Rivastigmine Transdermal Patches

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

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<tr>
<th>EAG/Panel/Working Party</th>
<th>Medicinal Chemicals 2</th>
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<tbody>
<tr>
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<td>Deadline for Comment</td>
<td>30 September 2020</td>
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<td>Target Publication Date (subject to change)</td>
<td>BP 2022</td>
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<td>Notes</td>
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<td>If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.</td>
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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 Transdermal Patches and with the following requirements.

Content of Rivastigmine, C₁₄H₂₂N₂O₂

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 prepared in methanol.

(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.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel F254 (Merck silica gel 60 F254 plates are suitable).

(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 16 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 peak corresponding to rivastigmine in the chromatogram obtained with solution (1) is similar to that obtained with solution (2).

TESTS

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions prepared in mobile phase. Prepare the solutions immediately before use and protect 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 Rivastigmine. Mix with the aid of ultrasound for 60 minutes. Allow the solution to cool to room temperature, dilute 1 volume to 5 volumes and filter (0.45 µm PTFE filter is suitable).
(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 2 volume of this solution to 10 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 octadecylsilyl silica gel 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 and 72 volumes of 10 mM sodium-1-heptane sulfonate, adjusted to pH 3.0 with orthophosphoric acid.

When the chromatograms are recorded under the prescribed conditions, the relative retention(s) 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 peak 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 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 peak corresponding to impurity B is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15%);

the area of any 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 any secondary peaks is not greater than 2.5 times 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 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, 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 Rivastigmine. Mix with the aid of ultrasound for 60 minutes. Allow the solution to cool to room temperature, dilute 1 volume to 10 volumes and filter (0.45 µm PTFE filter is suitable).

2. 0.016% w/v of rivastigmine hydrogen tartrate BPCRS.

**CHROMATOGRAPHIC CONDITIONS**

The chromatographic conditions described under Related substances may be used.

**DETERMINATION OF CONTENT**

Calculate the content of rivastigmine, C_{14}H_{22}N_{2}O_{2}, in the transdermal patch from the chromatograms obtained and using the declared content of C_{18}H_{28}N_{2}O_{8}, in rivastigmine hydrogen tartrate BPCRS. Each mg of C_{18}H_{28}N_{2}O_{8} is equivalent to 0.6251 mg of C_{14}H_{22}N_{2}O_{2}.

**ASSAY**

Use the average of the individual results determined in the test for Uniformity of content.
**IMPURITIES**

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