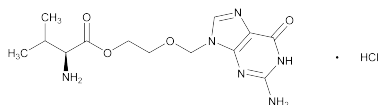


Valacyclovir Hydrochloride



$C_{13}H_{20}N_6O_4 \cdot HCl$ 360.80
L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy] ethyl ester, monohydrochloride;
L-Valine, ester with 9-[(2-hydroxyethoxy)methyl]guanine, monohydrochloride [124832-27-5].

DEFINITION

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

IDENTIFICATION

- A. INFRARED ABSORPTION** (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, Chloride** (191)
Sample solution: 50 mg/mL in water
Acceptance criteria: Meets the requirements

ASSAY

PROCEDURE

Mobile phase: Methanol, water, and perchloric acid (1: 19: 0.1)
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 \times 15-cm; 5- μ m packing L66
Column temperature: 10°
Flow rate: 0.75 mL/min
Injection size: 10 μ L

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): NMT 0.1% on a 2-g sample

Change to read:

- HEAVY METALS, Method II** (231): NMT 20 ppm (RB 1-Dec-2010)

Change to read:

- LIMIT OF PALLADIUM** (if present)
(See *Plasma Spectrochemistry* (730).)
Diluent: Water and nitric acid (99.8: 0.2) (IRA 1-Mar-2012)
Blank solution: *Diluent*
Standard solutions: Dilute with *Diluent* any commercially available standard stock solution of 1 mg/mL of palladium to prepare the following solutions: 0.03 μ g/mL, 0.19 μ g/mL, 0.30 μ g/mL, 0.38 μ g/mL, 0.75 μ g/mL, and 1.13 μ g/mL of palladium. (IRA 1-Mar-2012)

Sample solution: 30 mg/mL (IRA 1-Mar-2012) of Valacyclovir Hydrochloride in *Diluent*

Analytical wavelength: 340.458 nm

Spectrophotometric system: Use a suitable standard inductively coupled plasma–optical emission spectrophotometric system, and construct a calibration curve.

System suitability

Samples: *Blank solution* and *Standard solutions*

Suitability requirements

Relative standard deviation: NMT 10.0%, (IRA 1-Mar-2012) *Standard solutions*

Correlation coefficient: NLT 0.995, (IRA 1-Mar-2012) *Blank solution* and *Standard solutions*

Analysis

Samples: *Blank solution* and *Sample solution*

Calculate the concentration of palladium using the calibration curve corrected for the emission response of the *Blank solution* and sample weight. Calculate the amount of palladium in the Valacyclovir Hydrochloride taken to prepare the *Sample solution*.

Acceptance criteria: NMT 10 ppm

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. (IRA 1-Mar-2012) 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% volume of the flask. Cool, and dilute with alcohol to volume. Pass through a suitable filter of 0.45- μ m pore size.

2 Valacyclovir

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 size: 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 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
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-9H-purin-9-yl)methoxy]ethyl N-[(benzoyloxy)carbonyl]-L-valinate.

^c 2-Hydroxyethyl-L-valinate.

^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 (1:4)

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 size: 10 µL

System suitability

Sample: *System suitability solution*

Resolution: NLT 1.5 between valacyclovir and valacyclovir related compound C, and 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:

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

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*.

• (RB 1-Dec-2010)

Table 3

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

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

^b 2-Amino-1H-purin-6(9H)-one (guanine).

^c 9-[(2-Hydroxyethoxy)methyl]guanine (acyclovir).

^d 9-[(2-Hydroxyethoxy)methyl]guanine L-alaninate.

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

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

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

^h 9-[(2-Hydroxyethoxy)methyl]guanine L-isoleucinate.

ⁱ 9-[(2-Hydroxyethoxy)methyl]guanine N-formyl-L-valinate.

^j [N²-(Guanine-N²-yl)methyl]-9-[(2-hydroxyethoxy)methyl]guanine L-valinate.

^k 2,2'-[Methylenebis[imino(6-oxo-1,6-dihydro-9H-purine-9,2-diy)]methylene-oxy]diethyl di(L-valinate).

• 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 ^{a,b}	0.18	1.51	2.0
Acyclovir related compound A ^c	0.42	1.12	0.2
D-Valacyclovir ^d	0.55	1.0	3.0
Valacyclovir	1.0	—	—

^a 2-Amino-1H-purin-6(9H)-one (guanine).

^b 9-[(2-Hydroxyethoxy)methyl]guanine (acyclovir).

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

^d D-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy] ethyl ester, monohydrochloride.

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, Method I (921):** For the anhydrous form: NMT 2.0% (200 mg of sample); if labeled as the hydrous form: 5.0%–11.0% (RB 1-Dec-2010)

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.
- **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-9H-purin-9-yl)methoxy]ethyl acetate.
 $C_{10}H_{13}N_5O_4$ 267.24
 - USP Valacyclovir Hydrochloride RS
 USP Valacyclovir Related Compound C RS
 2-[(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl N-methyl-L-valinate hydrochloride.
 $C_{14}H_{22}N_6O_4 \cdot HCl$ 374.82
 - USP Valacyclovir Related Compound D RS
 2-[(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl N-ethyl-L-valinate.
 $C_{15}H_{24}N_6O_4$ 352.39
 - USP Valacyclovir Related Compound E RS
 2-[(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl N-benzyloxy)carbonyl]-L-valinate.
 $C_{21}H_{26}N_6O_6$ 458.47
 - USP Valacyclovir Related Compound F RS
 2-Hydroxyethyl valinate para-toluenesulfonate salt.
 $C_7H_{15}NO_3 \cdot C_7H_8O_3S$ 333.40
 - USP Valacyclovir Related Compound G RS
 N,N-Dimethylpyridin-4-amine.
 $C_7H_{10}N_2$ 122.17