Levetiracetam Oral Solution

DEFINITION
Levetiracetam Oral Solution contains NLT 90.0% and NMT 110.0% of the labeled amount of levetiracetam (C8H14N2O2).

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
A. Identification

Solution A: Levetiracetam Oral Solution

DEFINITION
Solution A:

Levetiracetam Oral Solution

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 1.


Table 1

<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 230 nm

Column: 4.6-mm × 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 the labeled amount of levetiracetam (C8H14N2O2) in the portion of Oral Solution taken:

\[ \text{Result} = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_i}{C_0} \right) \times 100 \]

\( r_0 \) = peak response of levetiracetam from the Sample solution

\( r_s \) = peak response of levetiracetam from the Standard solution

\( C_i \) = concentration of USP Levetiracetam RS in the Standard solution (mg/mL)

\( C_0 \) = nominal concentration of levetiracetam in the Sample solution (mg/mL)

Acceptance criteria: 90.0%–110.0%

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>100</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>95</td>
<td>5</td>
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<tr>
<td>20</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>30</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>35</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>41</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

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. 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 × 15-cm; 5-µm packing L1

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:

\[ \text{Result} = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_i}{C_0} \right) \times (1/F) \times 100 \]
Levetiracetam

$ r_0 $ = 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>
<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>Levetiracetam</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Levetiracetam related compound A$ ^a $</td>
<td>1.38</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Levetiracetam acid$ ^b $</td>
<td>1.46</td>
<td>0.92</td>
<td>0.3</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

$ ^a $(S)-N-(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.

**SPECIFIC TESTS**

* Change to read:

- **PH** (791): $ ^* $4.8$ ^* $(RB 1-Feb-2013)$ ^* $6.3

- **MICROBIAL ENUMERATION TESTS** (61) and **TESTS FOR SPECIFIED MICROORGANISMS** (62): The total aerobic microbial count does not exceed $ 10^2 $ cfu/mL. The total yeasts and molds count does not exceed $ 10^1 $ 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)-N-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide. $ C_{13}H_{15}ClN_2O_2 $ 206.67

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