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

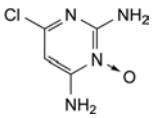
Dissolve 0.150 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

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

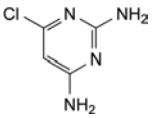
STORAGE

Protected from light.

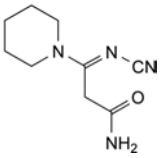
IMPURITIES



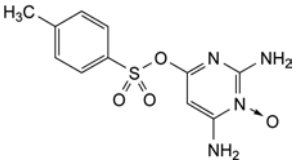
A. 6-chloropyrimidine-2,4-diamine 3-oxide,



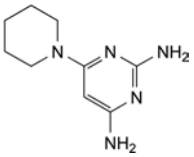
B. 6-chloropyrimidine-2,4-diamine,



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



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

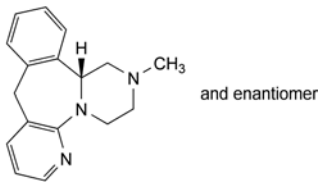


E. 6-(piperidin-1-yl)pyrimidine-2,4-diamine (desoxyminoxidil).

07/2009:2338

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.

TESTS

Optical rotation (*2.2.7*): – 0.10° to + 0.10° (anhydrous substance).

Dissolve 0.250 g in *anhydrous ethanol R* and dilute to 25.0 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile R, water R* (50:50 *V/V*).

Buffer solution. Dissolve 18.0 g of *tetramethylammonium hydroxide R* in 950 mL of *water R*. While stirring, adjust to pH 7.4 with *phosphoric acid R*, then dilute to 1000 mL with *water R* and mix.

Test solution. Dissolve 30 mg of the substance to be examined in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (a). Dissolve 3 mg of *mirtazapine for system suitability CRS* (containing impurities A, B, C, D, E and F) in 2 mL of the solvent mixture.

Reference solution (b). Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 40 °C.

Mobile phase: *tetrahydrofuran for chromatography R, methanol R, acetonitrile R,* buffer solution (7.5:12.5:15:65 *V/V/V/V*).

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 240 nm.

Injection: 10 µL.

Run time: twice the retention time of mirtazapine.

Identification of impurities: use the chromatogram supplied with *mirtazapine for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B, C, D, E and F.

Relative retention with reference to mirtazapine (retention time = about 25 min): impurity A = about 0.2; impurity B = about 0.3; impurity C = about 0.35; impurity D = about 0.4; impurity E = about 1.3; impurity F = about 1.35.

System suitability:

– *resolution*: minimum 1.5 between the peaks due to impurities E and F in the chromatogram obtained with reference solution (a);
– *symmetry factor*: 0.8 to 2.0 for the principal peak in the chromatogram obtained with reference solution (b).

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 1.3; impurity B = 1.3; impurity F = 0.2;
– *impurities A, B, C, D, E, F*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
– *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*): maximum 3.5 per cent, determined on 1.00 g.

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

ASSAY

Dissolve 0.100 g in 35 mL of *glacial acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

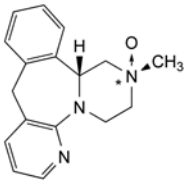
1 mL of *0.1 M perchloric acid* is equivalent to 13.27 mg of $C_{17}H_{19}N_3$.

STORAGE

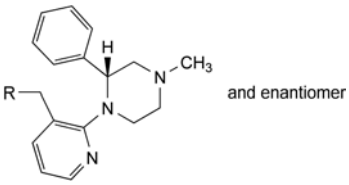
In an airtight container.

IMPURITIES

Specified impurities: A, B, C, D, E, F.

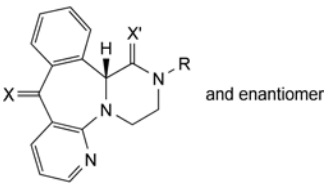


A. (14b*RS*)-2-methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine 2-oxide,



B. R = OH: [2-[(2*RS*)-4-methyl-2-phenylpiperazin-1-yl]pyridin-3-yl]methanol,

E. R = H: (2*RS*)-4-methyl-1-(3-methylpyridin-2-yl)-2-phenylpiperazine,



C. R = CH_3, X = H_2, X′ = O: (14b*RS*)-2-methyl-3,4,10,14b-tetrahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepin-1(2*H*)-one,

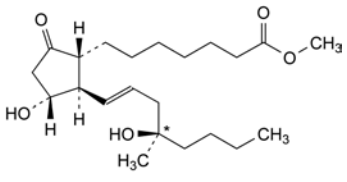
D. R = H, X = X′ = H_2: (14b*RS*)-1,2,3,4,10,14b-hexahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine,

F. R = CH_3, X = O, X′ = H_2: (14b*RS*)-2-methyl-1,3,4,14b-tetrahydropyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepin-10(2*H*)-one.

04/2010:1731

MISOPROSTOL

Misoprostolum



$C_{22}H_{38}O_5$ M_r 382.5

[59122-46-2]