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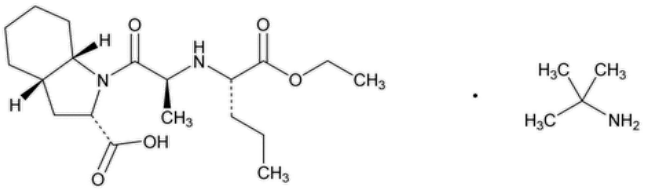
Perindopril Erbumine

Change to read:



$C_{19}H_{32}N_2O_5 \cdot C_4H_{11}N$ ▲441.60▲ (USP 1-Aug-2022)

1*H*-Indole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-, [2*S*-[1[*R**(*R**)],2α,3aβ,7aβ]]-, compound with 2-methyl-2-propanamine (1:1);

(2*S*,3a*S*,7a*S*)-1-[(*S*)-*N*-[(*S*)-1-Carboxybutyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, compound with *tert*-butylamine (1:1);

▲2-Methylpropan-2-amine (2*S*,3a*S*,7a*S*)-1-{[(*S*)-1-ethoxy-1-oxopentan-2-yl]-L-alanyl}octahydro-1*H*-indole-2-carboxylate▲ (USP 1-Aug-2022) CAS RN®: 107133-36-8; UNII: 1964X464OJ.

DEFINITION

Perindopril Erbumine contains NLT 98.0% and NMT 102.0% of perindopril erbumine ($C_{19}H_{32}N_2O_5 \cdot C_4H_{11}N$), calculated on the anhydrous 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 *System suitability solution 1*, as obtained in the test for *Limit of Perindopril Related Compound I*.

ASSAY

• **Procedure**

Buffer: Dissolve 0.92 g of sodium 1-heptanesulfonate in 1 L of water and add 1 mL of triethylamine. Adjust with a solution of perchloric acid and water (1:1) to a pH of 2.0.

Mobile phase: Acetonitrile and *Buffer* (35:65)

Standard solution: 0.1 mg/mL of USP Perindopril Erbumine RS in *Buffer*. Initially add *Buffer* to about 60% of the flask volume, sonicate to dissolve, and dilute with *Buffer* to volume.

Sample solution: 0.1 mg/mL of Perindopril Erbumine in *Buffer*. Initially add *Buffer* to about 60% of the flask volume, sonicate to dissolve, and dilute with *Buffer* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

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

Column temperature: 60°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of perindopril erbumine ($C_{19}H_{32}N_2O_5 \cdot C_4H_{11}N$) in the portion of Perindopril Erbumine taken:

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

r_U = peak area of perindopril from the *Sample solution*

r_S = peak area of perindopril from the *Standard solution*

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

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

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

IMPURITIES

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

Change to read:

• **Organic Impurities**

Solution A: Proceed as directed for the *Buffer* as described in the *Assay*.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
5	80	20
27	68	32
45	50	50
60	20	80
70	20	80
71	80	20
80	80	20

Diluent: *Solution B* and *Solution A* (20:80)

System suitability stock solution A: 0.03 mg/mL of USP Imidazole RS in *Diluent*

System suitability stock solution B: 0.03 mg/mL each of USP Perindopril Erbumine RS, USP Perindopril Related Compound B RS, USP Perindopril Related Compound C RS, USP Perindopril Related Compound D RS, and USP Perindopril Related Compound F RS in *Diluent*

System suitability solution: Transfer 5 mL each of *System suitability stock solution A* and *System suitability stock solution B* to a 50-mL volumetric flask and dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size, discard the first 3 mL of the filtrate, and use the clear filtrate.

Standard stock solution: 0.03 mg/mL of USP Perindopril Erbumine RS in *Diluent* prepared as follows. Dissolve a suitable quantity of USP Perindopril Erbumine RS in 80% of the total volume of *Diluent*, sonicate for about 5 min, and dilute with *Diluent* to volume.

Standard solution: 0.003 mg/mL of USP Perindopril Erbumine RS in *Diluent* from the *Standard stock solution*. Pass through a suitable filter of 0.45-µm pore size and discard the first 3 mL of the filtrate.

Sample solution: 3 mg/mL of Perindopril Erbumine in *Diluent* prepared as follows. Dissolve a suitable quantity of Perindopril Erbumine in 80% of the total volume of *Diluent*, sonicate for 5 min, and dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size and discard the first 3 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.0-mm × 25-cm; 4-µm packing L7

Column temperature: 60°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Tailing factor: NMT 1.5 for the perindopril peak

Relative standard deviation: NMT 5.0% for the perindopril peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Perindopril Erbumine 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 perindopril ▲▲ (USP 1-Aug-2022) from the *Standard solution*

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

C_U = concentration of Perindopril Erbumine 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 (%)
Imidazole[a]	0.08	—	—
Perindopril related compound B ▲▲ (USP 1-Aug-2022)	0.42	1.20	0.3
Perindopril related compound C ▲▲ (USP 1-Aug-2022)	0.74	0.96	0.1
Perindopril related compound D ▲▲ (USP 1-Aug-2022)	0.85	0.98	0.1
Perindopril erbumine	1.0	—	—
Isopropyl perindopril ▲[b]▲ (USP 1-Aug-2022)	1.22	1.00	0.40 (if present)
Perindopril related compound F ▲▲ (USP 1-Aug-2022)	1.38	0.85	0.2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Perindopril imidazolidinone analog ▲[c]▲ (USP 1-Aug-2022)	1.65	1.00	0.15 (if present)
Any individual unspecified impurity	—	—	0.10
Total impurities▲[d]▲ (USP 1-Aug-2022)	—	—	1

[a] Imidazole is quantitated using the test for *Limit of Perindopril Related Compound A and Imidazole* and is included in the table for identification purposes only.

[b] (2*S*,3a*S*,7a*S*)-1-{(*S*)-2-[(*S*)-1-isopropoxy-1-oxopentan-2-ylamino]propanoyl}octahydro-1*H*-indole-2-carboxylic acid.

[c] (2*S*,3a*S*,7a*S*)-1-[(2*S*)-2-(3-Cyclohexyl-2,4-dioxo-5-propylimidazolidin-1-yl)propanoyl]octahydro-1*H*-indole-2-carboxylic acid.

[d] Total impurities include all specified and unspecified impurities and imidazole from the test for *Limit of Perindopril Related Compound A and Imidazole*. Perindopril related compound A is not included.

Change to read:

• **Limit of Perindopril Related Compound A and Imidazole**

▲**Buffer:** Dissolve 1.84 g of sodium 1-heptanesulfonate and 5.23 g of dibasic potassium phosphate in 1 L of water. Add 1 mL of triethylamine and adjust the pH of the solution with phosphoric acid to 2.0.

Solution A: Acetonitrile and *Buffer* (17:83)

Solution B: Acetonitrile and *Buffer* (60:40)

Solution C: Dissolve 0.74 g of *tert*-butylamine in 100 mL of water.

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	100	0
7	100	0
8	0	100
20	0	100
21	100	0
33	100	0

Diluent: *Solution A*

Standard stock solution: 0.25 mg/mL of USP Perindopril Related Compound A RS and 0.1 mg/mL of USP Imidazole RS in *Diluent*. Sonicate if necessary.

Standard solution: 0.025 mg/mL of USP Perindopril Related Compound A RS and 0.01 mg/mL of USP Imidazole RS in *Diluent* prepared as follows. Transfer 1.0 mL of the *Standard stock solution* to a 10-mL volumetric flask. Add 2.5 mL of *Solution C*. Dilute with *Diluent* to volume.▲ (USP 1-Aug-2022)

Sample solution: 10 mg/mL of Perindopril Erbumine in *Diluent*

Chromatographic system

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

Mode: LC

Detectors

Perindopril related compound A: UV 210 nm

Imidazole: UV 225 nm

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

Temperatures

Column: 60°

▲Autosampler:▲ (USP 1-Aug-2022) 5°

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for imidazole and perindopril related compound A are 1.0 and ▲1.5,▲ (USP 1-Aug-2022) respectively.]

Suitability requirements

Tailing factor: ▲NMT 1.8 for imidazole and perindopril related compound A, respectively▲ (USP 1-Aug-2022)

Relative standard deviation: ▲NMT 5.0% for imidazole and perindopril related compound A, respectively▲ (USP 1-Aug-2022)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of perindopril related compound A or imidazole in the portion of Perindopril Erbumine taken:

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

r_U = peak response of perindopril related compound A or imidazole from the *Sample solution*

r_S = peak response of perindopril related compound A or imidazole from the *Standard solution*

C_S = concentration of USP Perindopril Related Compound A RS or USP Imidazole RS in the *Standard solution* (mg/mL)

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

Acceptance criteria

Perindopril related compound A: NMT 0.25%

Imidazole: NMT 0.1%

Change to read:

• **LIMIT OF PERINDOPRIL RELATED COMPOUND I**

▲▲ (USP 1-Aug-2022)

Solution A: Dissolve 5 g of potassium phosphate monobasic in 1900 mL of water. Adjust with triethylamine to a pH of 6.50 and add 100 mL of acetonitrile.

Solution B: Acetonitrile

Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	83	17
22	83	17
23	20	80
33	20	80
34	83	17
46	83	17

Diluent: *Solution B* and *Solution A* (17:83)

System suitability solution 1: 3 mg/mL of USP Perindopril Erbumine RS in *Diluent*. [NOTE—This solution is used in *Identification* test *B*.]

System suitability solution 2: 3 µg/mL of USP Perindopril Erbumine RS▲ (USP 1-Aug-2022) from *System suitability solution 1*▲and 6 µg/mL of USP Perindopril Related Compound I RS in *Diluent*▲ (USP 1-Aug-2022)

Sample solution: 3 mg/mL of Perindopril Erbumine in *Diluent* prepared as follows. Dissolve a suitable quantity of Perindopril Erbumine in 80% of the total volume of *Diluent*, sonicate for 5 min, and dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size and discard the first 3 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 60°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution 2*

[NOTE—The relative retention times for perindopril and perindopril related compound I are 1.0 and 1.6, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 ▲for perindopril▲ (USP 1-Aug-2022)

Relative standard deviation: NMT 5.0% ▲for perindopril▲ (USP 1-Aug-2022)

Analysis

Samples: ▲*System suitability solution 1* and▲ (USP 1-Aug-2022) *Sample solution*

▲[NOTE—*System suitability solution 1* is used in *Identification B*.]▲ (USP 1-AUG-2022)

Calculate the percentage of perindopril related compound I in the portion of Perindopril Erbumine taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of perindopril related compound I from the *Sample solution*

r_T = total of all peak responses from the *Sample solution*

Acceptance criteria: NMT 0.1%

SPECIFIC TESTS

- **WATER DETERMINATION ⟨921⟩, *Method Ia*:** NMT 1.0%; 3.00%–4.50% for the monohydrate
- **OPTICAL ROTATION ⟨781S⟩, *Specific Rotation***

Sample solution: 10 mg/mL of Perindopril Erbumine in ethanol

Acceptance criteria: −66° to −69°, at 20°

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers at controlled room temperature.

Change to read:

- **USP REFERENCE STANDARDS ⟨11⟩**

USP Imidazole RS

USP Perindopril Erbumine RS

USP Perindopril Related Compound A RS

(2*S*,3a*S*,7a*S*)-Octahydro-1*H*-indole-2-carboxylic acid.

$C_9H_{15}NO_2$ 169.22

USP Perindopril Related Compound B RS

(2*S*,3a*S*,7a*S*)-1-{(*S*)-2-[(*S*)-1-Carboxybutylamino]propanoyl}octahydro-1*H*-indole-2-carboxylic acid ▲monohydrate.▲ (USP 1-Aug-2022)

$C_{17}H_{28}N_2O_5 \cdot$▲H_2O▲ (USP 1-Aug-2022) ▲358.44▲ (USP 1-Aug-2022)

USP Perindopril Related Compound C RS

(*S*)-2-{(3*S*,5a*S*,9a*S*,10a*S*)-3-Methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl}pentanoic acid.

$C_{17}H_{26}N_2O_4$ ▲322.41▲ (USP 1-Aug-2022)

USP Perindopril Related Compound D RS

(*S*)-2-{(3*S*,5a*S*,9a*S*,10a*R*)-3-Methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl}pentanoic acid.

$C_{17}H_{26}N_2O_4$ ▲322.41▲ (USP 1-Aug-2022)

USP Perindopril Related Compound F RS

(*S*)-Ethyl 2-{(3*S*,5a*S*,9a*S*,10a*S*)-3-methyl-1,4-dioxodecahydropyrazino[1,2-*a*]indol-2(1*H*)-yl}pentanoate.

$C_{19}H_{30}N_2O_4$ ▲350.46

USP Perindopril Related Compound I RS

2-Methylpropan-2-amine (2*S*,3a*S*,7a*S*)-1-{(*S*)-2-[(*R*)-1-ethoxy-1-oxopentan-2-ylamino]propanoyl}octahydro-1*H*-indole-2-carboxylate.

$C_{19}H_{32}N_2O_5 \cdot C_4H_{11}N$ 441.60▲ (USP 1-Aug-2022)

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

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

Chromatographic Database Information: Chromatographic Database

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