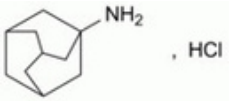
Edition: BP 2025 (Ph. Eur. 11.6 update)

Amantadine Hydrochloride

General Notices

(Ph. Eur. monograph 0463)



C10H18ClN 187.7 *665-66-7*

Action and use

Viral replication inhibitor (influenza A); dopamine receptor agonist; treatment of influenza and Parkinson's disease.

Preparations

Amantadine Capsules

Amantadine Oral Solution

Ph Eur

DEFINITION

Tricyclo[3.3.1.1^{3,7}]decan-1-amine hydrochloride.

Content

98.5 per cent to 101.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water and in ethanol (96 per cent).

It sublimes on heating.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infraredabsorptionspectrophotometry (2.2.24).

Comparison amantadine hydrochloride CRS.

B. To 0.1 g add 1 mL of *pyridine R*, mix and add 0.1 mL of *acetic anhydride R*. Heat to boiling for about 10 s. Pour the hot solution into 10 mL of *dilute hydrochloric acid R*, cool to 5 °C and filter. The precipitate, washed with *water R* and dried *in vacuo* at 60 °C for 1 h, melts (*2.2.14*) at 147 °C to 151 °C.
C. Dissolve 0.2 g in 1 mL of *0.1 M hydrochloric acid*. Add 1 mL of a 500 g/L solution of *sodium nitrite R*. A white precipitate is formed.
D. 1 mL of solution S (see Tests) gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S

Dissolve 2.5 g in *carbon dioxide-free water R* and dilute to 25 mL with the same solvent.

Appearance of solution

Solution S is clear(*2.2.1*)and not more intensely coloured than reference solution Y(7 *2.2.2, Method II*).

Acidity or alkalinity

Dilute 2 mL of solution S to 10 mL with *carbon dioxide-free water R*. Add 0.1 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solutionisyellow.Add0.4mLof *0.01 M hydrochloric acid*. The solution is red.

Related substances

Gas chromatography (*2.2.28*).

Internal standard solution Dissolve 0.500 g of *adamantane R* in *methylene chloride R* and dilute to 10.0 mL with the same solvent.
Test solution Weigh0.5gofthesubstancetobeexaminedintoacentrifugetube. Add 9 mL of *methylene chloride R* and 10mLofa210g/Lsolutionof *sodium hydroxide R*.Shakefor10min.Discardthe upper layer. Dry the lower layer over *anhydrous sodium sulfate R*.Filterandcollectthefiltrateinavolumetricflask.Add 0.1 mL of the internal standard solution anddilute to 10.0 mLwith *methylene chloride R*.

Reference solution Weigh5mgof *amantadine hydrochloride CRS* intoacentrifuge tube. Add 9 mL of *methylene chloride R* and10mLofa210g/Lsolutionof *sodium hydroxide R*.Shakefor10 min. Discard the upper layer. Dry the lowerlayerover *anhydrous sodium sulfate R*.Filterandcollectthefiltrateinavolumetric flask. Add 1.0 mL of the internal standard solution and dilute to 100.0 mLwith*methylene chloride R*.

Column:

— *material*: fused silica;

— *size*:*l*=30 m, Ø =0.53 mm;

— *stationary phase*:*base-deactivated phenyl(5)methyl(95)polysiloxane R* (film thickness 1 µm).

Carrier gas helium for chromatography R

Flow rate 4 mL/min.

Split ratio 1:50.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	70
	5 - 23	70 → 250
	23 - 40	250
Injection port		220
Detector		300

Detection Flame ionisation.

Injection 1 µL.

Relative retention With reference to amantadine (retention time = about 14 min): internal standard = about 0.8.

System suitability Reference solution:

— *resolution*: minimum 5.0 between the peaks due to the internal standard and amantadine.

Limits:

— *unspecified impurities*: calculate the ratio (*R*1) of the area of the peak due to amantadine to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with the test solution, calculate the ratio of the area of any peak, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than *R*1 (0.10 per cent);

— *total*: calculate the ratio (*R*2) of 3 times the area of the peak due to amantadine to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with the test solution, calculate the ratio of the sum of the areas of any peaks, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: this ratio is not greater than *R*2 (0.3 per cent);

— *disregard limit*: calculate the ratio (*R*3) of 0.5 times the area of the peak due to amantadine to the area of the peak due to the internal standard from the chromatogram obtained with the reference solution; from the chromatogram obtained with the test solution, calculate the ratio of the area of any peak, apart from the principal peak and the peak due to the internal standard, to the area of the peak due to the internal standard: disregard any peak with a ratio less than *R*3 (0.05 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 2.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

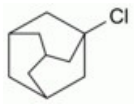
Dissolve 0.150 g in a mixture of 5.0 mL of *0.01 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 18.77 mg of C10H18ClN.

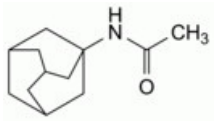
IMPURITIES

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) A, B.



A. 1-chlorotricyclo[3.3.1.1^{3,7}]decane,



B. *N*-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)acetamide.
