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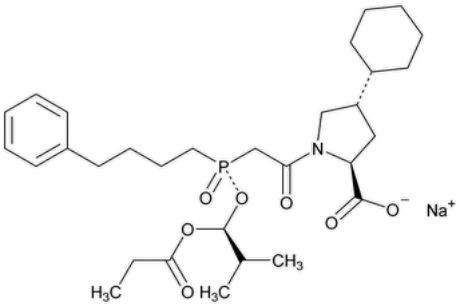
Fosinopril Sodium



$C_{30}H_{45}NNaO_7P$ 585.64

L-Proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, sodium salt, [1[*S**(*R**)],2α,4β]-;

(4*S*)-4-Cyclohexyl-1-[(*R*)-[(*S*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt CAS RN®: 88889-14-9; UNII: NW2RTH6T2N.

DEFINITION

Fosinopril Sodium contains NLT 97.5% and NMT 102.0% of fosinopril sodium ($C_{30}H_{45}NNaO_7P$), calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 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**

Mobile phase: Acetonitrile, phosphoric acid, and water (2000:1:10)

System suitability solution: 0.1 mg/mL of USP Fosinopril Sodium RS and 0.01 mg/mL of USP Fosinopril Related Compound B RS in *Mobile phase*

Standard solution: 0.10 mg/mL of USP Fosinopril Sodium RS in *Mobile phase*

Sample solution: 0.10 mg/mL of Fosinopril Sodium in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Column: 3.9-mm × 15-cm; 5-µm packing L3

Column temperature: 33°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

Run time: NLT 4 times the retention time of the fosinopril peak

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 2.0 between fosinopril related compound B and fosinopril

Relative standard deviation: NMT 0.73% for the fosinopril peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of fosinopril sodium ($C_{30}H_{45}NNaO_7P$) in the portion of Fosinopril Sodium taken:

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

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

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

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

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

Acceptance criteria: 97.5%–102.0% on the anhydrous basis

IMPURITIES

• **Organic Impurities, Procedure 1**

Mobile phase, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: 0.1 mg/mL of USP Fosinopril Sodium RS and 0.01 mg/mL each of USP Fosinopril Related Compound A RS and USP Fosinopril Related Compound B RS in *Mobile phase*

Analysis

Sample: *Sample solution*

Calculate the percentage of each individual related compound in the portion of Fosinopril Sodium taken:

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

r_U = individual peak response, other than the fosinopril peak

r_T = sum of all the peak responses

Acceptance criteria See *Table 1*.

Table 1

Name	Relative Retention Time	Procedure	Acceptance Criteria, NMT (%)
Impurity 3 (if present)[a]	0.37	1	0.15
Impurity 1[b]	0.53	1	0.3
Impurity 2[c]	0.67	1	0.2
Fosinopril related compound B[d]	0.7	1	1.0
Fosinopril related compound E[e]	0.8	3	0.3
Fosinopril related compound F[f]	0.9	3	0.3
Fosinopril related compound C[g]	1.2	2	0.3
Fosinopril related compound D[h]	1.3	2	0.3
Fosinopril related compound A[i]	2.0	1	0.75
Any individual unspecified impurity	—	1	0.1

Name	Relative Retention Time	Procedure	Acceptance Criteria, NMT (%)
Total impurities[j]	—	1, 2, 3	1.5

[a] (*S*)-4-Cyclohexyl-1-(3-oxopentanoyl)-L-proline.

[b] (2*S*,4*S*)-4-Cyclohexyl-1-pivaloylpyrrolidine-2-carboxylic acid.

[c] 2-((*RS*)-((*SR*)-2-Methyl-1-(propionyloxy)propoxy)(4-phenylbutyl)phosphinyl)acetic acid.

[d] (4*S*)-4-Cyclohexyl-1-[(*R*)-[(*S*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-D-proline propionate (ester). If present, two more diastereomers may not be resolved from fosinopril related compound B by this method. These peaks, appearing at a relative retention time of 0.7, should be integrated together to determine conformance with the limit.

[e] (4*S*)-4-Phenyl-1-[(*R*)-[(*S*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt.

[f] (4*S*)-4-Cyclohexyl-1-[(*R*)-[(*S*)-1-hydroxypropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt.

[g] Mixture of (4*S*)-4-cyclohexyl-1-[(*S*)-[(*S*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt and (4*S*)-4-cyclohexyl-1-[[(*R*)-[(*R*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt.

[h] (4*R*)-4-Cyclohexyl-1-[(*R*)-[(*S*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt.

[i] (4*S*)-4-Cyclohexyl-[(4-phenylbutyl)phosphinyl]acetyl-L-proline.

[j] Sum of all impurities from *Organic Impurities, Procedure 1; Organic Impurities, Procedure 2;* and *Organic Impurities, Procedure 3*.

- **Organic Impurities, Procedure 2**

Mobile phase: Acetonitrile, phosphoric acid, and water (2000:1:7.5)

System suitability solution: 0.1 mg/mL of USP Fosinopril Sodium RS and 0.01 mg/mL each of USP Fosinopril Related Compound C RS and USP Fosinopril Related Compound D RS in *Mobile phase*

Sample solution: Prepare as directed in the *Assay*.

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Column: 4.6-mm × 25-cm; 5-µm packing L14

Column temperature: 45°

Flow rate: 0.9 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time of the fosinopril peak

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between fosinopril and fosinopril related compound C

Analysis

Sample: *Sample solution*

Calculate the percentages of fosinopril related compound C and fosinopril related compound D only in the portion of Fosinopril Sodium taken:

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

r_U = peak response of fosinopril related compound C or fosinopril related compound D

r_T = sum of all the peak responses

Acceptance criteria: See *Table 1*.

- **Organic Impurities, Procedure 3**

Solution A: Phosphoric acid (1 in 500)

Mobile phase: Acetonitrile and *Solution A* (56:44)

System suitability solution: 0.01 mg/mL each of USP Fosinopril Sodium RS, USP Fosinopril Related Compound E RS, and USP Fosinopril Related Compound F RS in *Mobile phase*

Sample solution: 0.2 mg/mL of Fosinopril Sodium in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm × 25-cm; 5-µm packing L11

Column temperature: 45°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 4 times the retention time of the fosinopril peak

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between fosinopril related compound F and fosinopril; NLT 1.5 between fosinopril related compound E and fosinopril related compound F

Analysis

Sample: *Sample solution*

Calculate the percentages of fosinopril related compound E and fosinopril related compound F in the portion of Fosinopril Sodium taken:

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

r_U = peak response of fosinopril related compound E or fosinopril related compound F

r_T = sum of all the peak responses

Acceptance criteria: See *Table 1*.

SPECIFIC TESTS

• **Water Determination** ⟨921⟩, *Method I*: NMT 0.2%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.

• **USP Reference Standards** ⟨11⟩

USP Fosinopril Sodium RS

USP Fosinopril Related Compound A RS

(4*S*)-4-Cyclohexyl-[(4-phenylbutyl)phosphinyl]acetyl-L-proline.

$C_{23}H_{34}NO_5P$ 435.49

USP Fosinopril Related Compound B RS

(4*S*)-4-Cyclohexyl-1-[(*R*)-[(*S*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-D-proline propionate (ester), hemibarium salt, sesquihydrate.

$C_{30}H_{45}NO_7P \cdot ½Ba \cdot 1½H_2O$ 658.34

USP Fosinopril Related Compound C RS

(4*S*)-4-Cyclohexyl-1-[(*RS*)-[(*RS*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt.

$C_{30}H_{45}NNaO_7P$ 585.64

USP Fosinopril Related Compound D RS

(4*R*)-4-Cyclohexyl-1-[(*R*)-[(*S*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt.

$C_{30}H_{45}NNaO_7P$ 585.64

USP Fosinopril Related Compound E RS

(4*S*)-4-Phenyl-1-[(*R*)-[(*S*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt.

$C_{30}H_{39}NNaO_7P$ 579.60

USP Fosinopril Related Compound F RS

(4*S*)-4-Cyclohexyl-1-[(*R*)-[(*S*)-1-hydroxypropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt.

$C_{29}H_{43}NNaO_7P$ 571.62

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

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

Chromatographic Database Information: Chromatographic Database

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