

BRIEFING

Valacyclovir Hydrochloride. A new USP Pending monograph is proposed based on validated methods. The liquid chromatographic procedure in the tests for *Organic Impurities, Procedure 1* and *Procedure 2*, and in the *Assay* are based on analyses performed with the Inertsil ODS-3V brand of L1 column. The typical retention time for valacyclovir is 13 min in the test for *Organic Impurities, Procedure 1* and in the *Assay*. The typical retention time of valacyclovir related compound E is 5.4 min in the test for *Organic Impurities, Procedure 2*. The liquid chromatographic procedure in the test for *Enantiomeric Purity* is based on analyses performed with the Crownpak CR (+) brand of L66 column. The typical retention time for the valacyclovir L-isomer is 13.5 min.

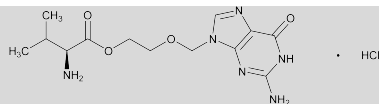
For *Description and Solubility*, refer to *Valacyclovir Hydrochloride* in the *Reference Tables* section of the current *USP–NF*.

(MD-AA: H. Ramanathan, B. Davani.)
 Correspondence Number—C74454

Add the following:

▶Valacyclovir Hydrochloride

Draft 1



$C_{13}H_{20}N_6O_4 \cdot HCl$ 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 98.0% and NMT 102.0% of $C_{13}H_{20}N_6O_4 \cdot HCl$, calculated on the anhydrous basis.

IDENTIFICATION

- A. INFRARED ABSORPTION (197K)**
- B. IDENTIFICATION TESTS—GENERAL, Chloride (191)**
 Sample solution: 10 mg/mL in water

ASSAY

PROCEDURE

Buffer: 1.4 g/L of monobasic potassium phosphate in water. Adjust with 10% phosphoric acid to a pH of 3.5.
Solution A: Acetonitrile and *Buffer* (1:49)
Solution B: Acetonitrile
Mobile phase: See the gradient table.

| Time (min) | Solution A (%) | Solution B (%) |
|------------|----------------|----------------|
| 0 | 100 | 0 |
| 5 | 100 | 0 |
| 32 | 87 | 13 |
| 33 | 100 | 0 |
| 40 | 100 | 0 |

Standard solution: 0.2 mg/mL of USP Valacyclovir Hydrochloride RS in *Solution A*
Sample solution: 0.2 mg/mL of Valacyclovir Hydrochloride in *Solution A*

Chromatographic system

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

Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm; 5-μm packing L1
Flow rate: 1.5 mL/min
Column temperature: 30°
Injection size: 20 μL

System suitability

Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*
 Calculate the percentage of $C_{13}H_{20}N_6O_4 \cdot HCl$ in the portion of Valacyclovir Hydrochloride taken:

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

r_U = peak response from the *Sample solution*
 r_S = peak response 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: 98.0%–102.0% on the anhydrous basis

IMPURITIES

Inorganic Impurities

- RESIDUE ON IGNITION, (281):** NMT 0.1%
- HEAVY METALS, Method I (231):** NMT 20 ppm

Organic Impurities

PROCEDURE 1 (FOR GUANINE, ACYCLOVIR, ACYCLOVIR RELATED COMPOUND A, AND VALCYCLOVIR RELATED COMPOUND M)

Solution A, Solution B, and Mobile phase: Proceed as directed in the *Assay*.

Standard stock solution 1: 0.05 mg/mL of USP Guanine RS prepared by first dissolving in 0.2 N sodium hydroxide using 10% of final volume, and diluting with *Solution A* to volume

Standard stock solution 2: 0.05 mg/mL each of USP Acyclovir RS and USP Acyclovir Related Compound A RS, in *Solution A*

System suitability solution: 0.8 mg/mL of USP Valacyclovir Hydrochloride RS and 4 μg/mL each of USP Guanine RS, USP Acyclovir RS, and USP Acyclovir Related Compound A RS, in *Solution A*, from *Standard stock solution 1* and *Standard stock solution 2*, respectively

Sample solution: 0.8 mg/mL of Valacyclovir Hydrochloride in *Solution A*

Chromatographic system: Proceed as directed in the *Assay*.

System suitability

Sample: *System suitability solution*
Resolution: NLT 15.0 between the guanine and acyclovir peaks
Tailing factor: NMT 2.0 for the valacyclovir peak
Relative standard deviation: NMT 5.0% each for the guanine and acyclovir peaks

Analysis

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

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
 r_T = sum of response of all the peaks from the *Sample solution*
 F = relative response factor (see *Impurity Table 1*)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.
Total unspecified impurities: NMT 0.5% (excluding acyclovir and valacyclovir related compound M)

2 / Valacyclovir

Impurity Table 1

| Name | Relative Retention Time | Relative Response Factor | Acceptance Criteria, NMT (%) |
|--|-------------------------|--------------------------|------------------------------|
| Guanine ^a | 0.30 | 1.6 | 0.10 |
| Acyclovir ^b | 0.69 | 1.7 | 0.70 |
| Valacyclovir | 1.0 | — | — |
| Acyclovir related compound A ^c | 1.5 | 1.4 | 0.10 |
| Valacyclovir related compound M ^d | 2.1 | 1.0 | 0.50 |
| Any individual, unspecified impurity | — | 1.0 | 0.05 |

^a 2-Amino-1,9-dihydro-6H-purin-6-one.^b 2-Amino-9-[(2-hydroxyethoxy)methyl]-1,9-dihydro-6H-purin-6-one.^c 2-[(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl acetate.^d 2-[(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl *N*-formyl-L-valinate.

• **PROCEDURE 2: LIMIT OF VALACYCLOVIR RELATED COMPOUND E**

Buffer, Solution A: Proceed as directed in the *Assay*.

Mobile phase: Acetonitrile and *Solution A* (33:67)

Standard solution: 0.8 µg/mL of USP Valacyclovir Related Compound E RS in *Mobile phase*

System suitability solution: 0.08 µg/mL of USP Valacyclovir Related Compound E RS in *Mobile phase*, from the *Standard solution*

Sample solution: 0.8 mg/mL of Valacyclovir Hydrochloride in *Mobile phase*

Chromatographic system: Proceed as directed in the *Assay*.

Run time: 2 times the retention time of valacyclovir related compound E

System suitability

Sample: *System suitability solution*

Tailing factor: NMT 1.7

Relative standard deviation: NMT 10.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of valacyclovir related compound E 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 related compound E from the *Sample solution*

r_S = peak response of valacyclovir related compound E from the *Standard solution*

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

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

Acceptance criteria: NMT 0.05%

SPECIFIC TESTS

• **ENANTIOMERIC PURITY**

Mobile phase: 18 g/L of perchloric acid in water

System suitability solution: 0.2 mg/mL of USP Valacyclovir Hydrochloride RS in *Mobile phase*. [NOTE—USP Valacyclovir Hydrochloride RS contains a detectable quantity of D-valacyclovir.]

Sample solution: 1 mg/mL of Valacyclovir Hydrochloride in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

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

Flow rate: 1 mL/min

Injection size: 20 µL

Run time: 2 times the retention time of the valacyclovir L-isomer

System suitability

[NOTE—The relative retention time is 0.7 for the valacyclovir D-isomer and 1.0 for the valacyclovir L-isomer.]

Samples: *System suitability solution*

Resolution: NLT 2.0 between the valacyclovir D-isomer and L-isomer peaks

Analysis

Samples: *Sample solution*

Calculate the percentage of valacyclovir D-isomer in the portion of Valacyclovir Hydrochloride taken:

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

r_U = peak response of D-isomer from the *Sample solution*

r_T = sum of the responses of both valacyclovir D-isomer and L-isomer from the *Sample solution*

Acceptance criteria: NMT 1.0% of the valacyclovir D-isomer

• **WATER DETERMINATION, Method I (921):** 4.5%–11.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers supplied with drying agent. Store at room temperature.

• **USP REFERENCE STANDARDS (11)**

USP Acyclovir RS

USP Valacyclovir Hydrochloride RS

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

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

(C₁₀H₁₃N₅O₄ 267.24)

USP Guanine RS

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

(C₅H₅N₅O 151.13)

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]

(C₂₀H₂₄N₆O₆ 444.44) ◀ (1-Nov-2010)