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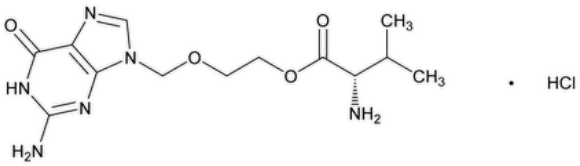
Valacyclovir Hydrochloride



$C_{13}H_{20}N_6O_4 \cdot HCl$ 360.80

L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy] ethyl ester, monohydrochloride;

L-Valine, ester with 9-[(2-hydroxyethoxy)methyl]guanine, monohydrochloride CAS RN®: 124832-27-5; UNII: G447S0T1VC.

DEFINITION

Valacyclovir Hydrochloride contains NLT 95.0% and NMT 102.0% of valacyclovir hydrochloride ($C_{13}H_{20}N_6O_4 \cdot HCl$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

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

Change to read:

• **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride***

Sample solution: 50 mg/mL ▲of Valacyclovir Hydrochloride▲ (USP 1-May-2023) in water

Acceptance criteria: Meets the requirements

ASSAY

Change to read:

• **Procedure**

Mobile phase: Methanol, water, and perchloric acid▲(5: 95: 0.5)▲ (USP 1-May-2023)

Standard solution: 0.5 mg/mL of USP Valacyclovir Hydrochloride RS in 0.05 M hydrochloric acid. [Note—USP Valacyclovir Hydrochloride RS contains a detectable quantity of D-valacyclovir.]

Sample solution: 0.5 mg/mL of Valacyclovir Hydrochloride in 0.05 M hydrochloric acid

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4-mm × 15-cm; 5-µm packing L66

Column temperature: 10°

Flow rate: 0.75 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between valacyclovir hydrochloride and D-valacyclovir

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of valacyclovir hydrochloride ($C_{13}H_{20}N_6O_4 \cdot HCl$) in the portion of Valacyclovir Hydrochloride taken:

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

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

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

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

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

Acceptance criteria: 95.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **Residue on Ignition** ⟨281⟩

Sample: 2 g

Acceptance criteria: NMT 0.1%

Delete the following:

▲• **Limit of Palladium** (if present)▲ (USP 1-May-2023)

Change to read:

• **Organic Impurities, Procedure 1** (for related compounds E, F, and G)

Developing solvent: Methylene chloride, methanol, tetrahydrofuran, and ammonia solution (54:34:12:3)

Standard stock solution: Transfer 5 mg each of USP Valacyclovir Related Compound D RS and USP Valacyclovir Related Compound G RS, 10 mg of USP Valacyclovir Related Compound E RS, and 8.4 mg of USP Valacyclovir Related Compound F RS into a 10-mL volumetric flask. Add 2 mL of water with swirling, followed by 6 mL of alcohol, and sonicate for 20 min. Allow to cool, and dilute with alcohol to volume.

Standard solutions: Transfer 1.0 and 0.5 mL of the *Standard stock solution* into two separate 10-mL volumetric flasks. Dilute the solution in both flasks with alcohol to volume.

Sample solution: Transfer 250 mg of Valacyclovir Hydrochloride into a 5-mL volumetric flask. Add 2 mL of water, and sonicate for 20 min to dissolve. Add alcohol to about 95% of the flask volume. Cool, and dilute with alcohol to volume. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: TLC

Detector: UV, long and short wavelength

Plate: TLC plate coated with a 0.25-mm layer of chromatographic silica gel mixture. Prewash the plate with methanol.

Developing distance: NLT 7 cm from the origin

Application volume: 4 µL

Analysis

Samples: *Standard solutions* and *Sample solution*

Develop the plate to the specified distance. Remove the plate from the solvent chamber, and allow to dry. Examine the plate under short-wavelength UV light, and visually estimate the valacyclovir related compounds E and G in the sample using the appropriate standard spots. The chromatograms obtained with the *Standard solutions* each show three clearly separated spots due to valacyclovir related compounds D, E, and G. Spray the plate with 0.01% fluorescamine in ethylene dichloride, and examine the sprayed plate under long-wavelength UV light to estimate the level of valacyclovir related compound F in the sample using the appropriate standard spot. The relative R_F values and limits for each impurity are provided in *Table 1*.

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative R_F Value	Acceptance Criteria, NMT (%)
Valacyclovir hydrochloride	1	—
Valacyclovir related compound D[a]	1.1	—
Valacyclovir related compound E[b]	1.3	0.2

Name	Relative R_F Value	Acceptance Criteria, NMT (%)
Valacyclovir related compound F[c]	1.8	0.1
Valacyclovir related compound G[d]	1.9	0.05

[a] This impurity is quantitated using *Procedure 2*.

[b] ▲2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-benzyloxycarbonyl-L-valinate.▲ (USP 1-May-2023)

[c] ▲2-Hydroxyethyl valinate 4-methylbenzenesulfonate.▲ (USP 1-May-2023)

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

Change to read:

• **Organic Impurities, Procedure 2**

Solution A: 0.3% w/w trifluoroacetic acid solution in water

Solution B: 0.3% w/w trifluoroacetic acid solution in methanol

Diluent: Alcohol and water▲(20:80)▲ (USP 1-May-2023)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	90	10
5	90	10
35	60	40
35.01	90	10
45	90	10

System suitability solution: 0.4 mg/mL of USP Valacyclovir Hydrochloride RS, 0.8 µg/mL of USP Valacyclovir Related Compound C RS, and 1.6 µg/mL of USP Acyclovir Related Compound A RS in *Diluent*

Sample solution: 0.4 mg/mL of Valacyclovir Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

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

Column temperature: 15°

Flow rate: 0.8 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between valacyclovir and valacyclovir related compound C; NLT 1.5 between valacyclovir related compound C and acyclovir related compound A

Tailing factor: NMT 1.5 for the valacyclovir hydrochloride peak

Analysis

Sample: *Sample solution*

Calculate the percentage of each individual impurity in the portion of Valacyclovir Hydrochloride taken:

Result = $(r_U/r_T) \times 100$

r_U = peak response of any impurity in the *Sample solution*

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

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Guanine (near solvent front)[a] ▲▲ (USP 1-May-2023)	0.31	—
Acyclovir[a,b]	0.42	—
Acyclovir alaninate[c]	0.54	0.2
Valacyclovir	1.00	—
Valacyclovir related compound C[d]	1.06	0.3
Acyclovir related compound A[a,e]	1.09	—
Valacyclovir related compound D[f]	1.17	0.5
Acyclovir isoleucinate[g]	1.30	0.2
N-Formyl valacyclovir[h]	1.61	0.8
Guaninyl valacyclovir[i]	1.66	0.2
Bis valacyclovir[j]	2.0	0.3
Any unspecified impurity	—	0.1

[a] This impurity is quantitated by the *Procedure 3* method.

[b] ▲9-[(2-Hydroxyethoxy)methyl]guanine.▲ (USP 1-May-2023)

[c] ▲2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-alaninate.▲ (USP 1-May-2023)

[d] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-methyl-L-valinate.

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

[f] 2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-ethyl-L-valinate.

[g] ▲2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-isoleucinate.▲ (USP 1-May-2023)

[h] ▲2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-formyl-L-valinate.▲ (USP 1-May-2023)

[i] ▲2-[(6-Oxo-2-{[(6-oxo-6,9-dihydro-1*H*-purin-2-yl)aminomethyl]amino}-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl L-valinate.▲ (USP 1-May-2023)

[j] ▲{Methylenebis[azanediyl(6-oxo-1,6-dihydro-9*H*-purine-2,9-diyl)methyleneoxyethan-2,1-diyl]} di-L-valinate.▲ (USP 1-May-2023)

Change to read:

• **Organic Impurities, Procedure 3**

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Valacyclovir Hydrochloride taken:

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

r_U = peak response of guanine plus acyclovir or acyclovir acetate or D-valacyclovir from the *Sample solution*

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

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

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

F = relative response factor (see *Table 4*)

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Guanine and acyclovir▲▲ (USP 1-May-2023) [a]	0.18	1.51	2.0
Acyclovir related compound A[b]	0.42	1.12	0.2
D-Valacyclovir[c]	0.55	1.0	3.0
Valacyclovir	1.0	—	—

a ▲9-[(2-Hydroxyethoxy)methyl]guanine.▲ (USP 1-May-2023)

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

c ▲2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl D-valinate.▲ (USP 1-May-2023)

Total organic impurities: NMT 5.0% for the sum of all impurities from *Organic Impurities, Procedures 1*, *2*, and *3*

SPECIFIC TESTS

Change to read:

• **Water Determination** ⟨921⟩, *Method I*: For the anhydrous form: NMT 2.0% (200 mg of sample); if labeled as the hydrous form: ▲3.0%▲ (USP 1-May-2023) –11.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and store at a temperature below 30°.

• **Labeling:** Where it is the hydrous form, the label so indicates.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Acyclovir Related Compound A RS

[Note—USP Acyclovir Related Compound A AS is equivalent.]

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

$C_{10}H_{13}N_5O_4$ ▲267.25▲ (USP 1-May-2023)

USP Valacyclovir Hydrochloride RS

USP Valacyclovir Related Compound C RS

2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-methyl-L-valinate hydrochloride.

$C_{14}H_{22}N_6O_4 \cdot HCl$ ▲374.83▲ (USP 1-May-2023)

USP Valacyclovir Related Compound D RS

2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9▲-▲ (USP 1-May-2023) yl)methoxy]ethyl *N*-ethyl-L-valinate.

$C_{15}H_{24}N_6O_4$ ▲352.40▲ (USP 1-May-2023)

USP Valacyclovir Related Compound E RS

▲2-[(2-Amino-6-oxo-1,6-dihydro-9*H*-purin-9-yl)methoxy]ethyl *N*-benzyloxycarbonyl-L-valinate.▲ (USP 1-May-2023)

$C_{21}H_{26}N_6O_6$ ▲458.48▲ (USP 1-May-2023)

USP Valacyclovir Related Compound F RS

▲2-Hydroxyethyl valinate 4-methylbenzenesulfonate.▲ (USP 1-May-2023)

$C_7H_{15}NO_3 \cdot C_7H_8O_3S$ 333.40

USP Valacyclovir Related Compound G RS

N,*N*-Dimethylpyridin-4-amine.

$C_7H_{10}N_2$ 122.17

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

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

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