Limits:

- *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.2 per cent);
- *any other impurity*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (1.2 per cent);
- *total of impurities other than A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent).

Heavy metals (*2.4.8*): maximum 50 ppm.

0.5 g complies with test C. Prepare the reference solution using 2.5 mL of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*): 5.0 per cent to 8.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*): maximum 0.5 per cent, determined on 1.0 g.

Bacterial endotoxins (*2.6.14*): less than 1.25 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

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

Injection: test solution (b) and reference solution (a).

System suitability:

- *repeatability*: maximum relative standard deviation of the peak area for minocycline of 1.5 per cent after 6 injections of reference solution (a).

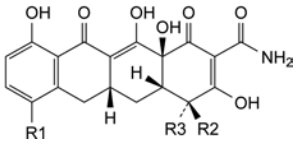
Calculate the percentage content of $C_{23}H_{28}ClN_3O_7$ from the declared content of *minocycline hydrochloride CRS*.

STORAGE

In an airtight container, protected from light. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

IMPURITIES

Specified impurities: A, B, C, D.



A. R1 = R3 = $N(CH_3)_2$, R2 = H: (4*R*,4a*S*,5a*R*,12a*S*)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (4-epiminocycline),

B. R1 = R3 = H, R2 = $N(CH_3)_2$: (4*S*,4a*S*,5a*R*,12a*S*)-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (sancycline),

C. R1 = NH-CH_3, R2 = $N(CH_3)_2$, R3 = H: (4*S*,4a*S*,5a*R*,12a*S*)-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-7-(methylamino)-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (7-monodemethylminocycline),

D. R1 = NH_2, R2 = $N(CH_3)_2$, R3 = H: (4*S*,4a*S*,5a*R*,12a*S*)-7-amino-4-(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide (7-aminosancycline).

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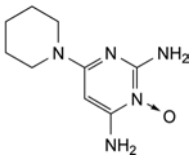
corrected 6.7

MINOXIDIL

Minoxidilum



$C_9H_{15}N_5O$ M_r 209.3
[38304-91-5]

DEFINITION

6-(Piperidin-1-yl)pyrimidine-2,4-diamine 3-oxide.

Content: 98.5 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: slightly soluble in water, soluble in methanol and in propylene glycol.

IDENTIFICATION

First identification: A, B.

Second identification: A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*).

Test solution (a). Dissolve 20.0 mg in *0.1 M hydrochloric acid* and dilute to 100.0 mL with the same acid (solution A). Dilute 2.0 mL of this solution to 100.0 mL with *0.1 M hydrochloric acid*.

Test solution (b). Dilute 2.0 mL of solution A to 100.0 mL with *0.1 M sodium hydroxide*.

Spectral range: 200-350 nm.

Absorption maxima: at 230 nm and 281 nm for test solution (a); at 230 nm, 262 nm and 288 nm for test solution (b);

Specific absorbances at the absorption maxima:

- at 230 nm: 1015 to 1120 for test solution (a); 1525 to 1685 for test solution (b);
- at 262 nm: 485 to 535 for test solution (b);
- at 281 nm: 1060 to 1170 for test solution (a);
- at 288 nm: 555 to 605 for test solution (b).

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *minoxidil CRS*.

C. Thin-layer chromatography (*2.2.27*).

Test solution. Dissolve 10 mg of the substance to be examined in *methanol R* and dilute to 10 mL with the same solvent.

Reference solution. Dissolve 10 mg of *minoxidil CRS* in *methanol R* and dilute to 10 mL with the same solvent.

Plate: *TLC silica gel GF_{254} plate R*.

Mobile phase: *concentrated ammonia R, methanol R* (1.5:100 *V/V*).

Application: 2 µL.

Development: over a path of 10 cm.

Drying: in air.

Detection: examine in ultraviolet light at 254 nm.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

D. Dissolve about 10 mg in 1 mL of *methanol R*. Add 0.1 mL of *copper sulfate solution R*. A green colour develops. The solution becomes greenish-yellow on the addition of 0.1 mL of *dilute hydrochloric acid R*.

TESTS

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

Dissolve 0.5 g in 12.5 mL of *methanol R* and dilute to 25 mL with *water R*.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

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

Reference solution (b). Dissolve the contents of a vial of *deoxyminoxidil CRS* (impurity E) with 1 mL of the mobile phase, add 1 mL of the test solution and dilute to 5 mL with the mobile phase.

Column:

– *size*: *l* = 0.10 m, Ø = 3 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 3.0 g of *docusate sodium R* in a mixture of 10 mL of *glacial acetic acid R*, 300 mL of *water R* and 700 mL of *methanol R*, and adjust to pH 3.0 with *perchloric acid R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 240 nm.

Injection: 10 µL.

Run time: twice the retention time of the principal peak.

System suitability: reference solution (b):

– *resolution*: minimum 2.0 between the peaks due to minoxidil and impurity E.

Limits:

– *total*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.5 per cent);
– *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test C. Prepare the reference solution using 2 mL of *lead standard solution (10 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.

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

ASSAY

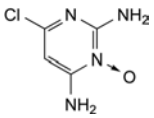
Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 mL of *0.1 M perchloric acid* is equivalent to 20.93 mg of $C_9H_{15}N_5O$.

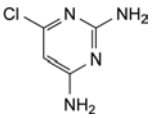
STORAGE

Protected from light.

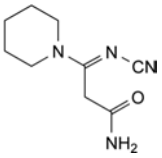
IMPURITIES



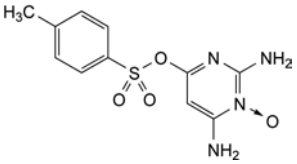
A. 6-chloropyrimidine-2,4-diamine 3-oxide,



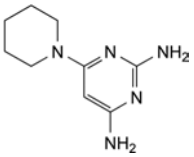
B. 6-chloropyrimidine-2,4-diamine,



C. 3-(cyanoimino)-3-(piperidin-1-yl)propanamide,



D. 6-[[(4-methylphenyl)sulfonyl]oxy]pyrimidine-2,4-diamine 3-oxide,



E. 6-(piperidin-1-yl)pyrimidine-2,4-diamine (desoxyminoxidil).

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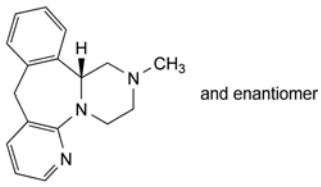
MIRTAZAPINE

Mirtazapinum



$C_{17}H_{19}N_3$ M_r 265.4
[61337-67-5]

DEFINITION

(14b*RS*)-2-Methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine.

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

CHARACTERS

Appearance: white or almost white powder, slightly hygroscopic to hygroscopic.

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

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *mirtazapine CRS*.

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