Cidofovir

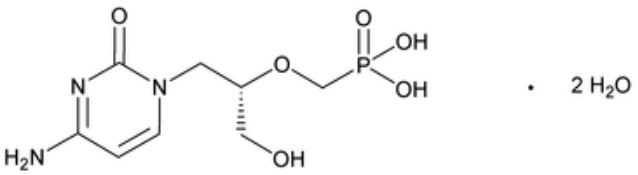
Type of Posting	Revision Bulletin
Posting Date	31–May–2019
Official Date	01–Jun–2019
Expert Committee	Chemical Medicines Monographs 1
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Cidofovir monograph. The purpose for the revision is to delete the *Residue on Ignition* test based on the comments received with supporting data indicating the test is not suitable for phosphoric compounds.

The Cidofovir Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Shankari Shivaprasad, Senior Scientific Liaison–Team Leader (301-230-7426 or sns@usp.org).

Cidofovir



$C_8H_{14}N_3O_6P \cdot 2H_2O$ 315.22
Phosphonic acid, [[2-(4-amino-2-oxo-1(2*H*)-pyrimidyl)-1-(hydroxymethyl)ethoxy]methyl]-, dihydrate, (*S*)-;
1-[(*S*)-3-Hydroxy-2-(phosphonylmethoxy)propyl]cytosine dihydrate [149394-66-1].
Anhydrous
$C_8H_{14}N_3O_6P$ 279.19
[113852-37-2].

DEFINITION

Cidofovir contains NLT 98.0% and NMT 102.0% of cidofovir ($C_8H_{14}N_3O_6P$), calculated on the anhydrous basis.

IDENTIFICATION

• **A. Infrared Absorption** ⟨197K⟩
• **B.** The retention time of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

[Note—Solutions containing cidofovir are stable at room temperature for 8 h.]
Solution A: Acetonitrile and water (40:60)
Buffer: Dissolve 1.2 g of dibasic ammonium phosphate and 2.0 g of tetrabutylammonium phosphate in 1 L of water. Adjust with ammonium hydroxide to a pH of 9.2.
Mobile phase: *Solution A* and *Buffer* (22:78)
Standard solution: 0.1 mg/mL of USP Cidofovir RS in water
Sample solution: 0.1 mg/mL of Cidofovir in water
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 274 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: 0.8–1.5
Relative standard deviation: NMT 0.73%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of cidofovir ($C_8H_{14}N_3O_6P$) in the portion of Cidofovir 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 Cidofovir RS in the *Standard solution* (mg/mL)
C_U = concentration of Cidofovir in the *Sample solution* (mg/mL)

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

IMPURITIES

Delete the following:

▲• **Residue on Ignition** ⟨281⟩
Analysis: Perform the ignition at 850 ± 50°; silica crucibles are suitable.
Acceptance criteria: NMT 0.5%▲ (RB 1-Jun-2019)

• **Organic Impurities**

[Note—Solutions containing cidofovir are stable at room temperature for 8 h.]
Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay* with a run time four times the retention time of cidofovir.
System suitability solution: 1.5 µg/mL each of USP Cidofovir Related Compound A RS and USP Cidofovir Related Compound B RS in water
Standard solution: 0.001 mg/mL of USP Cidofovir RS in water
Sample solution: 1 mg/mL of Cidofovir in water
System suitability
Samples: *System suitability solution* and *Standard solution*
[Note—See *Table 1* for relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between cidofovir related compound A and cidofovir related compound B, *System suitability solution*
Relative standard deviation: NMT 5%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each individual impurity in the portion of Cidofovir 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 cidofovir from the *Standard solution*
C_S = concentration of USP Cidofovir RS in the *Standard solution* (mg/mL)
C_U = concentration of Cidofovir in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 1*)

Acceptance criteria
Individual impurities: See *Table 1*. Disregard any impurity peaks less than 0.02%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Cidofovir diol analog[a]	0.30	1.3	0.15
Cidofovir related compound A	0.54	0.74	0.15
Cidofovir related compound B	0.63	0.69	0.15
Cidofovir	1.0	—	—
Cidofovir uracil analog[b]	1.4	0.56	0.15
Bromocidofovir[c]	2.0	0.62	0.15
Any individual unspecified impurity	—	1.0	0.10

Table 1 *(continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Total impurities	—	—	1.0

[a] 1-[(*S*)-2,3-Dihydroxypropyl]cytosine.
[b] 1-[(*S*)-3-Hydroxy-2-(phosphonomethoxy)propyl]uracil.
[c] 1-[(*S*)-3-Bromo-2-(phosphonomethoxy)propyl]cytosine.

• **ENANTIOMERIC PURITY**

Mobile phase: Dissolve 1.0 g of cupric sulfate in 1 L of water. Add 1.32 g of L-phenylalanine and sonicate to dissolve.

System suitability solution: 1 mg/mL of USP Cidofovir RS and 0.01 mg/mL of USP Cidofovir Enantiomer RS in water

Standard solution: 0.01 mg/mL of USP Cidofovir Enantiomer RS in water

Sample solution: 1 mg/mL of Cidofovir in water

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

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

Temperatures

Autosampler: 15°

Column: 15°

Flow rate: 0.5 mL/min

Injection volume: 10 µL

Run time: Two times the retention time of cidofovir

System suitability

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

[NOTE—Typical relative retention times for cidofovir and cidofovir enantiomer are 1.0 and 1.3, respectively.]

Suitability requirements

Resolution: NLT 2.0 between cidofovir and cidofovir enantiomer, *System suitability solution*

Relative standard deviation: NMT 5%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of cidofovir enantiomer in the portion of Cidofovir taken:

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

r_U = peak response of cidofovir enantiomer from the *Sample solution*

r_S = peak response of cidofovir enantiomer from the *Standard solution*

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

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

Acceptance criteria: NMT 1.0%

SPECIFIC TESTS

• **MICROBIAL ENUMERATION TESTS** ⟨61⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨62⟩**:** The total aerobic bacterial count is NMT 10^2 cfu/g. The total combined molds and yeasts count is NMT 10^1 cfu/g.

• **WATER DETERMINATION** ⟨921⟩**,** *Method I, Method Ia*

Sample: 0.2 g

Acceptance criteria: 10.5%–12.5%

• **PH** ⟨791⟩

Sample solution: 1 g in 100 mL of water

Acceptance criteria: 2.5–4.5

ADDITIONAL REQUIREMENTS

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

• **USP REFERENCE STANDARDS** ⟨11⟩

USP Cidofovir RS

USP Cidofovir Enantiomer RS

1-[(*R*)-3-Hydroxy-2-(phosphonomethoxy)propyl] cytosine dihydrate.

$C_8H_{14}N_3O_6P \cdot 2H_2O$ 315.22

USP Cidofovir Related Compound A RS

1-[(*S*)-3-Hydroxy-2-(*O*-ethylphosphonomethoxy)propyl] cytosine.

$C_{10}H_{18}N_3O_6P$ 307.24

USP Cidofovir Related Compound B RS

1-[(*S*)-3-Hydroxy-2-(*O*,*O*-diethylphosphonomethoxy) propyl]cytosine hydrochloride.

$C_{12}H_{22}N_3O_6P \cdot HCl$ 371.76