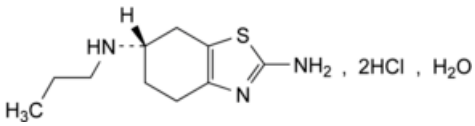
Edition: BP 2025 (Ph. Eur. 11.6 update)

Pramipexole Dihydrochloride Monohydrate

General Notices

(Ph. Eur. monograph 2416)



$C_{10}H_{19}Cl_2N_3S,H_2O$ 302.3 *191217-81-9*

Action and use

Dopamine receptor agonist; treatment of Parkinson's disease.

Preparations

Pramipexole Tablets

Pramipexole Prolonged-release Tablets

Ph Eur

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 or slightly soluble in ethanol (96 per cent), 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): -69.5 to -67.0 (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 for chromatography R*. Adjust to pH 3.0 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Solvent mixture *acetonitrile R*, buffer solution (20:80 *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 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 (50:50 *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 2.5 mL of *anhydrous ethanol R* 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*: *amylose derivative of silica gel for chiral separation R*.

Mobile phase *diethylamine R*, *anhydrous ethanol R*, *hexane R* (0.1:15:85 *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.

Relative retention With reference to pramipexole (retention time = about 11 min): impurity D = about 0.5.

System suitability:

— *resolution*: minimum 5.0 between the peaks due to impurity D and pramipexole in the chromatogram obtained with reference solution (a);

— *symmetry factor*: maximum 2.4 for the peak due to pramipexole in the chromatogram obtained with reference solution (b).

Limit:

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent).

Water (*2.5.12*)

5.0 per cent to 7.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

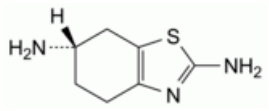
Dissolve 0.120 g in 150 mL of *water R*. Add 10 mL of *dilute nitric acid R2* and titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 14.213 mg of $C_{10}H_{19}Cl_2N_3S$.

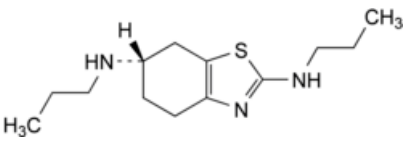
IMPURITIES

Specified impurities *A, B, C, D.*

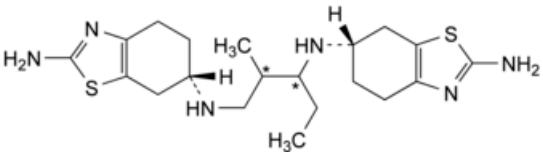
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



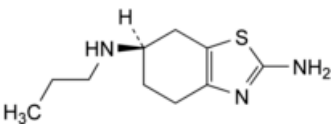
A. (6*S*)-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine,



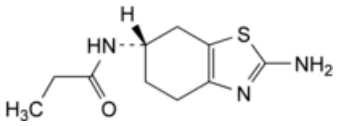
B. (6*S*)-*N*,*N*′-dipropyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine,



C. mixture of diastereoisomers of (6*S*)-6-*N*-[3-[[(6*S*)-2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl]amino]-1-ethyl-2-methylpropyl]-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine,



D. (6*R*)-6-*N*-propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine,



E. *N*-[(6*S*)-2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl]propanamide.

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