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

Ramipril Tablets

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Ramipril Tablets contain Ramipril.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of ramipril, $C_{23}H_{32}N_2O_5$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 25 mg of Ramipril with 50 mL of *acetone*, centrifuge for 10 minutes, filter the supernatant liquid through a 0.45-µm filter, evaporate the filtrate to dryness on a *water bath* and dry the residue for 3 hours at 60°. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of ramipril (*RS 417*).

TESTS

Dissolution

Comply with the requirements for Monographs of the British Pharmacopoeia in the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.
(b) Use 500 mL of *0.1M hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

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

(1) Withdraw a sample of the medium and filter immediately through a 0.45-µm glass-fibre filter (Whatman GD/X is suitable), discarding the first 5 mL of filtrate. Use the filtered medium, diluted with *0.1M hydrochloric acid* if necessary, expected to contain 0.00025% w/v of Ramipril.
(2) 0.00025% w/v of *ramipril BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-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 210 nm.
(f) Inject 40 µL of each solution.

MOBILE PHASE

420 volumes of *acetonitrile R1* and 580 volumes of a solution containing 1.4% w/v of *sodium perchlorate* and 0.58% w/v of *orthophosphoric acid* adjusted to pH 2.5 with *triethylamine*, and adjust the mixture to pH 2.1 with *orthophosphoric acid*.

DETERMINATION OF CONTENT

Calculate the total content of ramipril, $C_{23}H_{32}N_2O_5$, in the medium using the declared content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*.

Related substances

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

(1) Mix with the aid of ultrasound for 10 minutes, a quantity of the contents of the powdered tablets containing 25 mg of Ramipril with 50 mL of the mobile phase, centrifuge and use the clear supernatant liquid.
(2) Dilute 1 volume of solution (1) to 20 volumes with the mobile phase.
(3) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.
(4) 0.05% w/v of *ramipril BPCRS* and 0.0005% w/v of each of *ramipril impurity A EPCRS*, *ramipril impurity D EPCRS* and *ramipril impurity K BPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-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 210 nm.
(f) Inject 15 µL of each solution.
(g) For solution (1) allow the chromatography to proceed for 3 times the retention time of ramipril.

When the chromatograms are recorded under the prescribed conditions, the retention time of ramipril is about 10 minutes and retention times relative to ramipril are about 0.3 for ramipril impurity E (ramiprilat), about 0.5 for ramipril impurity K (diketopiperazine acid impurity), about 0.7 for ramipril impurity A (methyl ester impurity) and about 2.6 for ramipril impurity D (diketopiperazine impurity).

MOBILE PHASE

A mixture, adjusted to pH 2.6 with *orthophosphoric acid*, of 350 volumes of *acetonitrile R1* and 680 volumes of a solution adjusted to pH 3.9 with *triethylamine*, containing 1.4% w/v of *sodium perchlorate* and 0.58% w/v of *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution factor* between the peaks corresponding to ramipril impurity K and ramipril impurity A is at least 1.0.

LIMITS

For tablets containing more than 1.25 mg of Ramipril

In the chromatogram obtained with solution (1) the combined area of peaks corresponding to ramipril impurity D and ramipril impurity E is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution

(2) (6.0%); the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%). The sum of the areas of all the *secondary peaks* is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (6.0%).

For tablets containing 1.25 mg or less of Ramipril

In the chromatogram obtained with solution (1) the combined areas of peak corresponding to ramipril impurity D and ramipril impurity E is not greater than 1.6 times the area of the principal peak in the chromatogram obtained with solution (2) (8.0%); the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (3) (0.5%). The sum of the areas of all the *secondary peaks* is not greater than 1.6 times the area of the principal peak in the chromatogram obtained with solution (2) (8.0%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Ramipril 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. For solution (1) add 5 mL of *0.1M hydrochloric acid* to one tablet, mix with the aid of ultrasound for 10 minutes, dilute, if necessary, with sufficient *0.1M hydrochloric acid* to produce a solution containing 0.025% w/v of Ramipril, centrifuge and use the supernatant liquid. Solution (2) contains 0.025% w/v of *ramipril BPCRS* in *0.1M hydrochloric acid*.

The chromatographic conditions described under Dissolution may be used.

Calculate the content of $C_{23}H_{32}N_2O_5$ in each tablet using the declared content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*.

ASSAY

For tablets containing less than 2 mg and/or less than 2% w/w of Ramipril

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

For tablets containing 2 mg or more and 2% w/w or more of Ramipril

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

(1) Add 100 mL of *0.1M hydrochloric acid* to a quantity of powdered tablets containing 25 mg of Ramipril, mix with the aid of ultrasound for 10 minutes and centrifuge, use the supernatant liquid.
(2) 0.025% w/v of *ramipril BPCRS* in *0.1M hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{23}H_{32}N_2O_5$ in the tablets using the declared content of $C_{23}H_{32}N_2O_5$ in *ramipril BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed in the monograph for Ramipril.