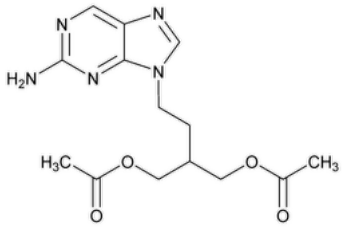
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-B1B3CB5D-8F07-4960-AA19-6B0FC0E7D199_4_en-US
DOI: https://doi.org/10.31003/USPNF_M32594_04_01
DOI Ref: 118c3

Famciclovir



$C_{14}H_{19}N_5O_4$ 321.33

1,3-Propanediol, 2-[2-(2-amino-9*H*-purin-9-yl)ethyl]-, diacetate (ester);

2-[2-(2-Amino-9*H*-purin-9-yl)ethyl]-1,3-propanediol diacetate (ester) CAS RN®: 104227-87-4; UNII: QIC03ANI02.

DEFINITION

Famciclovir contains NLT 98.0% and NMT 102.0% of famciclovir ($C_{14}H_{19}N_5O_4$), calculated on the dried basis.

IDENTIFICATION

Change to read:

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

Dilute acid: Dilute 5 mL of phosphoric acid with water to 50 mL.

Buffer: 2.72 g/L of monobasic potassium phosphate in water. Adjust with *Dilute acid* to a pH of 4.0 ± 0.05.

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

Diluent: Water

Standard solution: 25 µg/mL of USP Famciclovir RS in *Diluent*

Sample solution: 25 µg/mL of Famciclovir in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 5 times the retention time of famciclovir

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2500 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of famciclovir ($C_{14}H_{19}N_5O_4$) in the portion of Famciclovir taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

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

IMPURITIES

• **Organic Impurities, Procedure 1**

[Note—On the basis of the synthetic route resulting in different impurity profiles, perform *Procedure 1* or *Procedure 2*. *Procedure 1* is recommended when dimethylaminopyridine, penciclovir, deoxychloro famciclovir, propionyl famciclovir, and 6-alkylamino famciclovir may be present (see *Table 2*). *Procedure 2* is recommended when famciclovir malonate, acetoxybutyl aminopurine, famciclovir methoxycarbonyl analog, famciclovir related compound C, famciclovir 8, N^2-dimer, and famciclovir 6,6-dimer may be present (see *Table 4*).]

Dilute acid, Buffer, and **Diluent:** Proceed as directed in the *Assay*.

Solution A: *Buffer*

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
35	70	30
40	70	30
42	95	5
50	95	5

System suitability solution: 0.5 mg/mL of USP Famciclovir System Suitability Mixture RS in *Diluent*

Standard solution: 0.5 µg/mL of USP Famciclovir RS, 1 µg/mL of USP Famciclovir Related Compound A RS, and 3 µg/mL of USP Famciclovir Related Compound B RS in *Diluent*

Sample solution: 500 µg/mL of Famciclovir in *Diluent*. [Note—The solution is stable for 15 h at 6°.]

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between the propionyl famciclovir and 6-chloro famciclovir peaks, *System suitability solution*

Column efficiency: NLT 20,000 theoretical plates for the famciclovir peak, *System suitability solution*

Tailing factor: NMT 1.5 for the famciclovir peak, *System suitability solution*

Relative standard deviation: NMT 5.0% for the famciclovir peak; NMT 10.0% for the famciclovir related compound A and famciclovir related compound B peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

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

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

C_S = concentration of USP Famciclovir RS in the *Standard solution* (µg/mL)

C_U = concentration of Famciclovir in the *Sample solution* (µg/mL)

F = relative response factor for each individual impurity (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Dimethylaminopyridine[a]	0.12	0.59	0.05
Penciclovir[b]	0.16	0.29	0.50
Famciclovir related compound A[c]	0.19	1.3	0.20
Famciclovir related compound B[d]	0.51	1.1	0.60
N-7 Isomer of famciclovir[e]	0.89	0.92	0.10
Famciclovir	1.0	—	—
N-Acetyl famciclovir[f]	1.05	0.56	0.10
Deoxychloro famciclovir[g]	1.26	0.87	0.20
Propionyl famciclovir[h]	1.32	0.88	0.15
6-Chloro famciclovir[i]	1.36	0.85	0.15
6-Alkylamino famciclovir[j]	1.83	0.46	0.10
Any other unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] *N*,*N*-Dimethylpyridin-4-amine.

[b] 9-[4-Hydroxy-3-(hydroxymethyl)butyl]guanine.

[c] 2-[2-(2-Amino-9*H*-purin-9-yl)ethyl]propane-1,3-diol.

[d] 4-(2-Amino-9*H*-purin-9-yl)-2-(hydroxymethyl)butyl acetate.

[e] 2-[2-(2-Amino-7*H*-purin-7-yl)ethyl]propane-1,3-diyl diacetate.

[f] 2-[2-(2-Acetamido-9*H*-purin-9-yl)ethyl]propane-1,3-diyl diacetate.

[g] 4-(2-Amino-9*H*-purin-9-yl)-2-(chloromethyl)butyl acetate.

[h] 2-(Acetoxymethyl)-4-(2-amino-9*H*-purin-9-yl)butyl propionate.

[i] 2-[2-(2-Amino-6-chloro-9*H*-purin-9-yl)ethyl]propane-1,3-diyl diacetate.

[j] 2-(2-{6-[4-Acetoxy-3-(acetoxymethyl)butylamino]-2-amino-9*H*-purin-9-yl}ethyl)propane-1,3-diyl diacetate.

- **Organic Impurities, Procedure 2**

Buffer: 3.85 g/L of ammonium acetate in water. Adjust with acetic acid to a pH of 5.0.

Solution A: 4.14 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 2.2.

Solution B: Acetonitrile and *Solution A* (25:75)

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	99.5	0.5

Time (min)	Solution A (%)	Solution B (%)
5	92	8
30	92	8
65	20	80
70	20	80
70.1	99.5	0.5
79	99.5	0.5

Diluent: Acetonitrile and *Buffer* (5:95)

System suitability solution: 1 mg/mL of USP Famciclovir RS, 1 µg/mL of USP Famciclovir Related Compound A RS, 5 µg/mL of USP Famciclovir Related Compound B RS, and 4 µg/mL of USP Famciclovir Related Compound C RS prepared as follows. Dissolve an appropriate amount of Standard in 5% of the final volume of acetonitrile, and dilute with *Buffer* to final volume.

Standard stock solution: 1 mg/mL of USP Famciclovir RS prepared as follows. Dissolve USP Famciclovir RS in 5% of the final volume of acetonitrile, and dilute with *Buffer* to final volume.

Standard solution: 1 µg/mL of USP Famciclovir RS in *Diluent* from the *Standard stock solution*

Sensitivity solution: 0.3 µg/mL of USP Famciclovir RS in *Diluent* from the *Standard solution*

Sample solution: 1 mg/mL of Famciclovir prepared as follows. Dissolve Famciclovir in 5% of the final volume of acetonitrile, and dilute with *Buffer* to final volume.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 15-cm; 5-µm packing L60

Temperatures

Column: 35°

Sample: 6°

Flow rate: 1.5 mL/min

Injection volume: 25 µL

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

Suitability requirements

Resolution: NLT 0.6 between the famciclovir and famciclovir related compound C peaks; the famciclovir related compound A peak is resolved from peaks due to the solvent front, *System suitability solution*

Relative standard deviation: NMT 20% for famciclovir related compound A; NMT 10% for famciclovir related compound B; and NMT 10% for famciclovir related compound C, *System suitability 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 Famciclovir taken:

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

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

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

C_S = concentration of USP Famciclovir RS in the *Standard solution* (µg/mL)

C_U = concentration of Famciclovir in the *Sample solution* (µg/mL)

F = relative response factor for each individual impurity (see *Table 4*)

Acceptance criteria: See *Table 4*. Disregard peaks less than 0.03%.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Famciclovir related compound A[a]	0.09	1.4	0.1
Famciclovir related compound B[b]	0.28	1.1	0.5
Famciclovir malonate[c]	0.35	1.1	0.1
Acetoxybutyl aminopurine[d]	0.41	1.3	0.1
Hydroxy famciclovir[e]	0.43	1.0	—[f]
Famciclovir methoxycarbonyl analog[g]	0.54	0.96	0.1
N-7 Isomer of famciclovir[h]	0.88	0.69	0.1
Famciclovir related compound C[i]	0.94	1.2	0.4
Famciclovir	1.00	—	—
N^7-Acetyl famciclovir[j]	1.50	0.46	—[f]
N^2 Acetyl famciclovir[k]	1.67	0.55	—[f]
6-Methoxy famciclovir[l]	1.76	0.18	—[f]
6-Chloro famciclovir[m]	2.01	0.66	0.1
Famciclovir 8,N^2-dimer[n]	2.18	1.0	0.2
Famciclovir 6,6-dimer[o]	2.29	0.53	0.07
Any other unspecified impurity	—	1.0	0.06
Total impurities	—	—	0.8

[a] 2-[2-(2-Amino-9*H*-purin-9-yl)ethyl]propane-1,3-diol.

[b] 4-(2-Amino-9*H*-purin-9-yl)-2-(hydroxymethyl)butyl acetate.

[c] Dimethyl 2-[2-(2-amino-9*H*-purin-9-yl)ethyl]malonate.

[d] 4-(2-Amino-9*H*-purin-9-yl)butyl acetate.

[e] 2-[2-(2-Amino-9*H*-purin-9-yl)ethyl]-2-hydroxypropane-1,3-diyl diacetate.

[f] No individual limit but included in total impurities.

[g] Methyl 2-(acetoxymethyl)-4-(2-amino-9*H*-purin-9-yl)butanoate.

[h] 2-[2-(2-Amino-7*H*-purin-7-yl)ethyl]propane-1,3-diyl diacetate.

[i] 4-(2-Amino-9*H*-purin-9-yl)-2-methylbutyl acetate.

[j] 2-{2-[7-Acetyl-2-amino-7*H*-purin-9(8*H*)-yl]ethyl}propane-1,3-diyl diacetate.

[k] 2-[2-(2-Acetamido-9*H*-purin-9-yl)ethyl]propane-1,3-diyl diacetate.

[l] 2-[2-(2-Amino-6-methoxy-9*H*-purin-9-yl)ethyl]propane-1,3-diyl diacetate.

[m] 2-[2-(2-Amino-6-chloro-9*H*-purin-9-yl)ethyl]propane-1,3-diyl diacetate.

[n] 2-{2-[2-(1-{9-[4-Acetoxy-3-(acetoxymethyl)butyl]-2-amino-9*H*-purin-8-yl}ethylamino)-9*H*-purin-9-yl]ethyl}propane-1,3-diyl diacetate.

[o] 2,2'-[2,2'-(2,2'-Diamino-6,6'-bipurine-9,9'-diyl)bis(ethane-2,1-diyl)]bis(propane-3,2,1-triyl) tetraacetate.

• **Famciclovir Related Compound E and Famciclovir Related Compound F**

Perform this test if *Organic Impurities*, *Procedure 2* is used.

Buffer: 15.6 g/L of monobasic sodium phosphate in water. Adjust with 0.1 M sodium hydroxide to a pH of 4.5 ± 0.1 before final dilution.

Solution A: Methanol and *Buffer* (20:80)

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

Mobile phase: See *Table 5*.

Table 5

Time (min)	Solution A (%)	Solution B (%)
0	100	0
6	100	0
10	0	100
14	0	100
18	100	0
25	100	0

Standard stock solution: 28 µg/mL each of USP Famciclovir Related Compound E RS and USP Famciclovir Related Compound F RS prepared as follows. Transfer 7 mg of USP Famciclovir Related Compound E RS and USP Famciclovir Related Compound F RS to a 250-mL volumetric flask. Add 1 mL of 0.1 M sodium hydroxide and 50 mL of *Solution A*. Sonicate to dissolve, cool to room temperature, and dilute with *Solution A* to volume.

Standard solution: 0.28 µg/mL each of USP Famciclovir Related Compound E RS and USP Famciclovir Related Compound F RS in *Solution A* from the *Standard stock solution*

Sample solution: 30 mg/mL of Famciclovir in *Solution A*

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

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

Column temperature: 30°

Flow rate: 1.7 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 5.0 between famciclovir related compound E and famciclovir related compound F

Tailing factor: NMT 2.0 for the famciclovir related compound F peak

Relative standard deviation: NMT 5.0% for famciclovir related compound F

Signal-to-noise ratio: NLT 30 for the famciclovir related compound E and famciclovir related compound F peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate, in ppm, the amount of famciclovir related compound E and famciclovir related compound F in the portion of Famciclovir taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 10^6$$

r_U = peak response of famciclovir related compound E or famciclovir related compound F from the *Sample solution*

r_S = peak response of famciclovir related compound E or famciclovir related compound F from the *Standard solution*

C_S = concentration of USP Famciclovir Related Compound E RS or USP Famciclovir Related Compound F RS in the *Standard solution* (µg/mL)

C_U = concentration of Famciclovir in the *Sample solution* (µg/mL)

Acceptance criteria: NMT 10 ppm for famciclovir related compound E and NMT 5 ppm for famciclovir related compound F

SPECIFIC TESTS

• **Loss on Drying** ⟨731⟩

Analysis: Dry under vacuum at a pressure not exceeding 20 mm of mercury at 60° for 2 h.

Acceptance criteria: NMT 0.5%

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

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Store in a well-closed container at controlled room temperature.

• **Labeling:** If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.

• **USP Reference Standards** ⟨11⟩

USP Famciclovir RS

USP Famciclovir Related Compound A RS

[2-[2-(2-Amino-9*H*-purin-9-yl)ethyl]propane-1,3-diol] hydrochloride.

$C_{10}H_{15}N_5O_2 \cdot HCl$ 273.72

USP Famciclovir Related Compound B RS

4-(2-Amino-9*H*-purin-9-yl)-2-(hydroxymethyl)butyl acetate.

$C_{12}H_{17}N_5O_3$ 279.30

USP Famciclovir Related Compound C RS

4-(2-Amino-9*H*-purin-9-yl)-2-methylbutyl acetate.

$C_{12}H_{17}N_5O_2$ 263.30

USP Famciclovir Related Compound E RS

2-Aminopurine.

$C_5H_5N_5$ 135.13

USP Famciclovir Related Compound F RS

2-Amino-6-chloropurine.

$C_5H_4ClN_5$ 169.57

USP Famciclovir System Suitability Mixture RS

Contains famciclovir, propionyl famciclovir, and 6-chloro famciclovir.

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

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

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 39(1)

Current DocID: GUID-B1B3CB5D-8F07-4960-AA19-6B0FC0E7D199_4_en-US

DOI: https://doi.org/10.31003/USPNF_M32594_04_01

DOI ref: 118c3