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

Warfarin Oral Suspension

General Notices

Action and use

Vitamin K epoxide reductase inhibitor; oral anticoagulant (coumarin).

DEFINITION

Warfarin Oral Suspension is a suspension of Warfarin Sodium in a suitable flavoured vehicle.

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

Content of warfarin sodium, $C_{19}H_{15}NaO_4$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

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

Acidity

pH, 2.7 to 4.0, Appendix V L.

Related substances

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

(1) To a quantity of the oral suspension containing 10 mg of Warfarin Sodium add 30 mL of *acetonitrile* and mix; add 50 mL of *water*, mix with the aid of ultrasound for 10 minutes and allow the solution to cool to room temperature. Add sufficient *water* to produce 100 mL, mix and filter through a 0.45-µm cellulose acetate filter (GD/X is suitable).
(2) Dissolve 10 mg of *4-hydroxycoumarin* (warfarin impurity B) in 50 mL of *acetonitrile* and add sufficient *water* to produce 100 mL. Dilute 1 volume of this solution to 10 volumes with a mixture containing 30 volumes of *acetonitrile* and 70 volumes of *water* and further dilute 1 volume to 10 volumes with the same mixture of solvents.
(3) Dissolve 10 mg of *benzalacetone* (warfarin impurity C) in 50 mL of *acetonitrile* and add sufficient *water* to produce 100 mL. Dilute 1 volume of this solution to 10 volumes with a mixture containing 30 volumes of *acetonitrile* and 70 volumes of *water* and further dilute 1 volume to 10 volumes with the same mixture of solvents.
(4) Dissolve 10 mg of *(5RS)-3-(2-hydroxyphenyl)-5-phenylcyclohex-2-enone BPCRS* (warfarin impurity A) in 50 mL of *acetonitrile* and add sufficient *water* to produce 100 mL. Dilute 1 volume of this solution to 10 volumes with a mixture containing 30 volumes of *acetonitrile* and 70 volumes of *water* and further dilute 1 volume to 10 volumes with the same mixture of solvents.

(5) Dissolve 80 mg of *benzoic acid* in 50 mL of *acetonitrile* and add sufficient *water* to produce 100 mL. Dilute 1 volume of this solution to 10 volumes with a mixture containing 30 volumes of *acetonitrile* and 70 volumes of *water* and further dilute 1 volume to 10 volumes with the same mixture of solvents.
(6) Mix equal volumes of solution (2) and solution (5).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *phenylhexylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna Phenyl-Hexyl is suitable) fitted with a stainless steel guard column (4 mm × 3 mm) packed with *octadecylsilyl silica gel for chromatography*.
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 283 nm.
(f) Inject 50 µL of each solution.

When the chromatograms are recorded under the prescribed conditions the retention time of warfarin is about 19 minutes.

MOBILE PHASE

1 volume of *acetic acid*, 50 volumes of *methanol* and 50 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (6), the *resolution factor* between the peaks corresponding to 4-hydroxycoumarin and benzoic acid is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peaks corresponding to 4-hydroxycoumarin, benzalacetone and (5*RS*)-3-(2-hydroxyphenyl)-5-phenylcyclohex-2-enone are not greater than half the area of the principal peaks in the chromatograms obtained with solutions (2), (3) and (4) respectively (0.5% of each);

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

Disregard any peak corresponding to the peak in the chromatogram obtained with solution (5).

ASSAY

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

(1) To a weighed quantity of the oral suspension containing 10 mg of Warfarin Sodium add 30 mL of *acetonitrile* and mix; add 50 mL of *water*, mix with the aid of ultrasound for 10 minutes and allow the solution to cool to room temperature. Add sufficient *water* to produce 100 mL, mix and filter through a 0.45-µm cellulose acetate filter (GD/X is suitable).
(2) Dissolve 0.1 g of *warfarin BPCRS* in 100 mL of a mixture of equal volumes of *acetonitrile* and *water*; dilute 10 volumes of this solution to 100 volumes with a mixture containing 30 volumes of *acetonitrile* and 70 volumes of *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *phenylhexylsilyl silica gel for chromatography* (5 µm) (Phenomenex Luna Phenyl-Hexyl is suitable) fitted with a stainless steel guard column (4 mm × 3 mm) packed with *octadecylsilyl silica gel for chromatography*.
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 283 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

1 volume of *acetic acid*, 50 volumes of *methanol* and 50 volumes of *water*.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral suspension, Appendix V G, and calculate the content of $C_{19}H_{15}NaO_4$, weight in volume, using the declared content of $C_{19}H_{16}O_4$ in *warfarin BPCRS*. Each mg of $C_{19}H_{16}O_4$ is equivalent to 1.071 mg of $C_{19}H_{15}NaO_4$.

STORAGE

Warfarin Oral Suspension should be protected from light.