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

Rivastigmine Oral Solution

General Notices

Action and use

Cholinesterase inhibitor; treatment of dementia in Alzheimer's disease and Parkinson's disease.

DEFINITION

Rivastigmine Oral Solution contains Rivastigmine Hydrogen Tartrate in a suitable vehicle.

The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of rivastigmine, $C_{14}H_{22}N_2O_2$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Shake a volume of the oral solution containing the equivalent of 18 mg of rivastigmine with 25 mL of *methanol*. Add sufficient *methanol* to produce 50 mL and filter (a 0.45-µm Nylon filter is suitable).
(2) 0.058% w/v of *rivastigmine hydrogen tartrate BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

2 volumes of *formic acid*, 5 volumes of *water*, 30 volumes of *methanol* and 70 volumes of *dichloromethane*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the 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 prepared in the mobile phase. Prepare the solutions immediately before use and protect from light.

(1) Shake a volume of the oral solution containing the equivalent of 25 mg of rivastigmine with 15 mL and add sufficient mobile phase to produce 50 mL.
(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of the resulting solution to 5 volumes.
(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped polar-embedded octadecylsilyl amorphous organosilica polymer for chromatography* (5 µm) (XTerra RP 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 217 nm.
(f) Inject 10 µL of each solution.
(g) Allow the chromatography to proceed for 3.5 times the retention time of rivastigmine.

MOBILE PHASE

28 volumes of *acetonitrile R1* and 72 volumes of 0.01M *sodium heptanesulfonate*, adjusted to pH 3.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to rivastigmine (retention time about 7 minutes) are: impurity A, about 0.5; impurity B, about 0.7 and impurity C, about 2.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 7.0.

LIMITS

Identify any peak corresponding to impurity C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of all the *secondary peaks* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in the mobile phase and protected from light.

(1) Shake a weighed quantity of the oral solution containing the equivalent of 10 mg of rivastigmine with 50 mL of mobile phase. Add sufficient mobile phase to produce 100 mL.
(2) 0.016% w/v of *rivastigmine hydrogen tartrate BPCRS*.
(3) 0.1% w/v of *rivastigmine for system suitability EPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and impurity B is at least 7.0.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{14}H_{22}N_2O_2$, weight in volume, using the declared content of $C_{18}H_{28}N_2O_8$ in *rivastigmine hydrogen tartrate BPCRS*. Each mg of $C_{18}H_{28}N_2O_8$ is equivalent to 0.6251 mg of $C_{14}H_{22}N_2O_2$

STORAGE

Rivastigmine Oral Solution should be protected from light. It should not be refrigerated or allowed to freeze.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, B and C listed under Rivastigmine Hydrogen Tartrate.