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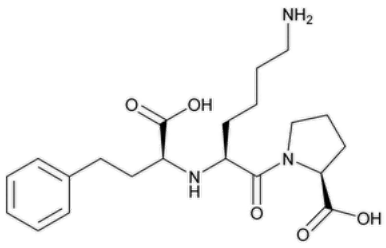
Lisinopril



• $2\,H_2O$

$C_{21}H_{31}N_3O_5 \cdot 2H_2O$ 441.52

L-Proline, 1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-, dihydrate, (*S*)-;
1-[N^2-[(*S*)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate CAS RN®: 83915-83-7; UNII: E7199S1YWR.

DEFINITION

Lisinopril contains NLT 98.0% and NMT 102.0% of lisinopril ($C_{21}H_{31}N_3O_5$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197M**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Solution A: 2.76 g/L of monobasic sodium phosphate in water prepared as follows. Dissolve 2.76 g of monobasic sodium phosphate in about 900 mL of water in a 1000-mL volumetric flask. Adjust with 1 N sodium hydroxide to a pH of 5.0 and dilute with water to volume.

Mobile phase: Acetonitrile and *Solution A* (4:96)

Standard solution: 0.3 mg/mL of USP Lisinopril RS in water

Sample solution: 0.3 mg/mL of Lisinopril in water

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.7

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of lisinopril ($C_{21}H_{31}N_3O_5$) in the portion of Lisinopril taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of lisinopril from the *Sample solution*

r_S = peak response of lisinopril from the *Standard solution*

C_S = concentration of USP Lisinopril RS in the *Standard solution* (mg/mL)

C_U = concentration of Lisinopril in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Organic Impurities**

Buffer: 3.53 g/L of monobasic sodium phosphate dihydrate in water adjusted with phosphoric acid to a pH of 4.1

Solution A: Acetonitrile and *Buffer* (7:193)

Solution B: Acetonitrile and *Buffer* (20:80)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
35	60	40
55	60	40
60	100	0

Standard solution: 0.006 mg/mL of USP Lisinopril RS in *Solution A*

Sensitivity solution: 1.0 µg/mL of USP Lisinopril RS in *Solution A* from *Standard solution*

Sample solution: 2 mg/mL of Lisinopril in *Solution A*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 45°

Flow rate: 1.8 mL/min

Injection volume: 20 µL

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Relative standard deviation: NMT 10.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Lisinopril taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of lisinopril from the *Standard solution*

C_S = concentration of USP Lisinopril RS in the *Standard solution* (mg/mL)

C_U = concentration of Lisinopril in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. Disregard any peak less than 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
N-Alkyl-L-lysine[a]	0.57	0.35	0.3
DL-Homophenylalanine[b]	0.72	1.08	0.30
Lisinopril	1.00	1.00	—
Lisinopril epimer[c]	1.33	0.76	0.3
Lisinopril cyclohexyl analog[d]	2.93	0.39	0.30
R,S,S-Diketopiperazine[e]	3.88	0.79	0.3
S,S,S-Diketopiperazine (lisinopril related compound A)[f]	4.04	0.76	0.3
N-Alkyl lisinopril[g]	4.60	0.86	0.15
Any individual unspecified impurity	—	1.00	0.1
Total impurities[h]	—	—	0.5

[a] [(*S*)-1-Carboxy-3-phenylpropyl]-L-lysine.

[b] 2-Amino-4-phenylbutanoic acid.

[c] [(*R*)-1-Carboxy-3-phenylpropyl]-L-lysyl-L-proline.

[d] [(*S*)-1-Carboxy-3-cyclohexylpropyl]-L-lysyl-L-proline.

[e] (*S*)-2-[(3*S*,8a*R*)-3-(4-Aminobutyl)-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-phenylbutanoic acid.

[f] (*S*)-2-[(3*S*,8a*S*)-3-(4-Aminobutyl)-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-4-phenylbutanoic acid.

[g] N^2,N^6-Bis[(*S*)-1-Carboxy-3-phenylpropyl]-L-lysyl-L-proline.

[h] Total impurities does not include lisinopril epimer.

SPECIFIC TESTS

- **Optical Rotation ⟨781S⟩, *Specific Rotation***

  Diluent: 0.25 M zinc acetate solution prepared as follows. Mix 600 mL of water with 150 mL of glacial acetic acid and 54.9 g of zinc acetate, and stir to dissolve the zinc acetate. While stirring, add 150 mL of ammonium hydroxide, cool to room temperature, and adjust with ammonium hydroxide to a pH of 6.4. Transfer the solution to a 1000-mL volumetric flask, and dilute with water to volume.

  Sample solution: 10 mg/mL of Lisinopril in *Diluent*

  Acceptance criteria: −115.3° to −122.5° (λ = 405 nm)

- **Water Determination ⟨921⟩, *Method I*:** 8.0%–9.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.
- **USP Reference Standards ⟨11⟩**

  USP Lisinopril RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
LISINOPRIL	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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