Valacyclovir Hydrochloride

\[ \text{C}_{13}\text{H}_{20}\text{N}_{6}\text{O}_{4} \cdot \text{HCl} \] 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 \( \text{C}_{13}\text{H}_{20}\text{N}_{6}\text{O}_{4} \cdot \text{HCl} \), 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 × 15-cm; 5-μm packing L66
Column temperature: 10°
Flow rate: 0.75 mL/min
Injection size: 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 (\( \text{C}_{13}\text{H}_{20}\text{N}_{6}\text{O}_{4} \cdot \text{HCl} \)) in the portion of Valacyclovir Hydrochloride taken:

\[
\text{Result} = \left( \frac{r_{s}}{r_{u}} \right) \times \left( \frac{C_{u}}{C_{s}} \right) \times 100
\]

\( r_{u} \) = 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
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 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 spots. The chromatograms obtained with the Standard solutions each show three clearly separated spots due to valacyclovir related compounds D, E, and G. The sprayed 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>Name</th>
<th>Relative Rf</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valacyclovir hydrochloride</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Valacyclovir related compound D</td>
<td>1.1</td>
<td>—</td>
</tr>
<tr>
<td>Valacyclovir related compound E</td>
<td>1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Valacyclovir related compound F</td>
<td>1.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Valacyclovir related compound G</td>
<td>1.9</td>
<td>0.05</td>
</tr>
</tbody>
</table>

a. This impurity is quantitated using Procedure 2.


c. 2-Hydroxyethyl-l-valinate.

d. N,N-Dimethyl pyridin-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>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>35</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>35.01</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>45</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

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: NMT 1.3 for the valacyclovir hydrochloride peak

Analysis

Sample: Sample solution

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

\[
\text{Result} = \left( \frac{r_U}{r_T} \right) \times 100
\]

\( r_U \) = 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>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanine (near solvent front)</td>
<td>0.31</td>
<td>—</td>
</tr>
<tr>
<td>Acyclovir alaninate</td>
<td>0.42</td>
<td>0.2</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Valacyclovir related compound C</td>
<td>1.06</td>
<td>0.3</td>
</tr>
<tr>
<td>Acyclovir related compound A</td>
<td>1.09</td>
<td>—</td>
</tr>
<tr>
<td>Valacyclovir related compound D</td>
<td>1.17</td>
<td>0.5</td>
</tr>
<tr>
<td>Acyclovir isoleucinate</td>
<td>1.30</td>
<td>0.2</td>
</tr>
<tr>
<td>N-Formyl valacyclovir</td>
<td>1.61</td>
<td>0.8</td>
</tr>
<tr>
<td>Guaninyl valacyclovir</td>
<td>1.66</td>
<td>0.2</td>
</tr>
<tr>
<td>Bis valacyclovir</td>
<td>2.00</td>
<td>0.3</td>
</tr>
<tr>
<td>Any unspecified impurity</td>
<td>—</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* This impurity is quantitated by the Procedure 3 method.

b. 2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl (guanine).

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

f. 9-[(2-Hydroxyethoxy)methyl]guanine - valinate.

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

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

k. 2-[(2-Hydroxyethoxy)methyl]guanine - isoleucinate.

l. 9-[(2-Hydroxyethoxy)methyl]guanine - formyl - valinate.

m. 9-[(2-Hydroxyethoxy)methyl]guanine - formyl - valinate.


o. 2,2′-[(Methylene)bis[iminobis(6-oxo-1,6-dihydro-9H-purin-9-yl)]diethyl (di-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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( 1/F \right) \times 100
\]

- \(r_U\) = 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

<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 acyclovina</td>
<td>0.18</td>
<td>1.51</td>
<td>2.0</td>
</tr>
<tr>
<td>Acyclovir related compound A</td>
<td>0.42</td>
<td>1.12</td>
<td>0.2</td>
</tr>
<tr>
<td>D-Valacyclovirb</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>

* 2-Amino-1H-purin-6(9H)-one (guanine).
* 9-[(2-Hydroxyethoxy)methyl]guanine (acyclovir).
* 2-[(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl acetate.
* 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% (RS 1-Dec-2010)

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**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.
    - C₁₀H₁₃N₅O₄ 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.
    - C₁₆H₂₀N₄O₄ • 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.
    - C₁₇H₂₂N₄O₄ 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.
    - C₂₁H₂₆N₆O₆ 458.47
  - USP Valacyclovir Related Compound F RS
    - 2-Hydroxyethyl valinate para-toluensulfonate salt.
    - C₁₅H₁₅NO₃ • C₇H₈O₃S 333.40
  - USP Valacyclovir Related Compound G RS
    - N,N-Dimethylpyridin-4-amine.
    - C₁₄H₁₉N₂ 122.17

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