Valacyclovir Hydrochloride

Valacyclovir Hydrochloride contains NLT 95.0% and NMT RS, and 8.4 mg of USP Valacyclovir Related Compound F RS.

DEFINITION
Valacyclovir Hydrochloride contains NLT 95.0% and NMT RS, and 8.4 mg of USP Valacyclovir Related Compound F RS.

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): 50 mg/mL in water

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 a-valacyclovir.]

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

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: TLC
Detector: UV, long and short wavelength
Plate: TLC plate coated with 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

Calculate the percentage of valacyclovir hydrochloride (C13H20N6O4·HCl) in the portion of Valacyclovir Hydrochloride taken:

Result = (r0/rS) × (C0/Cs) × 100

r0 = peak response of valacyclovir from the Sample solution
rS = peak response of valacyclovir from the Standard solution
Cs = concentration of valacyclovir hydrochloride in the Standard solution (mg/mL)
C0 = 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)
• 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, USP Valacyclovir Related Compound E RS, and USP Valacyclovir Related Compound G 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 mL and 0.5 mL of 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-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: TLC
Detector: UV, long and short wavelength
Plate: TLC plate coated with 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 Rf values and limits for each impurity are provided in Table 1.

Acceptance criteria: See Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
</tr>
<tr>
<td>Valacyclovir hydrochloride</td>
</tr>
<tr>
<td>Valacyclovir related compound D</td>
</tr>
<tr>
<td>Valacyclovir related compound E</td>
</tr>
</tbody>
</table>

*This impurity is quantitated using Procedure 2.
†2-{[(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl}N-[(benzyl-oxycarbonyl)]-l-valinate.
‡2-Hydroxyethyl-l-valinate.
§N,N-Dimethylpyridin-4-amine.

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Valacyclovir 1.00 Ð Valacyclovir
dNc 2-Hydroxyethyl-
ocyarbonyl]-
b2-
[2-Amino-6-oxo-1,6-dihydro-9-
This impurity is quantitated using
Valacyclovir related compound G
Valacyclovir

Chromatographic system
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°C
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: NLT 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 = \( \frac{r_U}{r_T} \times 100 \)

\( r_U \) = peak response of any impurity in the Sample solution
\( r_T \) = sum of the responses of all the peaks in the Sample solution

Acceptance criteria: See Table 3.

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

  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°C
  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: NLT 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 = \( \frac{r_U}{r_T} \times \frac{C_U}{C_O} \times \frac{1}{F} \times 100 \)

  \( r_U \) = peak response of guanine plus acyclovir or acyclovir acetate or 9-valacyclovir in the Sample solution
  \( r_T \) = peak response of valacyclovir in the Standard solution
  \( C_T \) = 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 as given in Table 4
Acceptance criteria: See Table 4.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanine and acyclovir&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.18</td>
<td>1.51</td>
<td>2.0</td>
</tr>
<tr>
<td>Acyclovir related compound A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.42</td>
<td>1.12</td>
<td>0.2</td>
</tr>
<tr>
<td>d-Valacyclovir&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.55</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup> 2-Amino-1,9-dihydro-6H-purin-6-one (guanine).
<sup>b</sup> 2-Amino-9-[2-(hydroxyethoxy)methyl]-1,9-dihydro-6H-purin-6-one (acyclovir).
<sup>c</sup> 2-[(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl acetate.
<sup>d</sup> 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: NMT 5.0%–11.0%.
- **LIMIT OF PALLADIUM (730)** (if present)
  - Diluent: Dimethyl sulfoxide and hydrochloric acid (98:2)
  - Blank solution: Diluent
  - Standard solutions: Dilute with Diluent any commercially available standard stock solution of 1 mg/mL of palladium to prepare the following two solutions: 1 µg/mL of palladium and 10 µg/mL of palladium.
  - Sample solution: 10 mg/mL of Valacyclovir Hydrochloride in Diluent
  - Analytical wavelength: 340.458 nm
  - Suitable spectrophotometer system: Use a suitable standard inductively coupled plasma-optical emission spectrometric system, and construct a calibration curve.
  - System suitability
    - Samples: Blank solution and Standard solutions
    - Suitability requirements
      - Relative standard deviation: NMT 2.0%, Standard solutions

**Correlation coefficient:** NLT 0.999, Blank solution and Standard solution

**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

**ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at a temperature below 30°.
- **LABELING:** Where it is the hydrour form, the label so indicates.
- **USP REFERENCE STANDARDS (11)**
  - USP Acyclovir Related Compound A RS
  - 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.
  - USP Acyclovir Related Compound C RS
  - USP Acyclovir Related Compound D RS
  - USP Acyclovir Related Compound E RS
  - USP Acyclovir Related Compound F RS
  - USP Acyclovir Related Compound G RS

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