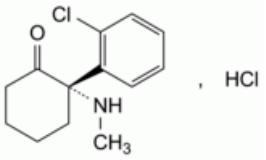
Edition: BP 2025 (Ph. Eur. 11.6 update)

Esketamine Hydrochloride

General Notices

(Ph. Eur. monograph 1742)



$C_{13}H_{17}Cl_2NO$ 274.2 *33643-47-9*

Action and use

General anaesthetic.

Ph Eur

DEFINITION

(2*S*)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride.

Content

99.0 per cent to 101.0 per cent.

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

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

IDENTIFICATION

A. Specific optical rotation (2.2.7): + 85.0 to + 95.0.
Dilute 12.5 mL of solution S (see Tests) to 40.0 mL with *water R*.

B. Infrared absorption spectrophotometry (2.2.24).

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

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

TESTS

Solution S

Dissolve 8.0 g in *carbon dioxide-free water R* and dilute to 50.0 mL with the same solvent.

Appearance of solution

Solution S is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

pH (*2.2.3*)

3.5 to 4.5.

Dilute 12.5 mL of solution S to 20 mL with *carbon dioxide-free water R*.

Impurity D

Liquid chromatography (*2.2.29*).

Test solution Dissolve 25.0 mg of the substance to be examined in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (a) Dissolve 5 mg of *esketamine impurity D CRS* in *water R*, add 20 mL of the test solution and dilute to 50 mL with *water R*. Dilute 10 mL of this solution to 100 mL with *water R*.

Reference solution (b) Dilute 5.0 mL of the test solution to 25.0 mL with *water R*. Dilute 5.0 mL of this solution to 50.0 mL with *water R*.

Reference solution (c) Dilute 2.5 mL of reference solution (b) to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

Precolumn:

— *size*: *l* = 0.01 m, Ø = 3.0 mm;

— *stationary phase*: *silica gel AGP for chiral chromatography R* (5 µm);

— *temperature*: 30 °C.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *silica gel AGP for chiral chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase Mix 16 volumes of *methanol R* and 84 volumes of a 6.8 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 7.0 with *potassium hydroxide R*.

Flow rate 0.8 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 20 min.

Relative retention With reference to esketamine (retention time = about 10 min): impurity D = about 1.3.

System suitability:

— *resolution*: minimum 2.0 between the peaks due to esketamine and impurity D in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 3 for the principal peak in the chromatogram obtained with reference solution (c).

Limit:

— *impurity D*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent).

Related substances

Liquid chromatography (*2.2.29*).

Test solution Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a) Dissolve 5 mg of *ketamine impurity A CRS* in the mobile phase (using ultrasound, if necessary) and dilute to 10 mL with the mobile phase. To 1 mL of the solution add 0.5 mL of the test solution and dilute to 100 mL with the mobile phase. Prepare immediately before use.

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

Column:

— *size*: *l* = 0.125 m, Ø = 4.0 mm;

— *stationary phase*: spherical *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Dissolve 0.95 g of *sodium hexanesulfonate R* in 1000 mL of a mixture of 25 volumes of *acetonitrile R* and 75 volumes of *water R* and add 4 mL of *acetic acid R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 215 nm.

Injection 20 µL.

Run time 10 times the retention time of esketamine.

Relative retention With reference to esketamine: impurity A = about 1.6; impurity B = about 3.3; impurity C = about 4.6.

System suitability Reference solution (a):

— *retention time*: esketamine = 3.0 min to 4.5 min;

— *resolution*: minimum 1.5 between the peaks due to impurity A and esketamine.

Limits:

— *impurities A, B, C*: for each impurity, not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

— *any other impurity*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent);

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

— *disregard limit*: 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.200 g in 50 mL of *methanol R* and add 1.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

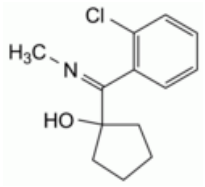
1 mL of *0.1 M sodium hydroxide* is equivalent to 27.42 mg of $C_{13}H_{17}Cl_2NO$.

STORAGE

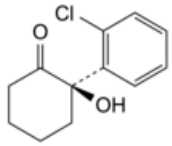
Protected from light.

IMPURITIES

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

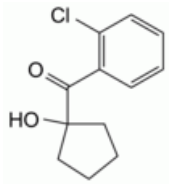


A. 1-[(2-chlorophenyl)(methylimino)methyl]cyclopentanol,

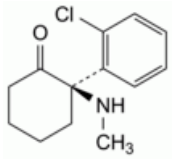


and enantiomer

B. (2*RS*)-2-(2-chlorophenyl)-2-hydroxycyclohexanone,



C. (2-chlorophenyl)(1-hydroxycyclopentyl)methanone,



D. (2*R*)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone ((*R*)-ketamine).

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