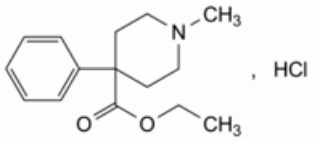
Edition: BP 2025 (Ph. Eur. 11.6 update)

Pethidine Hydrochloride

General Notices

(Ph. Eur. monograph 0420)



$C_{15}H_{22}ClNO_2$ 283.8 *50-13-5*

Action and use

Opioid receptor agonist; analgesic.

Preparations

Pethidine Injection

Pethidine Tablets

Ph Eur

DEFINITION

Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride.

Content

99.0 per cent to 101.0 per cent (dried substance).

PRODUCTION

If intended for use in the manufacture of parenteral preparations, the manufacturing process is validated to show that the content of impurity B is not more than 0.1 ppm.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Very soluble in water, freely soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: B, D.

Second identification: A, C, D.

A. Melting point (2.2.14): 187 °C to 190 °C.
B. Infrared absorption spectrophotometry (2.2.24).

Comparison *Ph. Eur. reference spectrum of pethidine hydrochloride*.

C. Dissolve 0.1 g in 10 mL of *ethanol R* and add 10 mL of *picric acid solution R*. A crystalline precipitate is formed which, when washed with *water R* and dried at 100-105 °C, melts (2.2.14) at 186 °C to 193 °C. Mix equal quantities of the precipitate and the substance to be examined and determine the melting point of the mixture. The melting point is at least 20 °C lower than that of the precipitate.
D. To 5 mL of solution S (see Tests) add 5 mL of *water R*. The solution gives reaction (a) of chlorides (2.3.1).

TESTS

Solution S

Dissolve 0.5 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 colourless (2.2.2, *Method II*).

Acidity or alkalinity

To 10 mL of solution S add 0.2 mL of *methyl red solution R* and 0.2 mL of *0.01 M sodium hydroxide*. The solution is yellow. Add 0.3 mL of *0.01 M hydrochloric acid*. The solution is red.

Impurity B

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 0.100 g of the substance to be examined in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 25.0 mL with the same mixture of solvents.

Test solution (b) Dissolve 0.125 g of the substance to be examined in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 10.0 mL with the same mixture of solvents.

Reference solution (a) Dilute 0.5 mL of test solution (a) to 100.0 mL with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Reference solution (b) Dissolve 10.0 mg of *pethidine impurity A CRS* in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 100.0 mL with the same mixture of solvents.

Reference solution (c) Dissolve 12.5 mg of *1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine R* in a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R* and dilute to 10.0 mL with the same mixture of solvents. Dilute 1.0 mL of the solution to 100.0 mL with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Reference solution (d) Dilute 5.0 mL of reference solution (b) and 1.0 mL of reference solution (c) to 100.0 mL with a mixture of 20 volumes of *acetonitrile R* and 80 volumes of *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.0 mm,

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm) with a specific surface area of 340 m^2/g, a pore size of 10 nm and a carbon loading of 19 per cent.

Mobile phase:

— *mobile phase A*: mix equal volumes of a 42.0 g/L solution of *sodium perchlorate R* and of a 11.6 g/L solution of *phosphoric acid R*, adjust to pH 2.0 with *triethylamine R*,

— *mobile phase B*: *acetonitrile R*,

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	80 → 75	20 → 25
15 - 31	75 → 55	25 → 45
31 - 40	55	45

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 50 µL; inject test solution (b) and reference solution (d).

Relative retention With reference to pethidine (retention time = about 24 min): impurity B = about 0.66; impurity A = about 0.68.

System suitability Reference solution (d):

— *signal-to-noise ratio*: minimum 10 for the first peak,

— *peak-to-valley ratio*: minimum 4, where H_p = height above the baseline of the peak due to impurity B, and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.

Limit:

— *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (d) (10 ppm) if intended for non-parenteral administration.

Related substances

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

Injection 20 µL; inject test solution (a) and reference solution (a).

Limits:

— *any impurity*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent),

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent),

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

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 0.220 g in 50 mL of *alcohol R*. Add 5.0 mL of *0.01 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide* determining the end-point potentiometrically (*2.2.20*). Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 28.38 mg of $C_{15}H_{22}ClNO_2$.

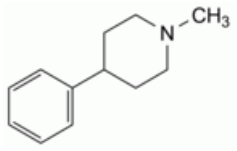
STORAGE

In an airtight container, protected from light.

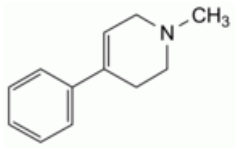
LABELLING

The label states, where applicable, that the substance is suitable for use in the manufacture of parenteral preparations.

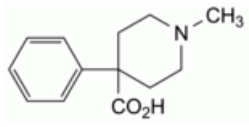
IMPURITIES



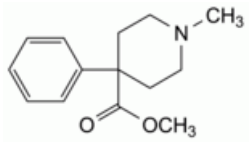
A. 1-methyl-4-phenylpiperidine (MPP),



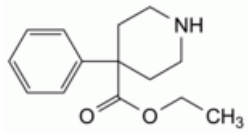
B. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP),



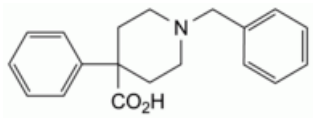
C. 1-methyl-4-phenylpiperidine-4-carboxylic acid,



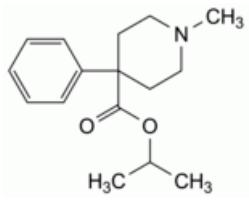
D. methyl 1-methyl-4-phenylpiperidine-4-carboxylate,



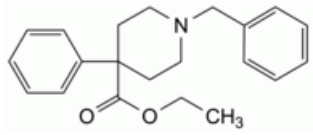
E. ethyl 4-phenylpiperidine-4-carboxylate,



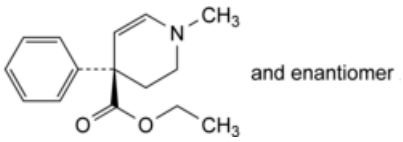
F. 1-benzyl-4-phenylpiperidine-4-carboxylic acid,



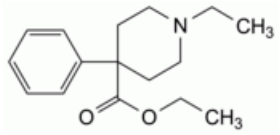
G. 1-methylethyl 1-methyl-4-phenylpiperidine-4-carboxylate,



H. ethyl 1-benzyl-4-phenylpiperidine-4-carboxylate,



I. ethyl (4*RS*)-1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine-4-carboxylate,



J. ethyl 1-ethyl-4-phenylpiperidine-4-carboxylate.

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