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

Lisinopril Oral Solution

General Notices

Action and use

Angiotensin converting enzyme inhibitor.

DEFINITION

Lisinopril Oral Solution is a solution of Lisinopril Dihydrate in a suitable aqueous vehicle.

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

Content of anhydrous lisinopril, $C_{21}H_{31}N_3O_5$

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.
(1) Shake a volume of the oral solution with sufficient of a mixture of 20 volumes of *water* and 80 volumes of *methanol* to produce a solution containing the equivalent of 0.05% w/v of anhydrous lisinopril.
(2) 0.055% w/v of *lisinopril dihydrate BPCRS* in a mixture of 20 volumes of *water* and 80 volumes of *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}*.
(b) Pre-wash the plate with *methanol* and allow to dry in air before use.
(c) Use the mobile phase as described below.
(d) Apply 20 µL of each solution.
(e) Develop the plate to 15 cm.
(f) After removal of the plate, dry in air, spray with a 0.2% w/v solution of *ninhydrin* in *absolute ethanol*, heat at 105° for 10 minutes and examine in daylight.

MOBILE PHASE

Equal volumes of *glacial acetic acid*, *butan-1-ol*, *ethyl acetate* and *water*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position and colour 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 the same as that of the principal 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.

(1) Dilute a volume of the oral solution containing the equivalent of 5 mg of anhydrous lisinopril to 20 mL with mobile phase A.
(2) Dilute 1 volume of solution (1) to 200 volumes with mobile phase A.
(3) Dilute 1 volume of solution (2) to 5 volumes with mobile phase A.
(4) Heat 20 mg of *lisinopril dihydrate BPCRS* at 175° under nitrogen for 4 hours. Allow to cool and dissolve the residue in 10 mL of mobile phase A (generation of lisinopril diketopiperazine).
(5) Boil 20 mL of a 0.1% w/v solution of *lisinopril dihydrate BPCRS* in *water* under a reflux condenser for 2 hours. Allow to cool to room temperature, dilute 5 mL of the resulting solution to 20 mL with mobile phase A and mix thoroughly.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases* (4 µm) (Phenomenex Synergi Hydro-RP is suitable) fitted with a guard column (4 mm × 3 mm) packed with the same material.
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 25 volumes of *methanol* and 75 volumes of a solution prepared by dissolving 13.7 g of *sodium dihydrogen orthophosphate*, 2.1 g of *disodium hydrogen orthophosphate dihydrate* and 6.8 g of *tetrabutylammonium hydrogen sulfate* in 2000 mL of *water* and adjusting the pH to 5.7 with either 5M *sodium hydroxide* or *orthophosphoric acid*.

Mobile phase B *acetonitrile R1*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-30	100	0	isocratic
30-31	100→50	0→50	linear gradient
31-39	50	50	isocratic
39-40	50→100	50→0	linear gradient
40-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to lisinopril (retention time about 8 minutes) is: lisinopril diketopiperazine, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (3), the *signal-to-noise ratio* of the peak due to lisinopril is at least 15;

in the chromatogram obtained with solution (5), a peak on the tail of the lisinopril peak is visible.

LIMITS

Identify any peak corresponding to lisinopril diketopiperazine in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (4), and multiply the area of this peak by a correction factor of 1.4.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to lisinopril diketopiperazine is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any other *secondary peak* is not greater than 0.6 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the sum of the areas of any such peaks is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.6%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%).

ASSAY

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

(1) Dilute a weighed quantity of the oral solution containing the equivalent of 5 mg of anhydrous lisinopril to 20 mL with mobile phase A.
(2) 0.027% w/v of *lisinopril dihydrate BPCRS* in mobile phase A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used but using isocratic elution and mobile phase A.

DETERMINATION OF CONTENT

Determine the *weight per mL* of the oral solution, Appendix V G, and calculate the content of $C_{21}H_{31}N_3O_5$, weight in volume, using the declared content of $C_{21}H_{31}N_3O_5$ in *lisinopril dihydrate BPCRS*.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous lisinopril.