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

Warfarin Tablets

General Notices

Warfarin Tablets prepared from Warfarin Sodium are not necessarily interchangeable with Warfarin Tablets prepared from Warfarin Sodium Clathrate.

Action and use

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

DEFINITION

Warfarin Tablets contain Warfarin Sodium or Warfarin Sodium Clathrate.

The tablets comply with the requirements stated under Tablets 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

Extract a quantity of the powdered tablets containing the equivalent of 0.1 g of warfarin sodium with 30 mL of *water*, add 0.1 mL of *2M hydrochloric acid*, filter, wash the precipitate with *water* and dry. Warm the residue gently with 3 mL of *ethanol* (*96%*), filter and add the filtrate to 25 mL of *water* containing 0.1 mL of *2M hydrochloric acid*. Filter, wash the precipitate with *water* and dry it at 105°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of warfarin (*RS 361*).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) Use 900 mL of 0.05M *potassium dihydrogen orthophosphate* adjusted to pH 6.8 by the addition of 1M *sodium hydroxide*, at a temperature of 37°, as the medium.
(c) For tablets containing 3 mg or less of warfarin sodium, place a whole number of tablets containing at least 3 mg of warfarin sodium in the basket for each test; for tablets containing more than 3 mg of warfarin sodium, place a single tablet in the basket for each test.

PROCEDURE

After 45 minutes, withdraw a sample of the medium. Measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium if necessary, at the maxima at 307 nm and 360 nm, Appendix II B, using the dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the difference between the two readings (ΔA). Calculate the total content of warfarin sodium, $C_{19}H_{15}NaO_4$, in the medium from the absorbances obtained and taking 428 as the value of ΔA(1%, 1 cm).

LIMITS

The amount of warfarin sodium released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in mixture of 20% v/v *methanol*.

(1) Shake a quantity of the powdered tablets containing the equivalent of 10 mg of warfarin sodium in 8 mL. Mix with the aid of ultrasound, dilute to produce 10 mL and filter.
(2) Dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of the resulting solution to 5 volumes.
(3) 0.002% w/v each of *4-hydroxycoumarin* (impurity B), *(E)-4-Phenylbut-3-en-2-one (benzalacetone)* (impurity C) and *(5RS)-3-(2-hydroxyphenyl)-5-phenylcyclohex-2-enone BPCRS* (impurity A).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Waters Spherisorb CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 283 nm.
(f) Inject 50 µL of each solution
(g) For solution (1) allow the chromatography to proceed for twice the retention time of warfarin.

MOBILE PHASE

1 volume of *glacial acetic acid*, 15 volumes of *acetonitrile* and 85 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to warfarin (retention time about 9 minutes) are: impurity B, about 0.4; impurity C, about 0.6 and impurity A, about 1.2.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity B and impurity C is at least 2.0.

LIMITS

Identify any peaks corresponding to impurity B and impurity C in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3). Multiply the area of any peak corresponding to impurity B by a correction factor of 0.5 and impurity C by a correction factor of 0.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to impurity B and impurity C is not greater than 0.75 times the area of the principal peak in the chromatogram obtained with solution (2) (0.15% of each);

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 any other *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

Tablets containing less than 2 mg and/or less than 2% w/w of warfarin sodium comply with the requirements stated under Tablets using the following method of analysis.

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

Shake one tablet with 10 mL of 0.01M *sodium hydroxide* for 15 minutes, add 10 mL of a 2% v/v solution of *glacial acetic acid* in *acetonitrile*, centrifuge for 10 minutes. Dilute the clear supernatant liquid, if necessary, with the mobile phase to produce a solution containing 0.0025% w/v of warfarin.
Dilute 1 volume of a 0.010% w/v solution of *warfarin BPCRS* in 0.01M *sodium hydroxide* to 4 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 283 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

1 volume of *glacial acetic acid*, 45 volumes of *water*, and 55 volumes of *acetonitrile*.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{15}NaO_4$ in each tablet 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 $C_{19}H_{15}NaO_4$.

ASSAY

For tablets containing 2 mg or less or 2% w/w or less of warfarin sodium

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

For tablets containing more than 2 mg and more than 2% w/w of warfarin sodium

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake a quantity of the powdered tablets containing the equivalent of 5 mg of warfarin sodium with 50 mL of 0.01M *sodium hydroxide* for 15 minutes, add 50 mL of a 2% v/v solution of *glacial acetic acid* in *acetonitrile*, centrifuge for 10 minutes and use the clear supernatant liquid.
(2) Dilute 5 mL of a 0.010% w/v solution of *warfarin BPCRS* in 0.01M *sodium hydroxide* to 10 mL with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Uniformity of content may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{19}H_{15}NaO_4$ in the tablets 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 Tablets should be protected from light.

LABELLING

When the active ingredient is Warfarin Sodium Clathrate the quantity is stated in terms of the equivalent amount of warfarin sodium.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Warfarin Sodium.