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Memantine Oral Solution

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 2
Contact Details	helen.corns@mhra.gov.uk rachael.feltham@mhra.gov.uk sophie.cherrington@mhra.gov.uk bpcom@mhra.gov.uk
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Notes	New monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Cholinesterase inhibitor; treatment of Alzheimer's disease.

DEFINITION

Memantine Oral Solution is a solution of [Memantine Hydrochloride](#) in a suitable vehicle.

The oral solution complies with the requirements stated under [Oral Liquids](#) and with the following requirements.

Content of memantine hydrochloride, $C_{12}H_{21}N, HCl$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Mix with the aid of ultrasound a quantity of the oral solution containing 75 mg of Memantine Hydrochloride with 25 mL of [water](#). Add 1 mL of [ammonia](#) and 5 mL of [dichloromethane](#), mix and allow the layers to separate. Filter (a cellulose filter is suitable) a portion of the lower organic layer through [anhydrous sodium sulfate](#) and evaporate the filtrate to dryness at 40° under [nitrogen](#). The [infrared absorption spectrum](#) of the oily residue, [Appendix II A](#), is concordant with the *reference spectrum* of memantine (RS XXX).

TESTS

Related substances

Carry out the method for [gas chromatography, Appendix III B](#), using the following solutions prepared immediately before use.

- (1) Mix with the aid of ultrasound a quantity of the oral solution containing 0.15 g of Memantine Hydrochloride with 50 mL of [water](#). Add 2 mL of [ammonia](#) and 10 mL of [dichloromethane](#), mix and allow the layers to separate. Filter (a 0.2-µm hydrophilic polypropylene filter is suitable) a portion of the lower organic layer through [anhydrous sodium sulfate](#) and use the solution.
- (2) Dilute 1 volume of solution (1) to 100 volumes with [dichloromethane](#). Further dilute 1 volume to 5 volumes with the same solvent.
- (3) 0.23% w/v of [memantine impurity standard BPCRS](#) in [water](#), mix with the aid of ultrasound, if necessary, to aid dissolution. To 13 volumes, add 0.4 volumes of [ammonia](#) and 2 volumes of [dichloromethane](#), mix and allow the layers to separate. Filter (a 0.2-µm hydrophilic polypropylene filter is suitable) a portion of the lower organic layer through [anhydrous sodium sulfate](#) and use the filtrate.

CHROMATOGRAPHIC CONDITIONS

- (a) Use a fused silica capillary column (60 m × 0.32 mm) bonded with a 0.25-µm layer of *phenyl(35)methyl(65)polysiloxane* (Rtx-35 is suitable).
- (b) Use [helium](#) as the carrier gas at 2.2 mL per minute.
- (c) Use the gradient conditions described below.
- (d) Use an inlet temperature of 290°.
- (e) Use a flame ionisation detector at a temperature of 290°.
- (f) Inject 1 µL of each solution
- (g) Use a split ratio of 1:10.

Time (Minutes)	Temperature	Comment
0-6	150°	isothermal
6-20	150°→290°	linear gradient
20-30	290°	isothermal

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the [resolution](#) between the peaks due to memantine and impurity 1 is at least 1.5.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of memantine hydrochloride in solution (2).

For the reporting threshold, use the concentration of memantine hydrochloride in solution (2).

For peak identification, use solution (3).

Memantine retention time: about 7 minutes.

Relative retentions: impurity 1, about 1.10; impurity C, about 1.13; and impurity G, about 2.3.

LIMITS

- impurity G: not more than 0.5%;
- unspecified impurities: for each impurity, not more than 0.2%;
- total impurities: not more than 1.0%;
- reporting threshold: 0.1%.

ASSAY

Carry out the method for [liquid chromatography, Appendix III D](#), using the following solutions.

Solution A 3.1% w/v of [boric acid](#), 3.75% w/v of [potassium chloride](#) and 0.15% w/v of [sodium hydroxide](#) in [water](#). Adjust the mixture to pH 8.5 with 5M [sodium hydroxide](#).

Solution B Dilute 1 volume of solution A to 10 volumes with [water](#), then mix equal volumes of the resulting solution and [acetonitrile](#).

- (1) Mix with the aid of ultrasound a weighed amount of the oral solution containing 50 mg of Memantine Hydrochloride with 25 mL of solution B and allow to cool. Dilute to produce 50 mL with the same solvent.
- (2) Mix with the aid of ultrasound 20 mg of [memantine hydrochloride BPCRS](#) with 10 mL of solution B and allow to cool. Dilute to produce 20 mL with the same solvent.
- (3) Solution B (blank).

Derivatise solutions (1) and (2) immediately prior to analysis using the following method.

Transfer 5 mL of each solution separately into 50-mL volumetric flasks. To each solution add 4 mL of solution A and shake for 3 minutes. Add 4 mL of a 0.39% w/v solution of 9-fluorenylmethyl chloroformate in [acetonitrile](#) and shake for 30 seconds. Allow to stand at room temperature for 30 minutes, then dilute to 50 mL with solution B and filter through a 0.45-µm nylon filter.

CHROMATOGRAPHIC CONDITIONS

- (a) Use a stainless steel column (15 cm × 4.6 mm) packed with [end-capped extra-dense bonded octadecylsilyl silica gel for chromatography](#) (5 µm) (Zorbax Eclipse XDB-C18 is suitable).
- (b) Use isocratic elution and the mobile phase described below.
- (c) Use a flow rate of 2.0 mL per minute.
- (d) Use a column temperature of 30°.
- (e) Use a detection wavelength of 265 nm.
- (f) Inject 10 µL of each solution.

MOBILE PHASE

1 volume of solution C and 4 volumes of [acetonitrile](#).

Solution C 0.2875% w/v of [potassium dihydrogen orthophosphate](#) in [water](#) containing 0.05% v/v of *orthophosphoric acid (85%)* and 0.06% v/v of [hexylamine](#).

When the chromatograms are recorded under the prescribed conditions, the retention time of memantine is about 8 minutes.

DETERMINATION OF CONTENT

Determine the [weight per mL](#) of the oral solution, [Appendix V G](#), and calculate the content of $C_{12}H_{21}N, HCl$, weight in volume, using the declared content of $C_{12}H_{21}N, HCl$ in [memantine hydrochloride BPCRS](#).

IMPURITIES

The impurities limited by the requirements of this monograph include C and G listed under [Memantine Hydrochloride](#) and:

1. 3,5-dimethyladamantane-1-ol.