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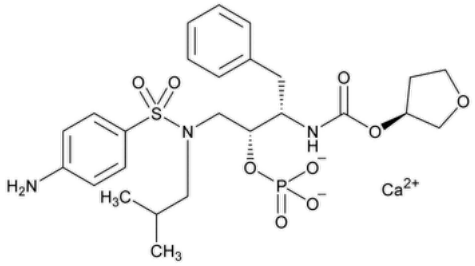
Fosamprenavir Calcium

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-fosamprenavir-calcium-20230127.



$C_{25}H_{34}CaN_3O_9PS$ 623.67

Carbamic acid, [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1-(phenylmethyl)-2-(phosphonooxy)propyl]-, *C*-[(3*S*)-tetrahydro-3-furanyl] ester, calcium salt (1:1);

(3*S*)-Tetrahydro-3-furyl [(α*S*)-α-[(1*R*)-1-hydroxy-2-(*N*[1]-isobutylsulfanilamido)ethyl]phenethyl]carbamate, calcium phosphate (ester) (1:1);

Calcium (2*R*,3*S*)-1-[(4-amino-*N*-isobutylphenyl)sulfonamide]-4-phenyl-3-[({[(*S*)-tetrahydrofuran-3-yl]oxy}carbonyl)amino]butan-2-yl phosphate. CAS RN®: 226700-81-8; UNII: ID1GU2627N.

DEFINITION

Fosamprenavir Calcium contains NLT 98.0% and NMT 102.0% of fosamprenavir calcium ($C_{25}H_{34}CaN_3O_9PS$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197M or 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*.
- **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Calcium*:** Meets the requirements

ASSAY

- **Procedure**

Buffer: 4.68 g/L of monobasic sodium phosphate dihydrate in water. Add 1.5 mL of phosphoric acid per 1 L of this solution.

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

Diluent: Acetonitrile and *Buffer* (20:80)

Standard solution: 0.26 mg/mL of USP Fosamprenavir Calcium RS in *Diluent*. Sonicate to dissolve prior to final dilution, if necessary.

Sample solution: 0.26 mg/mL of Fosamprenavir Calcium in *Diluent*. Sonicate to dissolve prior to final dilution, if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 266 nm

Column: 4.6-mm x 15-cm; 3.5-µm packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of fosamprenavir calcium ($C_{25}H_{34}CaN_3O_9PS$) in the portion of Fosamprenavir Calcium taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **Organic Impurities: Early-Eluting Impurities**

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

System suitability solution: 0.26 mg/mL of USP Fosamprenavir System Suitability Mixture RS in *Diluent*. Sonicate to dissolve prior to final dilution, if necessary.

Standard solution: 0.26 µg/mL of USP Fosamprenavir Calcium RS in *Diluent*. Sonicate to dissolve prior to final dilution, if necessary.

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between fosamprenavir pyrophosphate and fosamprenavir *n*-propyl homolog, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual early-eluting impurity in the portion of Fosamprenavir Calcium taken:

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

r_U = peak response of any individual impurity from the *Sample solution*

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

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

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

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*. The reporting threshold is 0.03%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Fosamprenavir amine[a]	0.4	1.0	0.3
Fosamprenavir pyrophosphate[b]	0.7	0.77	0.2
Fosamprenavir *n*-propyl homolog[c]	0.8	1.0	0.3
Fosamprenavir	1.0	1.0	—
Any unspecified impurity[d]	—	1.0	0.05
Total impurities[e]	—	—	1.3

[a] (2*R*,3*S*)-3-Amino-1-[(4-amino-*N*-isobutylphenyl)sulfonamide]-4-phenylbutan-2-yl dihydrogen phosphate.

[b] (*S*)-Tetrahydrofuran-3-yl {(2*S*,3*R*)-4-[(4-amino-*N*-isobutylphenyl)sulfonamide]-3-([hydroxy(phosphonooxy)phosphoryl]oxy)-1-phenylbutan-2-yl}carbamate.

[c] Calcium (2*R*,3*S*)-1-[(4-amino-*N*-propylphenyl)sulfonamide]-4-phenyl-3-[({[(*S*)-tetrahydrofuran-3-yl]oxy}carbonyl)amino]butan-2-yl phosphate.

[d] Exclude any individual unspecified impurity that elutes after fosamprenavir.

[e] Total impurities include the sum of all impurities determined in *Organic Impurities: Early-Eluting Impurities*, *Organic Impurities: Late-Eluting Impurities*, and *Limit of Fosamprenavir Related Compound A*.

- **Organic Impurities: Late-Eluting Impurities**

Buffer: 1.58 g/L of ammonium formate in water. Adjust with ammonia solution to a pH of 9.0.

Solution A: Acetonitrile and *Buffer* (19:81)

Solution B: Acetonitrile, tetrahydrofuran, and *Buffer* (45:5:50)

Solution C: 4.68 g/L of monobasic sodium phosphate dihydrate in water. Add 1.5 mL of phosphoric acid per 1 L of this solution.

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
15	100	0
40	0	100
43	0	100
45	100	0
55	100	0

Diluent: Acetonitrile and *Solution C* (20:80)

System suitability solution: 0.26 mg/mL of USP Fosamprenavir System Suitability Mixture RS in *Diluent*. Sonicate to dissolve prior to final dilution, if necessary.

Standard solution: 0.26 µg/mL of USP Fosamprenavir Calcium RS in *Diluent*. Sonicate to dissolve prior to final dilution, if necessary.

Sample solution: 0.26 mg/mL of Fosamprenavir Calcium in *Diluent*. Sonicate to dissolve prior to final dilution, if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 266 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 2 between fosamprenavir and fosamprenavir *n*-butyl isomer, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual late-eluting impurity in the portion of Fosamprenavir Calcium taken:

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

r_U = peak response of any individual impurity from the *Sample solution*

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

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

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

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.03%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Fosamprenavir	1.0	1.0	—
Fosamprenavir *n*-butyl isomer[a]	1.2	1.0	0.3
Fosamprenavir ethyl ester[b]	1.9	1.0	0.2
Bisfosamprenavir triphosphate[c]	2.6	1.0	0.2
Bisfosamprenavir pyrophosphate[d]	2.7	1.0	0.7
Bisfosamprenavir oxazolone[e]	2.8	0.66	0.2
Amprenavir oxazolone[f]	3.0	0.59	0.2
Amprenavir[g]	3.1	1.0	0.3
Any unspecified impurity[h]	—	1.0	0.05
Total impurities[i]	—	—	1.3

[a] Calcium (2*R*,3*S*)-1-[(4-amino-*N*-butylphenyl)sulfonamide]-4-phenyl-3-[({[(*S*)-tetrahydrofuran-3-yl]oxy}carbonyl)amino]butan-2-yl phosphate.

[b] Ethyl {(2*S*,3*R*)-4-[(4-amino-*N*-isobutylphenyl)sulfonamide]-1-phenyl-3-(phosphonooxy)butan-2-yl}carbamate.

[c] Bis[(3*S*)-tetrahydro-3-furanyl] (3*S*,4*R*,12*R*,13*S*)-4,12-bis({[(4-aminophenyl)sulfonyl](2-methylpropyl)amino}methyl)-6,8,10-trihydroxy-3,13-bis(phenylmethyl)-5,7,9,11-tetroxa-2,14-diaza-6,8,10-triphosphapentadecanedioate 6,8,10-trioxide.

[d] Bis[(3*S*)-tetrahydro-3-furanyl] (3*S*,4*R*,10*R*,11*S*)-4,10-bis({[(4-aminophenyl)sulfonyl](2-methylpropyl)amino}methyl)-6,8-dihydroxy-3,11-bis(phenylmethyl)-5,7,9-trioxa-2,12-diaza-6,8-diphosphatridecanedioate 6,8-oxide.

[e] (3*S*)-Tetrahydro-3-furanyl (3*S*,4*R*)-4-({[(4-aminophenyl)sulfonyl]isobutylamino}methyl)-6-[(4*S*,5*R*)-5-({[(4-aminophenyl)sulfonyl]isobutylamino}methyl)-2-oxo-4-benzyl-3-oxazolidinyl]-8,8-dihydroxy-6-oxo-3-benzyl-5,7-dioxa-2-aza-6,8-diphosphaoctanoate 8-oxide.

[f] 4-Amino-*N*-{[(4*S*,5*R*)-4-benzyl-2-oxooxazolidin-5-yl]methyl}-*N*-isobutylbenzenesulfonamide.

[g] (*S*)-Tetrahydrofuran-3-yl {(2*S*,3*R*)-4-[(4-amino-*N*-isobutylphenyl)sulfonamide]-3-hydroxy-1-phenylbutan-2-yl}carbamate.

[h] Exclude any individual unspecified impurity that elutes before fosamprenavir.

[i] Total impurities include the sum of all impurities determined in *Organic Impurities: Early-Eluting Impurities*, *Organic Impurities: Late-Eluting Impurities*, and *Limit of Fosamprenavir Related Compound A*.

- **Limit of Fosamprenavir Related Compound A**

Buffer: 1.54 g/L of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 4.0.

Solution A: 0.5 mL/L of trifluoroacetic acid in water

Solution B: 0.5 mL/L of trifluoroacetic acid in acetonitrile

Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	68	32
40	45	55
50	5	95
50.1	68	32
65	68	32

Diluent: Methanol and *Buffer* (50:50)

Sensitivity solution: 0.3 µg/mL of USP Fosamprenavir Calcium RS in *Diluent*. Sonicate to dissolve prior to final dilution, if necessary.

Standard solution: 0.003 mg/mL of USP Fosamprenavir Related Compound A RS in *Diluent*. Sonicate to dissolve prior to final dilution, if necessary.

Sample solution: 1 mg/mL of Fosamprenavir Calcium in *Diluent*. Sonicate to dissolve prior to final dilution, if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 266 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *Sensitivity solution* and *Standard solution*

[NOTE—The relative retention times for fosamprenavir and fosamprenavir related compound A are 1.0 and 3.6, respectively.]

Suitability requirements

Tailing factor: NMT 2, *Standard solution*

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

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of fosamprenavir related compound A in the portion of Fosamprenavir Calcium taken:

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

r_U = peak response of fosamprenavir related compound A from the *Sample solution*

r_S = peak response of fosamprenavir related compound A from the *Standard solution*

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

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

Acceptance criteria: NMT 0.3% of fosamprenavir related compound A

SPECIFIC TESTS

Change to read:

• **WATER DETERMINATION ⟨921⟩, *Method I*:** ▲NMT 14.5%▲ (RB 1-Feb-2023)

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Fosamprenavir Calcium RS

USP Fosamprenavir Related Compound A RS

Calcium (6*R*,7*S*,16*S*,17*R*)-4,19-bis[(4-aminophenyl)sulfonyl]-7,16-dibenzyl-2,21-dimethyl-9,14-dioxo-10,13-dioxa-4,8,15,19-tetraazadocosane-6,17-diyl bis(phosphate).

$C_{44}H_{58}Ca_2N_6O_{16}P_2S_2$ 1133.20

USP Fosamprenavir System Suitability Mixture RS

A mixture of fosamprenavir calcium, fosamprenavir pyrophosphate, fosamprenavir *n*-propyl homolog, and fosamprenavir *n*-butyl isomer. Other impurities may also be present.

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

Topic/Question	Contact	Expert Committee
FOSAMPRENAVIR CALCIUM	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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