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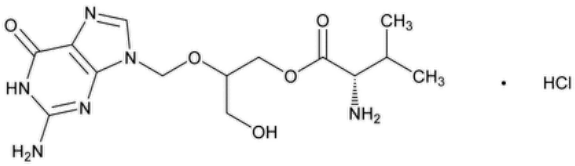
Valganciclovir Hydrochloride



$C_{14}H_{22}N_6O_5 \cdot HCl$ 390.82

L-Valine, ester with 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine, monohydrochloride.

L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride CAS RN®: 175865-59-5; UNII: 4P3T9QF9NZ.

DEFINITION

Valganciclovir Hydrochloride contains NLT 97.0% and NMT 102.0% of valganciclovir hydrochloride ($C_{14}H_{22}N_6O_5 \cdot HCl$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

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

• **B.** The retention times of valganciclovir diastereomeric peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

• **C. Identification Tests—General ⟨191⟩, *Chloride*:** Meets the requirements

ASSAY

• **Procedure**

Buffer: 11.5 g/L of monobasic ammonium phosphate in water. Adjust with phosphoric acid (85%) to a pH of 2.8 ± 0.2 prior to final dilution.

Mobile phase: Methanol and *Buffer* (8:92)

System suitability solution: 0.2 mg/mL of USP Valganciclovir Hydrochloride RS and 0.01 mg/mL of USP Methoxymethylguanine RS in 0.001 N hydrochloric acid

Standard solution: 0.2 mg/mL of USP Valganciclovir Hydrochloride RS in 0.001 N hydrochloric acid

Sample solution: 0.2 mg/mL of Valganciclovir Hydrochloride in 0.001 N hydrochloric acid

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

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

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 2.5 times the retention time of valganciclovir diastereomer peak 2

System suitability

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

[Note—The relative retention times for methoxymethylguanine and valganciclovir diastereomer peak 1 are 0.93 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.0 between methoxymethylguanine and valganciclovir diastereomer peak 1; NLT 3.0 between valganciclovir diastereomer peak 1 and valganciclovir diastereomer peak 2, *System suitability solution*

Tailing factor: NMT 2.0 for valganciclovir diastereomer peak 2, *System suitability solution*

Relative standard deviation: NMT 1.0% for the sum of valganciclovir diastereomer peak 1 and valganciclovir diastereomer peak 2, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of valganciclovir hydrochloride ($C_{14}H_{22}N_6O_5 \cdot HCl$) in the portion of Valganciclovir Hydrochloride taken:

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

r_U = sum of the peak responses of valganciclovir diastereomer peaks 1 and 2 from the *Sample solution*

r_S = sum of the peak responses of valganciclovir diastereomer peaks 1 and 2 from the *Standard solution*

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

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

Acceptance criteria: 97.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.10%
- **Limit of Isopropyl Alcohol**

Internal standard solution: Transfer 0.1 mL of 1,4-dioxane to a 100-mL volumetric flask and dilute with dimethylformamide to volume.

Standard stock solution: Transfer 1.0 mL of isopropyl alcohol and 0.1 mL of toluene to a 100-mL volumetric flask, and dilute with dimethylformamide to volume. [Note—Toluene is used to verify the system suitability.]

Standard solution: Combine 2.0 mL of the *Internal standard solution* and 0.1 mL of the *Standard stock solution*.

Sample solution: Transfer 90–100 mg of Valganciclovir Hydrochloride to a vial, add 2.0 mL of the *Internal standard solution*, and mix.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 30-m capillary; coated with 3.0-µm film of phase G43

Carrier gas: Helium

Temperatures

Injection port: 250°

Detector: 300°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	—	40	10
40	25	240	—
240	—	240	15

Flow rate: 10.5 mL/min

Injection volume: 0.5 µL

Injection type: Split, split ratio 1:1

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 8 between 1,4-dioxane and toluene

Relative standard deviation: NMT 15% of the peak area ratio of isopropyl alcohol to 1,4-dioxane

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of isopropyl alcohol in the portion of Valganciclovir Hydrochloride taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak area ratio of isopropyl alcohol to the internal standard from the *Sample solution*

R_S = peak area ratio of isopropyl alcohol to the internal standard from the *Standard solution*

C_S = concentration of isopropyl alcohol in the *Standard solution* (mg/mL)

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

Acceptance criteria: NMT 1.0%

Change to read:

• **Organic Impurities**

Solution A: 11.5 g/L of monobasic ammonium phosphate in water. Adjust with phosphoric acid (85%) to a pH of 2.8 ± 0.2 prior to final dilution.

Solution B: Methanol

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	92	8
5	92	8
15	80	20
30	30	70
30.1	92	8
45	92	8

System suitability solution: 0.2 mg/mL of USP Valganciclovir Hydrochloride RS and 0.01 mg/mL of USP Methoxymethylguanine RS in 0.001 N hydrochloric acid

Sample solution: 0.2 mg/mL of Valganciclovir Hydrochloride in 0.001 N hydrochloric acid

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

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

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[Note— See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.0 between methoxymethylguanine and valganciclovir diastereomer peak 1; NLT 3.0 between valganciclovir diastereomer peak 1 and valganciclovir diastereomer peak 2

Tailing factor: NMT 2.0 for valganciclovir diastereomer peak 2

Analysis

Sample: *Sample solution*

Calculate the percentage of any individual impurity in the portion of Valganciclovir Hydrochloride taken:

$$\text{Result} = \{(r_i/F_i)/[r_S + \Sigma(r_i/F_i)]\} \times 100$$

r_i = peak response for each individual impurity in the *Sample solution*

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

r_S = sum of the peak responses for valganciclovir diastereomers from the *Sample solution*

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Guanine[a]	0.28	1.9	0.25
Ganciclovir[b]	0.42	1.4	1.5
Methoxymethylguanine	0.81	1.0	0.3
Valganciclovir diastereomer peak 1	0.86	—	—
Valganciclovir diastereomer peak 2	1.0	—	—
Isovalganciclovir[c]	1.26	1.0	0.5
Monoacetoxyganciclovir[d]	1.36	1.3	0.15
Isomonochloroganciclovir[e]	1.47	1.3	0.1
Monochloroganciclovir[f]	1.52	1.4	0.1
Bis-valine ester of ganciclovir[g]	1.61	0.71	0.1
Homolog of valganciclovir[h]	1.66	1.0	0.25
Ganciclovir monopropionate[i]	2.09	1.1	0.15
Valganciclovir dimer (stereoisomer A)[j]	2.49	1.0	0.1
Valganciclovir dimer (stereoisomer B)[j]	2.52	1.0	0.1
Valganciclovir dimer (stereoisomer C)[j]	2.54	1.0	0.1
Any individual unspecified impurity	—	1.0	0.1
Total impurities[k]	—	—	3.0

[a] 2-Amino-1,9-dihydro-6*H*-purin-6-one.

[b] 2-Amino-9-{[(1,3-dihydroxypropan-2-yl)oxy]methyl}-1,9-dihydro-6*H*-purin-6-one.

[c] ▲3-[(2-Amino-6-oxo-1,6-dihydropurin-9-yl)methoxy]-2-hydroxypropyl L-valinate hydrochloride.▲ (ERR 1-Sep-2023)

[d] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl acetate.

[e] 2-Amino-9-[(2-chloro-3-hydroxypropoxy)methyl]-1,9-dihydro-6*H*-purin-6-one.

[f] 2-Amino-9-{[(1-chloro-3- hydroxypropan-2-yl)oxy]methyl}-1,9-dihydro-6*H*-purin-6-one.

[g] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]propane-1,3-diyl (2*S*,2'*S*)-bis(2-amino-3-methylbutanoate).

[h] 2-{[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]methoxy}-3-hydroxypropyl L-valinate hydrochloride.

[i] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl propionate.

[j] 2-{[2-({[(7-[({1-[(L-Valyl)oxy]-3-hydroxypropan-2-yl}oxy)methyl]-4-oxo-4,5,6,7-tetrahydro-3*H*-pyrrolo[2,3-d]pyrimidin-2-yl)amino]methyl}amino)-6-oxo-1,6-dihydro-9*H*-purin-9-yl]methoxy}-3-hydroxypropyl L-valinate dihydrochloride.

[k] Includes impurities from the tests for *Organic Impurities* and *Limit of Ganciclovir Mono-N-methyl Valinate*.

- **Limit of Ganciclovir Mono-*N*-methyl Valinate**

Solution A: 2.5 mL/L of triethylamine in water. Adjust with trifluoroacetic acid to a pH of 3.0 ± 0.05.

Solution B: Methanol

Mobile phase: See *Table 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	93	7
10	93	7
20	70	30
20.1	93	7
35	93	7

Standard solution: 0.2 mg/mL of USP Valganciclovir Hydrochloride RS in 0.001 N hydrochloric acid

Sample solution: 0.2 mg/mL of Valganciclovir Hydrochloride in 0.001 N hydrochloric acid

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L11

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[Note— The relative retention times for valganciclovir diastereomeric peak 2 and ganciclovir mono-*N*-methyl valinate are 1.0 and 1.2, respectively.]

Suitability requirements

Resolution: NLT 1.3 between valganciclovir diastereomeric peak 1 and valganciclovir diastereomeric peak 2

Tailing factor: NMT 1.5 for valganciclovir diastereomer peak 2

Analysis

Sample: *Sample solution*

Calculate the percentage of ganciclovir mono-*N*-methyl valinate in the portion of Valganciclovir Hydrochloride taken:

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

r_U = sum of the peak responses of ganciclovir mono-*N*-methyl valinate (diastereomers) from the *Sample solution*

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

Acceptance criteria: See *Table 5*.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Valganciclovir diastereomer peak 1	0.92	—
Valganciclovir diastereomer peak 2	1.0	—
Ganciclovir mono-*N*-methyl valinate diastereomer peak 1[a,b]	1.1	0.3
Ganciclovir mono-*N*-methyl valinate diastereomer peak 2[a,b]	1.2	

[a] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl methyl-L-valinate.

[b] Reported as the sum of diastereomers.

• **Enantiomeric Purity of Valganciclovir**

Mobile phase: 16.2 g/L of perchloric acid in water

System suitability solution: 0.2 mg/mL of USP Valganciclovir Hydrochloride RS and 0.02 mg/mL of USP D-Valganciclovir RS in 0.001 N hydrochloric acid

Sample solution: 0.2 mg/mL of Valganciclovir Hydrochloride in 0.001 N hydrochloric acid

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.0-mm × 15-cm; 5-µm packing L66

Temperature: Ambient

Flow rate: 0.8 mL/min

Injection volume: 20 µL

System suitability

Sample: *System suitability solution*

[Note—The typical retention times for the two D-valganciclovir diastereomer peaks and valganciclovir diastereomer peaks 1 and 2 are 8.9, 9.6, 13.2, and 14.7 min, respectively.]

Suitability requirements

Resolution: NLT 2.5 between the second peak of the D-valganciclovir pair and valganciclovir diastereomer peak 1

Analysis

Sample: *Sample solution*

Calculate the percentage of enantiomeric purity in the portion of Valganciclovir Hydrochloride taken:

$$\text{Result} = [r_S/(r_S + r_{IM})] \times 100$$

r_S = sum of the peak responses of valganciclovir diastereomer peaks 1 and 2 (*R* and *S* esters of L-valine) from the *Sample solution*

r_{IM} = sum of the peak responses of the D-valganciclovir diastereomeric peaks (*R* and *S* esters of D-valine) from the *Sample solution*

Acceptance criteria: NLT 97.0%

SPECIFIC TESTS

• **Diastereomer Ratio**

Analysis:

Using the chromatogram for the *Sample solution* in the test for *Organic Impurities*, calculate the percentage of valganciclovir diastereomers (*R* and *S* esters of L-valine):

$$\text{Result} = [r_A/(r_A + r_B)] \times 100$$

$$\text{Result} = [r_B/(r_A + r_B)] \times 100$$

r_A = peak response for valganciclovir diastereomer peak 1

r_B = peak response for valganciclovir diastereomer peak 2

Acceptance criteria: The diastereomer ratio is 45:55–55:45

- **Water Determination ⟨921⟩, *Method I*:** NMT 8.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **USP Reference Standards ⟨11⟩**

USP Methoxymethylguanine RS
2-Amino-9-(methoxymethyl)-1,9-dihydro-6*H*-purin-6-one.
$C_7H_9N_5O_2$ 195.18

USP D-Valganciclovir RS
2-(*RS*)-[(2-Amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl D-valinate hydrochloride.
$C_{14}H_{22}N_6O_5 \cdot HCl$ 390.83

USP Valganciclovir Hydrochloride RS

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

Topic/Question	Contact	Expert Committee
VALGANCICLOVIR HYDROCHLORIDE	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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