Levetiracetam Tablets

Type of Posting  Revision Bulletin
Posting Date    23–Feb–2018
Official Date   01–Mar–2018
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 Monographs—Chemical Medicines 4 Expert Committee has revised the Levetiracetam Tablets monograph. The purpose for the revision is to add a dissolution test to accommodate drug products which were approved with different conditions and acceptance criteria.

- **Dissolution Test 4** was validated using a Inertsil ODS 2 brand of 4.6-mm x 25-cm, 5-µm packing L1 column. The typical retention time for levetiracetam is 5 min.

The Levetiracetam Tablets Revision Bulletin supersedes the currently official Levetiracetam Tablets monograph. The Revision Bulletin will be incorporated into the USP 42–NF 37.

Should you have any questions, please contact Ren-Hwa Yeh, Ph.D., Senior Scientific Liaison, (301–998–6818 or RHY@usp.org).
Levetiracetam Tablets

DEFINITION
Levetiracetam Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of levetiracetam (C8H14N2O2).

IDENTIFICATION

**A. INFRARED ABSORPTION** *(197K)* *(197A)*

**Standard solution:** 1 mg/mL solution of USP Levetiracetam RS in solution prepared as follows. Transfer a suitable quantity of USP Levetiracetam RS to a suitable volumetric flask. Add 70% of the flask volume of acetone. Sonicate for 15 min. Dilute with acetone to volume.

**Standard:** Pass 10 mL of the Standard solution through a membrane filter of 0.45-µm pore size. Evaporate acetonitrile from the filtrate completely to form crystals. Scratch the crystals. Weigh 2–4 mg of the residue and 200 mg of KBr in a mortar and pestle. Mix and grind well, and prepare the KBr pellet.

**Sample solution:** Transfer an amount of finely powdered Tablets (NLT 20) equivalent to 250 mg of levetiracetam to a 50-mL volumetric flask. Add 35 mL of acetonitrile. Sonicate for 15 min. Dilute with acetone to volume.

**Sample:** Pass 10 mL of the Sample solution through a membrane filter of 0.45-µm pore size. Evaporate acetonitrile from the filtrate completely to form crystals. Scratch the crystals. Weigh 2–4 mg of the residue and 200 mg of KBr in a mortar and pestle. Mix and grind well, and prepare the KBr pellet.

**Analysis:** Record the spectra of the Standard and Sample between 4000 cm⁻¹ and 650 cm⁻¹.

**Acceptance criteria:** The spectrum of the Sample corresponds to that of the Standard.

**B.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY

**PROCEDURE**

**Buffer:** 1.4 g/L of monobasic potassium phosphate and 0.6 g/L of sodium 1-heptanesulfonate, adjusted with phosphoric acid to a pH of 2.8

**Mobile phase:** Acetonitrile and Buffer (8:92)

**Diluent:** Acetonitrile and water (20:80)

**Standard solution:** 0.35 mg/mL of USP Levetiracetam RS in Diluent. Sonication may be used to aid dissolution.

**Sample solution:** Nominally 0.4 mg/mL of levetiracetam from NLT 20 Tablets, finely crushed, in Diluent. Sonication may be used to aid dissolution.

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

<table>
<thead>
<tr>
<th>Tablet Strength (mg/Tablet)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>15</td>
</tr>
<tr>
<td>500</td>
<td>15</td>
</tr>
<tr>
<td>750</td>
<td>15</td>
</tr>
<tr>
<td>1000</td>
<td>30</td>
</tr>
</tbody>
</table>

Buffer: 6.8 g/L of monobasic potassium phosphate, adjusted with dilute potassium hydroxide to a pH of 5.6

**Mobile phase:** Acetonitrile and Buffer (15:85)

**Standard solution:** (L/1000) mg/mL in Medium, where L is the Tablet label claim, in mg

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L1

**Flow rate:** 1.2 mL/min

**Injection volume:** 10 µL

**System suitability** *(See Chromatography (621), 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 (C8H14N2O2) dissolved:

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

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C197405-M44660-CHM42015 Rev. 0, 20180223
Levetiracetam

2. Levetiracetam

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Test 2: If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 2.

Medium: Water; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Buffer: 6.8 g/L of monobasic potassium phosphate
Mobile phase: Acetonitrile and Buffer (15:85)
Standard solution: 0.28 mg/mL of USP Levetiracetam RS in Medium
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 2 mL. Dilute an aliquot of the filtrate with Medium, if necessary, to obtain a concentration similar to that of the Standard solution.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: NLT 2 times the retention time of levetiracetam

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 (C8H14N2O2) dissolved:

Result = (rU/rS) × (CQ/L) × D × V × 100

rU = peak response from the Standard solution
rS = peak response from the Sample solution
CQ = concentration of USP Levetiracetam RS in the Standard solution (mg/mL)
L = label claim (mg/Tablet)
D = dilution factor of the Sample solution
V = volume of Medium, 900 mL

Tolerances: NLT 85% (Q) of the labeled amount of levetiracetam (C8H14N2O2) is dissolved.

• UNIFORMITY OF DOSAGE UNITS (905): Meet the requirements

IMPURITIES

• ORGANIC IMPURITIES

Buffer: 6.8 g/L of monobasic potassium phosphate and 0.85 g/L of sodium 1-heptanesulfonate, adjusted with phosphoric acid to a pH of 2.8
Mobile phase: Acetonitrile and Buffer (5:95)
System suitability solution: 3.6 µg/mL of USP Levetiracetam RS and 3.6 µg/mL of USP Levetiracetam Related Compound B RS in Mobile phase
Standard solution: 3.6 µg/mL of USP Levetiracetam RS in Mobile phase
Sample solution: Equivalent to 1.2 mg/mL of levetiracetam from NLT 20 Tablets, finely crushed, in Mobile phase. [Note—Sonicate if necessary, and centrifuge the solution before passing through a suitable filter.]

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 200 nm
Column: 4.6-mm × 25-cm; 4-µm packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL

System suitability
Samples: System suitability solution and Standard solution
Suitability requirements

Resolution: NLT 2.0 between levetiracetam related compound B and levetiracetam, System suitability solution
Tailing factor: NMT 2.0, Standard solution
Relative standard deviation: NMT 10.0%, Standard solution

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of each impurity in the portion of Tablets taken:

Result = \( \left( \frac{r_i}{r_0} \right) \times \left( \frac{C_i}{C_0} \right) \times \left( \frac{1}{F} \right) \times 100 \)

\( r_0 \) = peak response of each impurity 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)
\( F \) = relative response factor (see Table 2)

Acceptance criteria: See Table 2.

### Table 2 (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>Levetiracetam related compound B(^a)</td>
<td>0.54</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\) These impurities are listed for information only; they are process impurities, which are controlled in the drug substance.

\(^b\) (S)-N-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide.

\(^c\) (S)-2-(2-Oxopyrrolidine-1-yl)butanoic acid.

### ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.
- **LABELING:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.
- **USP REFERENCE STANDARDS** (11)
  - USP Levetiracetam RS
  - USP Levetiracetam Related Compound B RS
  - (S)-2-Aminobutanamide hydrochloride. 
  - C\(_{10}\)H\(_{18}\)N\(_2\)O \cdot HCl 138.60

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