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

Rivastigmine Transdermal Patches

General Notices

Action and use

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

DEFINITION

Rivastigmine Transdermal Patches contain Rivastigmine.

The transdermal patches comply with the requirements stated under Patches and with the following requirements.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of rivastigmine.

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

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Remove the release liner from an amount of patches containing 18 mg of Rivastigmine and dissolve the contents in 50 mL of *methanol*. Mix with the aid of ultrasound for 60 minutes, allow to cool and centrifuge at 3000 rpm for 10 minutes.
(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 and protected from light.

(1) Remove the release liners from the patches. Mix with the aid of ultrasound a quantity of whole patches with sufficient *tetrahydrofuran* to produce a solution containing 0.1% w/v of Rivastigmine, for about 60 minutes. Allow to cool, dilute 1 volume of the solution to 5 volumes and filter (a 0.45-µm PTFE filter is suitable).
(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%).

Uniformity of content

Comply with the requirements stated under uniformity of content, Appendix XII C3, Test C, with respect to the individual content of each dosage unit and using the following method of analysis.

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

(1) Remove the release liner from one patch and dissolve the contents in sufficient *tetrahydrofuran* to produce a solution containing 0.1% w/v of Rivastigmine. Mix with the aid of ultrasound for 60 minutes. Allow to cool, dilute 1 volume to 10 volumes and filter (a 0.45-µm PTFE filter is suitable).
(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

Calculate the content of rivastigmine, $C_{14}H_{22}N_2O_2$, in each patch from the chromatograms obtained and 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 $C_{14}H_{22}N_2O_2$.

ASSAY

Use the average of the individual results obtained in the test for Uniformity of content.

IMPURITIES

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