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Ketamine Oral Solution

General Notices

NOTE: This monograph has been developed to cover unlicensed formulations.

Action and use

Treatment of chronic pain.

DEFINITION

Ketamine Oral Solution is a solution containing Ketamine Hydrochloride in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements. Where appropriate, the oral solution also complies with the requirements stated under Unlicensed Medicines.

Content of ketamine, $C_{13}H_{16}ClNO$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dilute a quantity of the oral solution with a mixture of 1 volume of 1M *sodium hydroxide* and 49 volumes of *methanol* to produce a solution containing the equivalent of 0.1% w/v of ketamine. The *light absorption*, Appendix II B, in the range 230 to 350 nm of this solution exhibits a maximum at 301 nm and shoulders at 274, 268 and 261 nm.
B. Dilute a quantity of the oral solution with 0.1M *hydrochloric acid* to produce a solution containing the equivalent of 0.025% w/v of ketamine. The *light absorption*, Appendix II B, in the range 230 to 350 nm of this solution exhibits two maxima at 276 nm and at 269 nm and a shoulder at 260 nm.
C. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Dilute a quantity of the oral solution to contain the equivalent of 0.1% w/v of ketamine.
(2) Dilute 1 volume of solution (1) to 200 volumes.
(3) Dilute 1 volume of solution (2) to 2 volumes.
(4) Add 2 volumes of a 0.05% w/v solution of *ketamine impurity A EPCRS* in *methanol* to 1 volume of solution (1) and dilute the resulting solution to 100 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 10 times the retention time of ketamine.

When the chromatograms are recorded under the prescribed conditions, the retention time of ketamine is about 5 to 6 minutes and the relative retention of the peak due to impurity A is about 1.6.

MOBILE PHASE

25 volumes of *acetonitrile R1* and 75 volumes of a 0.1% w/v solution of *sodium hexanesulfonate* containing 0.05% w/v of *glacial acetic acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to ketamine and ketamine impurity A is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

not more than one such peak has an area greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.25%);

the sum of the areas of all the *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than 0.4 times the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in *water*.

(1) Dilute the oral solution to contain the equivalent of 0.005% w/v of ketamine.
(2) 0.005% w/v of *ketamine hydrochloride BPCRS*.
(3) Mix equal volumes of a 0.0025% w/v solution of *ketamine hydrochloride BPCRS* in *water* and a 0.0025% w/v solution of *ketamine impurity A EPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Kromasil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

35 volumes of *methanol* and 65 volumes of a 0.575% w/v solution of *ammonium dihydrogen orthophosphate* adjusted to pH 3.0 using *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to ketamine and ketamine impurity A is at least 2.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{13}H_{16}ClNO$ in the oral solution using the declared content of $C_{13}H_{16}ClNO$ in *ketamine hydrochloride BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A listed under Ketamine Hydrochloride.

STORAGE

Ketamine Oral Solution should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of ketamine.