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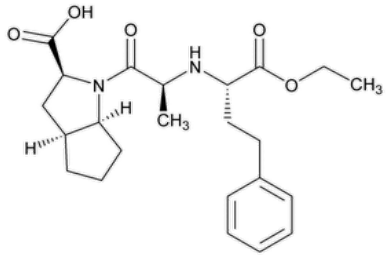
Ramipril

Change to read:



$C_{23}H_{32}N_2O_5$ ▲416.52▲ (USP 1-Aug-2022)

Cyclopenta[*b*]pyrrole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, [2*S*-[1[*R**(*R**)],2α,3aβ,6aβ]]-; (2*S*,3a*S*,6a*S*)-1-[(*S*)-*N*-[(*S*)-1-Carboxy-3-phenylpropyl]alanyl]octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid, 1-ethyl ester

▲(2*S*,3a*S*,6a*S*)-1-{[(*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl}octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid▲ (USP 1-Aug-2022) CAS RN®: 87333-19-5; UNII: L35JN3I7SJ.

DEFINITION

Ramipril contains NLT 98.0% and NMT 102.0% of ramipril ($C_{23}H_{32}N_2O_5$), calculated on the dried basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K
- **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

Change to read:

- **Procedure**

Buffer: 0.1% solution of sodium dodecyl sulfate. Adjust with phosphoric acid to a pH of 2.4 ± 0.1.

Mobile phase: Acetonitrile and *Buffer* (45:55). Adjust with phosphoric acid to a pH of 2.75 ± 0.1.

System suitability solution: 0.2 mg/mL of USP Ramipril RS and 0.01 mg/mL of USP Ramipril Related Compound A RS, in *Mobile phase*

Standard solution: 0.2 mg/mL of USP Ramipril RS in *Mobile phase*

Sample stock solution: 1 mg/mL of Ramipril prepared as follows. Dissolve 100 mg of Ramipril in 10 mL of Acetonitrile in a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Sample solution: 0.2 mg/mL of Ramipril in *Mobile phase* from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; ▲5 µm▲ (USP 1-Aug-2022) packing L1

Flow rate: 1.8 mL/min

Injection volume: 20 µL

▲**Run time:** NLT 2 times the retention time of ramipril▲ (USP 1-Aug-2022)

System suitability

Samples: *System suitability solution* ▲and *Standard solution*

[Note—The relative retention time for ramipril related compound A and ramipril are 0.8 and 1.0, respectively.]▲ (USP 1-Aug-2022)

Suitability requirements

Resolution: NLT 2.0 between ramipril and ramipril related compound A, *System suitability solution*

▲▲ (USP 1-Aug-2022)

Relative standard deviation: NMT ▲0.73%, *Standard solution*▲ (USP 1-Aug-2022)

Analysis

Samples: *Standard solution* and *Sample solution*

▲Calculate the percentage of ramipril ($C_{23}H_{32}N_2O_5$) in the portion of Ramipril taken:▲ (USP 1-Aug-2022)

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

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

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

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

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

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

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

Delete the following:

▲• **Limit of Palladium**

Diluent: Water and nitric acid (997:3)

Standard stock solution: Dissolve 50 mg of palladium metal taken in a 100-mL volumetric flask, in 9 mL of hydrochloric acid, and dilute with water to volume.

Standard solutions: 0.02, 0.03, and 0.05 µg/mL of palladium in *Diluent* from *Standard stock solution*

Sample solution: 2 mg/mL of Ramipril in *Diluent*

Blank solution: 1.5 mg/mL of magnesium nitrate in *Diluent*

Instrumental conditions

(See *Atomic Absorption Spectroscopy ⟨852⟩*.)

Mode: Atomic absorption spectrophotometry

Analytical wavelength: 247.6 nm palladium emission line

Lamp: Palladium hollow-cathode

Flame: Air–acetylene

Injection volume: 20 µL each for the *Standard solutions* and *Sample solution*, and 10 µL for the *Blank solution*

Analysis: Concomitantly determine the absorbances of the *Standard solutions*, *Sample solution*, and the *Blank solution*. Plot the absorbances of the *Standard solutions* versus the concentration, in µg/mL, of palladium, and draw the straight line best fitting the three plotted points. From the graph so obtained, determine the concentration, C_P, in µg/mL, of palladium in the *Sample solution*.

Calculate the percentage of palladium in the portion of Ramipril taken:

$$\text{Result} = (C_P/C_R) \times 100$$

C_P = concentration of palladium in the *Sample solution* (µg/mL)

C_R = concentration of Ramipril in the *Sample solution* (µg/mL)

Acceptance criteria: 20 ppm▲ (USP 1-Aug-2022)

Change to read:

• **Organic Impurities**

Solution A: 2.0 g of sodium perchlorate in a mixture of 800 mL of water and 0.5 mL of triethylamine. Adjust with phosphoric acid to a pH of about 3.6 ± 0.1, and add 200 mL of acetonitrile.

Solution B: 2.0 g of sodium perchlorate in a mixture of 300 mL of water and 0.5 mL of triethylamine. Adjust with phosphoric acid to a pH of about 2.6 ± 0.1, and add 700 mL of acetonitrile.

System suitability solution: 0.5 mg/mL each of USP Ramipril RS, USP Ramipril Related Compound A RS, USP Ramipril Related Compound B RS, USP Ramipril Related Compound C RS, and USP Ramipril Related Compound D RS in *Solution B*

Standard solution: 5 µg/mL of USP Ramipril RS in *Solution B*

▲**Sensitivity solution:** 0.5 µg/mL of USP Ramipril RS in *Solution B* from *Standard solution*▲ (USP 1-Aug-2022)

Sample solution: 1 mg/mL of Ramipril in *Solution A*. Keep the *Sample solution* cold until injected.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
6	90	10
7	75	25
20	65	35
30	25	75
40	25	75
45	90	10
55	90	10

▲▲ (USP 1-Aug-2022)

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.0-mm × 25-cm; 3-µm packing L1

Column temperature: 65°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *System suitability solution*, *Standard solution*, and ▲*Sensitivity solution*▲ (USP 1-Aug-2022)

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 3.0 between ramipril related compound A and ramipril, *System suitability solution*

▲▲ (USP 1-Aug-2022)

Relative standard deviation: NMT 5.0% for ramipril, *Standard solution*

▲**Signal-to-noise ratio:** NLT 10, *Sensitivity solution*▲ (USP 1-Aug-2022)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each specified and any unspecified impurity in the portion of Ramipril taken:

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

r_U = ▲peak▲ (USP 1-Aug-2022) response of each individual ▲impurity▲ (USP 1-Aug-2022) from the *Sample solution*

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

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

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

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

Acceptance criteria: See *Table 2*. ▲The reporting threshold is 0.05%.▲ (USP 1-Aug-2022)

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ramipril related compound A	0.8	1.0	0.5
Ramipril	1.0	—	—
Ramipril related compound B	1.3	1.0	0.5
Ramipril related compound C	1.5	0.42	0.5
Ramipril related compound D	1.6	1.0	0.5
Any unspecified impurity	—	—	▲0.10▲ (USP 1-Aug-2022)
Total impurities	—	—	1.0

SPECIFIC TESTS

• **Optical Rotation** ⟨781S⟩, *Procedures, Specific Rotation*

Sample solution: 10 mg/mL of Ramipril in 0.1 M methanolic hydrochloric acid

Acceptance criteria: +32.0° to +38.0°, at 20°

• **Loss on Drying** ⟨731⟩

Analysis: Dry under vacuum at a pressure not exceeding 5 mm of mercury at 60° for 6 h.

Acceptance criteria: NMT 0.2%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Ramipril RS

USP Ramipril Related Compound A RS

▲(2*S*,3a*S*,6a*S*)-1-{[(*S*)-1-carboxy-3-phenylpropyl]-L-alanyl}octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid.▲ (USP 1-Aug-2022)

$C_{22}H_{30}N_2O_5$ ▲402.49▲ (USP 1-Aug-2022)

USP Ramipril Related Compound B RS

▲(2*S*,3a*S*,6a*S*)-1-{[(*S*)-1-Methoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl}octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid;
Also known as Ramipril isopropylester.▲ (USP 1-Aug-2022)

$C_{24}H_{34}N_2O_5$ ▲430.55▲ (USP 1-Aug-2022)

USP Ramipril Related Compound C RS

▲(2*S*,3a*S*,6a*S*)-1-{[(*S*)-4-Cyclohexyl-1-ethoxy-1-oxobutan-2-yl]-L-alanyl}octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid hydrochloride;
Also known as Hexahydroramipril hydrochloride.▲ (USP 1-Aug-2022)

$C_{23}H_{38}N_2O_5$▲ · HCl 459.02▲ (USP 1-Aug-2022)

USP Ramipril Related Compound D RS

▲Ethyl (*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoate.▲ (USP 1-Aug-2022)

$C_{23}H_{30}N_2O_4$ 398.50

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

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

Topic/Question	Contact	Expert Committee
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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