m, Ø = 4.6 mm,

– *stationary phase*: *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer R* (3.5 µm),

– *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: mix 25 volumes of *acetonitrile R*, and 75 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.5 ± 0.1 with *phosphoric acid R*;

– *mobile phase B*: mix equal volumes of *acetonitrile R*, and a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 2.2 ± 0.1 with *phosphoric acid R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 20	95	5
20 - 35	95 → 5	5 → 95
35 - 45	5	95

Flow rate: 1.3 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 20 µL.

Relative retention with reference to trandolapril (retention time = about 14.5 min): impurity C = about 2.1; impurity D = about 2.5.

System suitability: reference solution (b):

– *resolution*: minimum 4 between the peaks due to impurity C and impurity D.

Limits:

– *correction factor*: for the calculation of content, multiply the peak area of impurity C by 2.2,

– *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent),

– *impurity D*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent),

– *sum of impurities other than D*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 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).

Palladium: maximum 5 ppm.

Atomic absorption spectrometry (*2.2.23, Method I*).

Solvent mixture: *nitric acid R, water R* (1:99 *V/V*).

Test solution. To the residue of the test for sulfated ash add 3 mL of *hydrochloric acid R* and 1 mL of *fuming nitric acid R*. Cover the crucible with a watch glass and heat at 160-170 °C for 1 h to dissolve the residue. Afterwards continue heating in the open crucible and evaporate the solution. Stop heating before the residue is completely dried, add 1 mL of *nitric acid R*, heat at 160-170 °C for further 10 min, and after cooling dilute to 10.0 mL with *water R*.

Reference solutions. Prepare reference solutions containing 0.5 µg, 1.0 µg and 1.5 µg of Pd per millilitre by diluting *palladium standard solution (500 ppm Pd) R* with the solvent mixture.

Source: palladium hollow-cathode lamp.

Wavelength: 244.8 nm.

Atomisation device: air-acetylene flame.

Water (*2.5.32*): maximum 0.2 per cent, determined on 1.000 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 2.0 g in a porcelain or quartz crucible.

ASSAY

Dissolve 0.300 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 43.05 mg of $C_{24}H_{34}N_2O_5$.

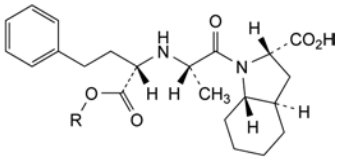
STORAGE

Protected from light.

IMPURITIES

Specified impurities: C, D.

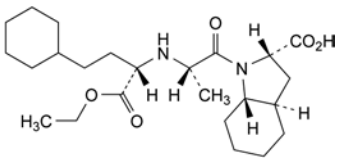
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



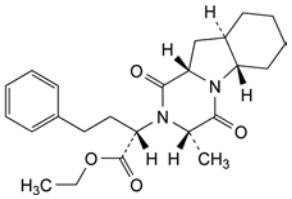
A. R = CH_3: (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(methoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (methyl ester derivative),

B. R = $CH(CH_3)_2$: (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-[(1-methylethoxy)carbonyl]-3-phenylpropyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (isopropyl ester derivative),

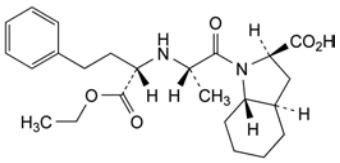
E. R = H: (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (trandolaprilate),



C. (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-3-cyclohexyl-1-(ethoxycarbonyl)propyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (hexahydrotrandolapril),



D. ethyl (2*S*)-2-[(3*S*,5a*S*,9a*R*,10a*S*)-3-methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl]-4-phenylbutanoate (trandolapril diketopiperazine),

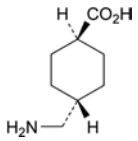


F. (2*R*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid.

01/2008:0875
corrected 6.0

TRANEXAMIC ACID

Acidum tranexamicum



$C_8H_{15}NO_2$ M_r 157.2
[1197-18-8]

DEFINITION

trans-4-(Aminomethyl)cyclohexanecarboxylic acid.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water and in glacial acetic acid, practically insoluble in acetone and in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Preparation: discs.

Comparison: *tranexamic acid CRS*.

TESTS

pH (*2.2.3*): 7.0 to 8.0.

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 50 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.20 g of the substance to be examined in *water R* and dilute to 20.0 mL with the same solvent.

Reference solution (a). Dilute 5.0 mL of the test solution to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Reference solution (b). Dissolve 20 mg of *tranexamic acid CRS* (containing impurity C) in *water R* and dilute to 2 mL with the same solvent.

Reference solution (c). Dissolve 12 mg of *4-aminomethylbenzoic acid R* (impurity D) in *water R* and dilute to 100 mL with the same solvent. Dilute 1 mL of the solution to 50 mL with *water R*. Dilute 5 mL of this solution to 200 mL with *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm or *l* = 0.25 m, Ø = 6.0 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 11.0 g of *anhydrous sodium dihydrogen phosphate R* in 500 mL of *water R* and add 5 mL of *triethylamine R* and 1.4 g of *sodium laurilsulfate R*. Adjust to pH 2.5 with *dilute phosphoric acid R* and dilute to 600 mL with *water R*. Add 400 mL of *methanol R* and mix.

Flow rate: 0.9 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 20 µL.

Run time: 3 times the retention time of tranexamic acid.

Identification of impurities: use the chromatogram supplied with *tranexamic acid CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention with reference to tranexamic acid (retention time = about 13 min): impurity C = about 1.1; impurity D = about 1.3; impurity B = about 1.5; impurity A = about 2.1.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to tranexamic acid and impurity C.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity B = 1.2; impurity C = 0.005; impurity D = 0.006;
– *impurity A*: not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
– *impurity B*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
– *sum of unspecified impurities*: not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.025 per cent).