Limit:

- *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (10 ppm).

Impurity B. Liquid chromatography (*2.2.29*).

Test solution. Dissolve a quantity of the substance to be examined equivalent to 0.100 g of the anhydrous substance in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution. Dissolve 0.100 g of *2-pyrrolidone R* in *water R* and dilute to 100.0 mL with the same solvent. Dilute 3.0 mL of this solution to 50.0 mL with *water R*.

Precolumn:

- *size*: *l* = 0.025 m, Ø = 3 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 μm).

Column:

- *size*: *l* = 0.25 m, Ø = 3 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 μm);
- *temperature*: 30 °C.

Mobile phase: *water R*, adjusted to pH 2.4 with *phosphoric acid R*.

Flow rate: adjusted so that the retention time of impurity B is about 11 min.

Detection: spectrophotometer at 205 nm.

Injection: 50 μL. After each injection of the test solution, wash away the polymeric material of povidone from the precolumn by passing the mobile phase through the column backwards for about 30 min at the same flow rate as applied in the test.

System suitability:

- *repeatability*: maximum relative standard deviation of 2.0 per cent after 6 injections of the reference solution.

Limit:

- *impurity B*: not more than the area of the principal peak in the chromatogram obtained with the reference solution (3.0 per cent).

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

2.0 g complies with test D. Prepare the reference solution using 2.0 mL of *lead standard solution (10 ppm Pb) R*.

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

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

ASSAY

Place 100.0 mg of the substance to be examined (*m* mg) in a combustion flask, add 5 g of a mixture of 1 g of *copper sulfate R*, 1 g of *titanium dioxide R* and 33 g of *dipotassium sulfate R*, and 3 glass beads. Wash any adhering particles from the neck into the flask with a small quantity of *water R*. Add 7 mL of *sulfuric acid R*, allowing it to run down the insides of the flask. Heat the flask gradually until the solution has a clear, yellowish-green colour, and the inside wall of the flask is free from a carbonised material, and then heat for a further 45 min. After cooling, add cautiously 20 mL of *water R*, and connect the flask to the distillation apparatus previously washed by passing steam through it. To the absorption flask add 30 mL of a 40 g/L solution of *boric acid R*, 3 drops of *bromocresol green-methyl red solution R* and sufficient water to immerse the lower end of the condenser tube. Add 30 mL of a solution of *strong sodium hydroxide solution R* through the funnel, rinse the funnel cautiously with 10 mL of *water R*, immediately close the clamp on the rubber tube, then start distillation with steam to obtain 80-100 mL of distillate. Remove the absorption flask from the lower end of the condenser tube, rinsing the end part with a small quantity of *water R*, and titrate the distillate with *0.025 M sulfuric acid* until the colour of the solution changes from green through pale greyish blue to pale greyish reddish-purple. Carry out a blank determination.

1 mL of *0.025 M sulfuric acid* is equivalent to 0.7004 mg of N.

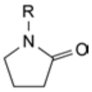
STORAGE

In an airtight container.

LABELLING

The label indicates the nominal *K*-value.

IMPURITIES



A. R = $CH=CH_2$: 1-ethenylpyrrolidin-2-one (1-vinylpyrrolidin-2-one),

B. R = H: pyrrolidin-2-one (2-pyrrolidone).

01/2008:1142
corrected 6.0

POVIDONE, IODINATED

Povidonum iodinatum

DEFINITION

Complex of iodine and povidone.

Content: 9.0 per cent to 12.0 per cent of available iodine (dried substance).

PRODUCTION

It is produced using povidone that complies with the monograph on *Povidone (0685)*, except that the povidone used may contain not more than 2.0 per cent of formic acid and not more than 8.0 per cent of water.

CHARACTERS

Appearance: yellowish-brown or reddish-brown, amorphous powder.

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

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *iodinated povidone CRS*.

B. Dissolve 10 mg in 10 mL of *water R* and add 1 mL of *starch solution R*. An intense blue colour is produced.

C. Dissolve 0.1 g in 5 mL of *water R* and add a 10 g/L solution of *sodium sulfite R* dropwise, until the solution becomes colourless. Add 2 mL of *potassium dichromate solution R* and 1 mL of *hydrochloric acid R*. A light brown precipitate is formed.

TESTS

pH (*2.2.3*): 1.5 to 5.0.

Dissolve 1.0 g in 10 mL of *carbon dioxide-free water R*.

Iodide: maximum 6.0 per cent (dried substance).

Dissolve 0.500 g in 100 mL of *water R*. Add *sodium metabisulfite R* until the colour of the iodine has disappeared. Add 25.0 mL of *0.1 M silver nitrate*, 10 mL of *nitric acid R* and 5 mL of *ferric ammonium sulfate solution R2*. Titrate with *0.1 M ammonium thiocyanate*. Carry out a blank titration.

1 mL of *0.1 M silver nitrate* is equivalent to 12.69 mg of total iodine. From the percentage of total iodine, calculated with reference to the dried substance, subtract the percentage of available iodine as determined in the assay to obtain the percentage of iodide.

Loss on drying (*2.2.32*): maximum 8.0 per cent, determined on 0.500 g by drying in an oven at 105 °C for 3 h.

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

ASSAY

Transfer 1.000 g into a ground-glass-stoppered flask containing 150 mL of *water R* and stir for 1 h. Add 0.1 mL of *dilute acetic acid R* and titrate with *0.1 M sodium thiosulfate* using *starch solution R* as indicator.

1 mL of *0.1 M sodium thiosulfate* is equivalent to 12.69 mg of available iodine.

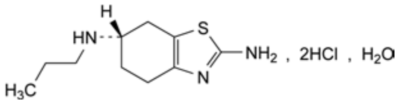
STORAGE

Protected from light.

07/2010:2416

PRAMIPEXOLE DIHYDROCHLORIDE MONOHYDRATE

Pramipexoli dihydrochloridum monohydricum



$C_{10}H_{19}Cl_2N_3S,H_2O$ M_r 302.3

[191217-81-9]

DEFINITION

(6*S*)-6-*N*-Propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine dihydrochloride monohydrate.

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

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: freely soluble in water, soluble in methanol, sparingly soluble to slightly soluble in ethanol (96 per cent) and practically insoluble in methylene chloride.

IDENTIFICATION

Carry out either tests B, C, D or tests A, B, D.

A. Specific optical rotation (*2.2.7*): – 67.0 to – 69.5 (anhydrous substance).

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

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *pramipexole dihydrochloride monohydrate CRS.*

C. Enantiomeric purity (see Tests).

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

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 0.1 g in *water R* and dilute to 10 mL with the same solvent.

pH (*2.2.3*): 2.8 to 3.4.

Dissolve 0.4 g in *carbon dioxide-free water R* and dilute to 20 mL with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Buffer solution. Dissolve 5 g of *sodium octanesulfonate monohydrate R* and 9.1 g of *potassium dihydrogen phosphate R* in 900 mL of *water R*. Adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with *water R.*

Solvent mixture: *acetonitrile R,* buffer solution (200:800 *V/V*).

Test solution. Dissolve 75 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a). 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.

Reference solution (b). Dissolve 7.5 mg of *pramipexole for system suitability CRS* (containing impurities A, B and C) in 5.0 mL of the solvent mixture.

Column:

- *size*: *l* = 0.125 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 μm);
- *temperature*: 40 °C.

Mobile phase:

- *mobile phase A*: buffer solution;
- *mobile phase B*: *acetonitrile R,* buffer solution (500:500 *V/V*);

Time (min)	**Mobile phase A (per cent *V/V*)**	**Mobile phase B (per cent *V/V*)**
0 - 15	60 → 20	40 → 80

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 264 nm.

Injection: 5 μL.

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

Relative retention with reference to pramipexole (retention time = about 6 min): impurity A = about 0.7; impurity B = about 1.5; impurity C = about 1.7.

System suitability: reference solution (b):

- *resolution*: minimum 6.0 between the peaks due to impurity A and pramipexole.

Limits:

- *impurities A, B, C*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: 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).

Enantiomeric purity. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 6 mg of the substance to be examined in 5 mL of *anhydrous ethanol R* and dilute to 20.0 mL with the mobile phase.

Reference solution (a). Dissolve 2 mg of *pramipexole impurity D CRS* in the mobile phase and dilute to 10 mL with the mobile phase. To 1 mL of this solution add 1 mL of the test solution and dilute to 20 mL with the mobile phase.

Reference solution (b). Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *silica gel OD for chiral separations R.*

Mobile phase: *diethylamine R, anhydrous ethanol R, hexane R* (1:150:850 *V/V/V*).

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 75 μL.

Run time: 1.5 times the retention time of pramipexole.