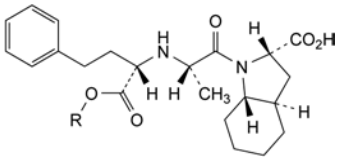
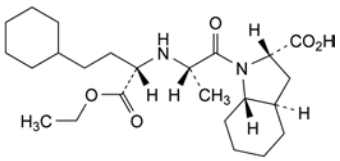


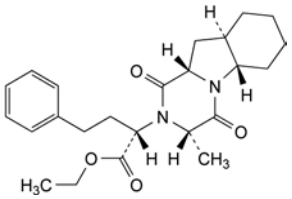
A. R = CH_3: (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-(methoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (methyl ester derivative),

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),

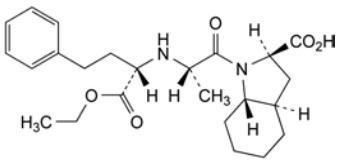
E. R = H: (2*S*,3a*R*,7a*S*)-1-[(2*S*)-2-[[(1*S*)-1-carboxy-3-phenylpropyl]amino]propanoyl]octahydro-1*H*-indole-2-carboxylic acid (trandolaprilate),



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.

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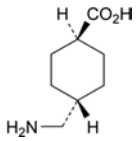
corrected 6.0

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).

Halides expressed as chlorides (*2.4.4*): maximum 140 ppm.

Dissolve 1.2 g in *water R* and dilute to 50 mL with the same solvent.

Heavy metals (*2.4.8*): maximum 10 ppm.

Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent. 12 mL of this solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

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 2 h.

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

ASSAY

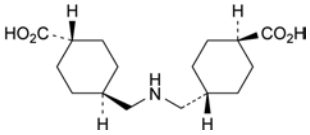
Dissolve 0.140 g in 20 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 15.72 mg of $C_8H_{15}NO_2$.

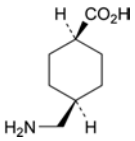
IMPURITIES

Specified impurities: A, B.

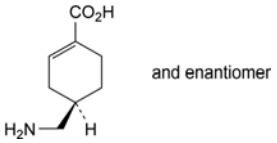
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



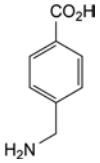
A. *trans*,*trans*-4,4′-(iminodimethylene)di(cyclohexanecarboxylic) acid,



B. *cis*-4-(aminomethyl)cyclohexanecarboxylic acid,



C. (*RS*)-4-(aminomethyl)cyclohex-1-enecarboxylic acid,

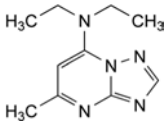


D. 4-aminomethylbenzoic acid.

01/2008:1576

TRAPIDIL

Trapidilum



$C_{10}H_{15}N_5$ M_r 205.3
[15421-84-8]

DEFINITION

N,N-Diethyl-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine.

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, soluble in ethanol and in methylene chloride.

mp: about 102 °C.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *trapidil CRS*.

TESTS

Solution S. Dissolve 2.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Acidity or alkalinity. To 10 mL of solution S 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*).

Test solution. Dissolve 20.0 mg of the substance to be examined in the mobile phase and dilute to 10.0 mL with the mobile phase.

Reference solution (a). Dissolve 5.0 mg of *trapidil impurity A CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (b). Dissolve 5.0 mg of *trapidil impurity B CRS* in the mobile phase and dilute to 50.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

Reference solution (c). Mix equal volumes of reference solution (a) and reference solution (b).

Column:

– *size*: *l* = 0.125 m, Ø = 4.0 mm,
– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm),

Mobile phase: 50 mL of *methanol R*, 75 mL of *acetonitrile R* and 800 mL of a 1.7 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 2.45 with *phosphoric acid R*; dilute to 1000 mL with *water R*.

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 205 nm.

Injection: 10 µL.

Run time: 3 times the retention time of trapidil.

System suitability:

– *resolution*: minimum of 4.0 between the peaks due to impurity A and impurity B in the chromatogram obtained with reference solution (c).