Levetiracetam Oral Solution

Type of Posting  Revision Bulletin
Posting Date  22–Nov–2019
Official Date  01–Dec–2019
Expert Committee  Chemical Medicines Monographs 4
Reason for Revision  Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Levetiracetam Oral Solution monograph. The purpose for the revision is to widen the upper limit of pH range from 6.3 to 7.0 to be consistent with the FDA-approved specification.

The Levetiracetam Oral Solution Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Ren-Hwa Yeh, Senior Scientific Liaison (301-998-6818 or rhy@usp.org).
Levetiracetam Oral Solution

DEFINITION
Levetiracetam Oral Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of levetiracetam (C11H14N2O2).

IDENTIFICATION
• A. The retention time of the major peak in the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY
• PROCEDURE
Solution A: Dilute 1 mL of phosphoric acid with water to 1 L.
Solution B: Acetonitrile
Mobile phase: See Table 1.

System suitability
Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm x 15-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection volume: 20 µL
System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of levetiracetam (C11H14N2O2) in the portion of Oral Solution taken:

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

\[ r_U = \text{peak response of levetiracetam from the Sample solution} \]
\[ r_S = \text{peak response of levetiracetam from the Standard solution} \]
\[ C_S = \text{concentration of USP Levetiracetam RS in the Standard solution (mg/mL)} \]

Solution A

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>15</td>
<td>92</td>
<td>8</td>
</tr>
</tbody>
</table>

Standard solution: 1.0 mg/mL of USP Levetiracetam RS in Solution A
Sample solution: Nominally 1.0 mg/mL of levetiracetam prepared as follows. Transfer a suitable volume of the Oral Solution to a suitable volumetric flask to obtain 1.0 mg/mL final concentration of levetiracetam. Add 60% of the flask volume of Solution A, and sonicate at room temperature for 5 min with intermittent shaking. Allow the solution to cool, and dilute with Solution A to volume. Pass a portion of the solution under test through a suitable filter.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm x 15-cm; 5-µm packing L1
Column temperature: 45°
Flow rate: 1 mL/min
Injection volume: 20 µL
System suitability
Sample: Standard solution
Suitability requirements
Resolution: NLT 2.0 between levetiracetam related compound A and levetiracetam acid,
Relative standard deviation: NMT 5.0%, Standard solution
Analysis
Samples: Standard solution and Sample solution

Acceptance criteria: 90.0%–110.0%

IMPURITIES
• ORGANIC IMPURITIES
Solution A: Dilute 2 mL of phosphoric acid with water to 1 L.
Solution B: Acetonitrile
Diluent: Acetonitrile and Solution A (5:95)
Mobile phase: See Table 2.

System suitability solution: 0.2 mg/mL of USP Levetiracetam RS and 0.1 mg/mL of USP Levetiracetam Related Compound A RS in Diluent prepared as follows. Dissolve the required amount of USP Levetiracetam RS in 10% of the final volume of 0.1 N potassium hydroxide. Let the mixture react at room temperature for about 15 min, and then neutralize by adding 0.1 N hydrochloric acid at 10% of the flask volume. Add the required amount of USP Levetiracetam Related Compound A RS, sonicate to dissolve, and dilute with Diluent to volume. [NOTE—This solution contains levetiracetam, levetiracetam acid, and levetiracetam related compound A.]

Standard solution: 3 µg/mL of USP Levetiracetam RS in Solution A
Sample solution: Nominally 2 mg/mL of levetiracetam prepared as follows. Transfer a suitable volume of the Oral Solution to a suitable volumetric flask. Add 60% of the flask volume of Solution A, and sonicate at room temperature for 5 min with intermittent shaking. Allow the solution to cool, and dilute with Solution A to volume. Pass a portion of the solution through a suitable filter.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm x 15-cm; 5-µm packing L1
Column temperature: 45°
Flow rate: 1 mL/min
Injection volume: 20 µL
System suitability
Samples: System suitability solution and Standard solution
Suitability requirements
Resolution: NLT 2.0 between levetiracetam related compound A and levetiracetam acid, System suitability solution
Tailing factor: NMT 2.0, Standard solution
Relative standard deviation: NMT 5.0%, Standard solution
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each impurity in the portion of Oral Solution taken:

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

- \( r_U \) = peak response of the impurity from the Sample solution
- \( r_S \) = peak response of levetiracetam from the Standard solution
- \( C_S \) = concentration of USP Levetiracetam RS in the Standard solution (mg/mL)
- \( C_U \) = nominal concentration of levetiracetam in the Sample solution (mg/mL)
- \( F \) = relative response factor for each impurity (see Table 3)

Acceptance criteria: See Table 3.

### Table 3 (continued)

<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>Total impurities</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
<tr>
<td>(^a) (S)-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide. (^b) This is a process impurity and included for peak identification purposes only. (^c) (S)-2-(2-Oxopyrrolidin-1-yl)butanoic acid.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SPECIFIC TESTS

**Change to read:**

- **pH (791):** 4.8–7.0 (RB 1-Dec-2019)
- **Microbial Enumeration Tests (61) and Tests for Specified Microorganisms (62):** The total aerobic microbial count does not exceed 10² cfu/mL. The total yeasts and molds count does not exceed 10¹ cfu/mL. It meets the requirement of the test for absence of *Escherichia coli*.

### ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in light-resistant containers. Store at controlled room temperature.
- **USP Reference Standards (11)**
  - USP Levetiracetam RS
  - USP Levetiracetam Related Compound A RS
    - (S)-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide.
    - \( C_8H_{15}ClN_2O_2 \) 206.67