Levetiracetam Extended-Release Tablets

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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 Extended-Release Tablets monograph. The purpose for the revision is to add tolerance limits for additional strengths to the existing Dissolution Test 7 based on FDA approval. The revision also necessitates a change in the table numbering in the Performance Tests and Organic Impurities sections.

The Levetiracetam Extended-Release Tablets 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 Extended-Release Tablets

**DEFINITION**
Levetiracetam Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of levetiracetam (C7H14N2O5).

**IDENTIFICATION**
- A. 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 anhydrous dibasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.
  - **Mobile phase:** Acetonitrile and Water (50:50) to volume. Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Alternatively, the Sample solution, having a nominal concentration of 3 mg/mL of levetiracetam, may be prepared as follows. Finely grind NLT 10 Tablets, and transfer an amount equivalent to 750 mg of levetiracetam to a volumetric flask containing tetrahydrofuran to fill approximately 5% of flask volume. Sonicate for 10 min using a mechanical shaker. Add methanol to fill 10% of flask volume. Dilute with Mobile phase to volume. The solution is the label claim in mg/Tablet. Transfer the Tablets containing tetrahydrofuran to fill about 4% of flask volume. Sonicate in cold water to dissolve. Equilibrate to room temperature. Dilute with Mobile phase to volume. The solution through a suitable filter of 0.45-µm pore size.
  - **Standard solution:** Nominally (L/100) mg/mL of levetiracetam from NLT 5 Tablets prepared as follows, where L is the label claim in mg/Tablet. Transfer the Tablets to a volumetric flask containing tetrahydrofuran to fill about 4% of flask volume. Stir for 30 min, and allow to stand for 5 min. Sonicate for 10 min with intermittent shaking. Add Mobile phase to fill 80% of final volume, and sonicate in cold water for 20 min with intermittent shaking. Add methanol to fill 10% of flask volume. Dilute with Mobile phase to volume. Centrifuge for 15 min, and pass a portion of the solution through a suitable filter of 0.2-µm pore size.
  - **Sample stock solution:** Nominally (L/100) mg/mL of levetiracetam from NLT 5 Tablets prepared as follows. Weigh a suitable quantity of the Reference Standard into a volumetric flask. Add Mobile phase to fill 60% of flask volume and tetrahydrofuran to fill 4% of flask volume. Sonicate in cool water to dissolve. Equilibrate to room temperature. Dilute with Mobile phase to volume.
  - **Standard stock solution:** 1.0 mg/mL of USP Levetiracetam RS in Buffer A: 6.8 g of potassium dihydrogen phosphate and 0.2 g of sodium hydroxide in 1 L of water. If necessary, adjust with 1 N sodium hydroxide to a pH of 6.0.
  - **Mobile phase:** Acetonitrile and Buffer B (10:90) to fill 60% of flask volume and tetrahydrofuran to fill about 4% of flask volume. Sonicate in cold water to dissolve. Equilibrate to room temperature. Dilute with Mobile phase to volume. The solution through a suitable filter of 0.45-µm pore size.

**PERFORMANCE TESTS**

- **DISSOLUTION (711)**
  - **Test 1**
    - **Buffer A:** Dissolve 6.8 g of potassium dihydrogen phosphate and 0.2 g of sodium hydroxide in 1 L of water. If necessary, adjust with 1 N sodium hydroxide to a pH of 3.5.
    - **Medium:** Buffer A; 900 mL
    - **Apparatus:** 100 rpm
    - **Times:** 1, 2, 4, and 8 h
    - **Buffer B:** 1.4 g/L of anhydrous dibasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.
    - **Mobile phase:** Acetonitrile and Buffer B (10:90) to fill 60% of flask volume and tetrahydrofuran to fill about 4% of flask volume. Sonicate in cold water to dissolve. Equilibrate to room temperature. Dilute with Mobile phase to volume. The solution through a suitable filter of 0.45-µm pore size.
    - **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 205 nm
**Column:** 4.6-mm x 25-cm; 5-µm packing L7
**Temperatures**
**Column:** 30°C
**Autosampler:** 10°C
**Flow rate:** 1.5 mL/min
**Injection volume:** 5 µL
**Run time:** 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 (C7H14N2O5) in the portion of Tablets taken:
    
    \[
    \text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_s}{C_i} \right) \times 100
    \]
    
    \( r_u \) = peak response from the Sample solution
    
    \( r_s \) = peak response from the Standard solution
    
    \( C_s \) = concentration of the Standard solution (mg/mL)
    
    \( C_i \) = concentration of the Sample solution (mg/mL)

**Acceptance criteria:** 90.0%–110.0%
2 Leviracetam

Calculate the percentage of the labeled amount of leviracetam (C\textsubscript{6}H\textsubscript{12}N\textsubscript{4}O\textsubscript{3}) dissolved at each time point (t):

\[ \text{Result}_t = C_i \times V \times (1/L) \times 100 \]

\[ \text{Result}_2 = \left[ (C_i \times V) + (C_L \times V_1) \right] \times (1/L) \times 100 \]

\[ \text{Result}_3 = \left[ (C_i \times V) + (C_L + C_S \times V_1) \right] \times (1/L) \times 100 \]

\[ \text{Result}_4 = \left[ (C_i \times V) + (C_L + C_S + C_O \times V_1) \right] \times (1/L) \times 100 \]

C\textsubscript{i} = concentration of leviracetam in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of Medium, 900 mL

L = label claim (mg/Tablet)

V\textsubscript{i} = volume of the Sample solution withdrawn at each time point and replaced with Medium (mL)

**Tolerances:** See Table 1.

<table>
<thead>
<tr>
<th>Time Point (t)</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>500 mg/Tablet (%)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>45–65</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>60–80</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of leviracetam (C\textsubscript{6}H\textsubscript{12}N\textsubscript{4}O\textsubscript{3}) dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

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

**Buffer A:** Dissolve 6.8 g of potassium dihydrogen phosphate and 0.2 g of sodium hydroxide in 1 L of water. If necessary, adjust with 1 N sodium hydroxide to a pH of 6.0.

**Medium:** Buffer A; 900 mL

**Apparatus 1:** 100 rpm

**Times:** 1, 2, 4, and 8 h

**Buffer B:** 2.82 g/L of potassium dihydrogen phosphate in water

**Mobile phase:** Acetonitrile and Buffer B (5:95). Adjust with phosphoric acid to a pH of 2.0.

**Standard solution:** (L/900) mg/mL of USP Leviracetam RS in Medium, where L is the label claim in mg/Tablet

**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 235 nm

**Columns:** Guard: 4.6-mm x 1-cm, 4.6-mm x 2-cm, or 4.0-mm x 2-cm; 5-µm packing L1

Analitical: 4.6-mm x 5-cm; 5-µm packing L1

**Flow rate:** 0.8 mL/min

**Injection volume:** 10 µL

**Run time:** 2 times the retention time of leviracetam

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 1.5% for five replicate injections

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the concentration, C\textsubscript{i}, of leviracetam (C\textsubscript{6}H\textsubscript{12}N\textsubscript{4}O\textsubscript{3}) in Medium (mg/mL) after time point i:

\[ \text{Result}_i = (r_i/r_S) \times C_i \]

r\textsubscript{i} = peak response from the Sample solution

r\textsubscript{S} = peak response from the Standard solution

C\textsubscript{i} = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of leviracetam (C\textsubscript{6}H\textsubscript{12}N\textsubscript{4}O\textsubscript{3}) dissolved at each time point (t):

\[ \text{Result}_t = C_i \times V \times (1/L) \times 100 \]

\[ \text{Result}_2 = \left[ (C_i \times V) + (C_L \times V_2) \right] \times (1/L) \times 100 \]

\[ \text{Result}_3 = \left[ (C_i \times V) + (C_L + C_S \times V_2) \right] \times (1/L) \times 100 \]

\[ \text{Result}_4 = \left[ (C_i \times V) + (C_L + C_S + C_O \times V_2) \right] \times (1/L) \times 100 \]

C\textsubscript{i} = concentration of leviracetam in Medium in the portion of sample withdrawn at time point i (mg/mL)

V = volume of Medium, 900 mL

L = label claim (mg/Tablet)

V\textsubscript{i} = volume of the Sample solution withdrawn from the Medium (mL)

**Tolerances:** See Table 2.

<table>
<thead>
<tr>
<th>Time Point (t)</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>500 mg/Tablet (%)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>22–42</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>39–59</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>62–82</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of leviracetam (C\textsubscript{6}H\textsubscript{12}N\textsubscript{4}O\textsubscript{3}) dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

**Test 3:** If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 3.

**Buffer A:** Dissolve 6.8 g of potassium dihydrogen phosphate and 0.5 g of sodium hydroxide in 1 L of water. Adjust to a pH of 6.0.

**Medium:** Buffer A; 900 mL

**Apparatus 1:** 100 rpm

**Times:** 1, 2, 4, and 8 h

**Buffer B:** 7.8 g/L of monobasic sodium phosphate dihydrate in water. Adjust with sodium hydroxide to a pH of 5.6.

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

**Standard solution:** (L/900) mg/mL of USP Leviracetam RS in Medium, where L is the label claim in mg/Tablet

**Sample solution:** Centrifuge a portion of the solution under test.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 220 nm

**Columns:** 4.6-mm x 15-cm; 5-µm packing L1

**Column temperature:** 30°
Flow rate: 1.5 mL/min  
Injection volume: 10 μL  
Run time: 2 times the retention time of levetiracetam  

System suitability  
Sample: Standard solution  
Suitability requirements  
Column efficiency: NLT 1500 theoretical plates  
Relative standard deviation: NMT 2.0% for six replicate injections  

Analysis  
Samples: Standard solution and Sample solution  
Calculate the concentration, Ci, of levetiracetam (C1H11N2O2) in Medium (mg/mL) after time point i:

\[
C_i = \frac{r_i}{r_s} \times L_i
\]

Calculate the percentage of the labeled amount of levetiracetam (C1H11N2O2) dissolved at each time point (i):

\[
\text{Result}_i = C_i \times V \times (1/L) \times 100
\]

Tolerances: See Table 3.

The percentages of the labeled amount of levetiracetam (C1H11N2O2), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

Test 4: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 4. Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with sodium hydroxide to a pH of 6.0. Medium: Buffer: 900 mL Apparatus 1: 100 rpm Times: 1, 2, 4, and 8 h

Standard solution: (L/900) mg/mL of USP Levetiracetam RS in Medium, where L is the label claim in mg/Tablet  
Sample solution: Pass a suitable portion of the solution under test through a suitable filter of 0.45-μm pore size.  

Discard the first 3 mL of the filtrate. Dilute a known volume of the remaining filtrate quantitatively with Medium.  
Blank: Medium  
Instrumental conditions  
Mode: UV  
Analytical wavelength: 210 nm  

Analysis  
Samples: Standard solution and Sample solution  
Calculate the concentration, Ci, of levetiracetam (C1H11N2O2) in Medium (mg/mL) after time point i:

\[
\text{Result}_i = (A_i/A_s) \times C_s
\]

Calculate the percentage of the labeled amount of levetiracetam (C1H11N2O2) dissolved at each time point (i):

\[
\text{Result}_i = C_i \times V \times (1/L) \times 100
\]

Tolerances: See Table 4.

Table 4  
<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
<th>500 mg/Tablet (%)</th>
<th>750 mg/Tablet (%)</th>
<th>1000 mg/Tablet (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>42–62</td>
<td>35–55</td>
<td>35–55</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>59–79</td>
<td>50–70</td>
<td>50–70</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>78–98</td>
<td>70–90</td>
<td>70–90</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 80</td>
<td>NLT 80</td>
<td>NLT 80</td>
<td></td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C1H11N2O2), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.  

Test 5: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 5.  
Medium: pH 6.0 phosphate buffer (6.8 g/L of monobasic potassium phosphate in water. Adjust with sodium hydroxide to a pH of 6.0.); 900 mL  
Apparatus 1: 100 rpm  
Times: For 500- and 750-mg Tablets: 1, 4, 8, and 12 h For 1000-mg Tablets: 1, 2, 4, and 8 h  
Buffer: 2.7 g/L of monobasic potassium phosphate in water  
Mobile phase: Acetonitrile and Buffer (10:90)  
Standard stock solution: 2.8 mg/mL of USP Levetiracetam RS in Medium prepared as follows. Transfer a suitable quantity of USP Levetiracetam RS to a suitable volumetric flask. Dissolve in 20% of the flask volume of methanol. Dilute with Medium to volume.
Levetiracetam

Standard solution: (L/900) mg/mL of USP Levetiracetam RS in Medium from Standard stock solution, where L is the label claim in mg/Tablet.

Sample solution: At each time point withdraw 1 mL of the solution under test, and pass it 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 x 15-cm; 5-µm packing L11
Flow rate: 1 mL/min
Injection volume
For 500- and 750-mg Tablets: 10 µL
For 1000-mg Tablets: 5 µL
Run time: 2 times the retention time of levetiracetam

System suitability
Sample: Standard solution
Suitability requirements
Column efficiency: NLT 4000 theoretical plates
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0% for five replicate injections

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of levetiracetam (C₈H₁₄N₂O₂) dissolved in Medium (mg/mL) after time point i:

Resultᵢ = \((rᵢ/r_S) \times C_S \times V \times (1/L) \times 100\)

where:
- \(rᵢ\) = peak response from the Sample solution
- \(r_S\) = peak response from the Standard solution
- \(C_S\) = concentration of USP Levetiracetam RS in the Standard solution (mg/mL)
- \(V\) = volume of Medium, 900 mL
- \(L\) = label claim (mg/Tablet)

Tolerances: See Table 5.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time for 500 and 750 mg/Tablet (h)</th>
<th>Time for 1000 mg/Tablet (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>NMT 40</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>2</td>
<td>55–80</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>4</td>
<td>NLT 75</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>8</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C₈H₁₄N₂O₂) dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

Test 6: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 6.

Medium: pH 6.0 phosphate buffer (6.9 g of monobasic potassium phosphate, and 0.23 g of sodium hydroxide in 1 L of water. Adjust with sodium hydroxide or phosphoric acid to a pH of 6.0); 900 mL

Apparatus 1: 100 rpm
Times: 1, 2, 4, and 8 h
Mobile phase: Acetonitrile and water (10:90)

Standard solution: 0.5 mg/mL of USP Levetiracetam RS in Medium prepared as follows. Transfer a suitable quantity of USP Levetiracetam RS to a suitable volumetric flask. Add 4% of the flask volume of methanol and 60% of the flask volume of the Medium. Sonicate for NLT 5 min. Dilute with Medium to volume.

Sample solution: At the end of specified time interval, withdraw a known volume of the solution from the dissolution vessel. Pass a suitable 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 230 nm
Column: 4.6-mm x 5-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 0.9 mL/min
Injection volume: 10 µL
Run time: 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 concentration, \(Cᵢ\), of levetiracetam (C₈H₁₄N₂O₂) in Medium (mg/mL) after time point i:

Resultᵢ = \((rᵢ/r_S) \times C_S\)

where:
- \(rᵢ\) = peak response from the Sample solution
- \(r_S\) = peak response from the Standard solution
- \(C_S\) = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of levetiracetam (C₈H₁₄N₂O₂) dissolved at each time point (i):

Resultᵢ = \(Cᵢ \times V \times (1/L) \times 100\)

where:
- \(V\) = volume of Medium, 900 mL
- \(L\) = label claim (mg/Tablet)
- \(Vᵢ\) = volume of the Sample solution withdrawn from the solution under test (mL)

Tolerances: See Table 6.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>45–65</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>60–80</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C₈H₁₄N₂O₂) dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

Test 7: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 7.
Medium: Acetate buffer, pH 4.5, prepared as follows. Dissolve 3.0 g of sodium acetate in 1 L of water and add 1.4 mL of glacial acetic acid. Adjust with 5 N sodium hydroxide or glacial acetic acid to a pH of 4.5: 230 mL.

Apparatus 3: 15 dips per min, with suitable screens.

Times:
- For 500-mg Tablets: 1, 2, 4, and 8 h
- For 750-mg Tablets: 1, 2, 4, and 10 h
- For 1000- and 1500-mg Tablets: 1, 4, and 12 h

Buffer: 13.6 g/L of monobasic potassium phosphate in water. Adjust with 5 N sodium hydroxide to a pH of 6.0.

Mobile phase: Methanol and Buffer (15:85)

Standard solution: 0.55 mg/mL of USP Levetiracetam RS in Medium. Sonication may be used to aid in dissolution.

Sample solution: Pass a suitable portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first 5 mL. Dilute a suitable volume of the filtrate with Medium, as needed.

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

Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 10-cm; 3-µm packing L1
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: 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 concentration, C, of levetiracetam (C\textsubscript{9}H\textsubscript{12}N\textsubscript{3}O\textsubscript{2}) in Medium (mg/mL) after time point i:

\[ R_f = \frac{(r_f/r_s) \times D \times C_i}{C_j} \]

Calculate the percentage of the labeled amount of levetiracetam (C\textsubscript{9}H\textsubscript{12}N\textsubscript{3}O\textsubscript{2}) dissolved at each time point (i):

\[ \text{Result}_i = C_j \times V \times (1/L) \times 100 \]

The percentages of the labeled amount of levetiracetam (C\textsubscript{9}H\textsubscript{12}N\textsubscript{3}O\textsubscript{2}) dissolved at times specified, conform to Dissolution (711), Acceptance Table 2.

Test 8: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 8.

Medium: Phosphate buffer, pH 6.0, prepared as follows. Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water. Adjust with 10 N sodium hydroxide solution to a pH of 6.0: 900 mL.

Apparatus 1: 100 rpm
Times: 1, 2, 4, and 12 h
Buffer: 0.26 g/L of monobasic potassium phosphate in water. Adjust with 20 g/L aqueous potassium hydroxide to a pH of 5.5.

Solution A: Acetonitrile and Buffer (5:95)
Mobile phase: Acetonitrile and Solution A (10:90)
Standard solution: (L/900) mg/mL of USP Levetiracetam RS in Medium, where L is the label claim in mg/Tablet. Sonicate to dissolve as needed.

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
Column temperature: 20°
Flow rate: 1 mL/min
Injection volume: 5 µL
Run time: NLT 1.6 times the retention time of levetiracetam

System suitability:
Sample: Standard solution
Suitability requirements:
Tailing factor: NMT 1.5
Relative standard deviation: NMT 1.8%

Analysis:
Samples: Standard solution and Sample solution
Calculate the concentration, C, of levetiracetam (C\textsubscript{9}H\textsubscript{12}N\textsubscript{3}O\textsubscript{2}) in Medium (mg/mL) after time point i:

\[ \text{Result}_i = (r_f/r_s) \times C_i \]

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Point (h)</td>
<td>Time (h)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Point (h)</td>
<td>Time (h)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
</tr>
</tbody>
</table>
6 Levetiracetam

Levetiracetam

Revision Bulletin

Official January 1, 2020

Cᵢ = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of levetiracetam (C₂H₁₄N₂O₅) dissolved at each time point (i):

\[
\text{Result}_i = C_i \times V \times (1/L) \times 100
\]

\[
\text{Result}_i = [(\text{C}_i \times [V - (2 \times V_i)]) + ([C_i + C_i] \times V_i)] \times (1/L) \times 100
\]

\[
\text{Result}_i = ((\text{C}_i \times [V - (3 \times V_i)]) + ([C_i + C_i + C_i] \times V_i)] \times (1/L) \times 100
\]

Cᵢ = concentration of levetiracetam in the portion of sample withdrawn at time point i (mg/mL)

V = volume of Medium, 900 mL

L = label claim (mg/Tablet)

Vₛ = volume of the Sample solution withdrawn from the Medium (mL)

Tolerances: See Table 9.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>25–45</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>40–60</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>55–75</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C₂H₁₄N₂O₅), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

Test 9: If the product complies with this procedure, the labeling indicates that it meets USP Dissolution Test 9.

Medium: Phosphate buffer, pH 6.0, prepared as follows. Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water. Adjust with 50% (w/v) potassium hydroxide solution to a pH of 6.0; 900 mL.

Apparatus 1: 100 rpm

Times: 1, 2, 4, and 12 h

Buffer: 5.0 g/L of monobasic potassium phosphate in water

Mobile phase: Acetonitrile and Buffer (5:95)

Standard solution: 0.56 mg/mL of USP Levetiracetam RS in Medium. Sonicate to dissolve as necessary.

Sample solution: Centrifuge a portion of the solution under test and use the clear supernatant. [Note—The use of a centrifuge speed of 2500 rpm for 10 min may be suitable.]

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm x 15-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 5 µL

Run time: NLT 2 times the retention time of levetiracetam

Result:

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 concentration, Cᵢ, of levetiracetam (C₂H₁₄N₂O₅) in Medium (mg/mL) after time point i:

\[
\text{Result}_i = (r_i/r_s) \times C_i
\]

rᵢ = peak response from the Sample solution

rₛ = peak response from the Standard solution

Cᵢ = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of levetiracetam (C₂H₁₄N₂O₅) dissolved at each time point (i):

\[
\text{Result}_i = C_i \times V \times (1/L) \times 100
\]

\[
\text{Result}_i = [(\text{C}_i \times [V - (2 \times V_i)]) + ([C_i + C_i] \times V_i)] \times (1/L) \times 100
\]

\[
\text{Result}_i = ((\text{C}_i \times [V - (3 \times V_i)]) + ([C_i + C_i + C_i] \times V_i)] \times (1/L) \times 100
\]

Cᵢ = concentration of levetiracetam in the portion of sample withdrawn at time point i (mg/mL)

V = volume of Medium, 900 mL

L = label claim (mg/Tablet)

Vₛ = volume of the Sample solution withdrawn from the Medium (mL)

Tolerances: See Table 10.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>10–30</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>25–45</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>45–70</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of levetiracetam (C₂H₁₄N₂O₅), dissolved at the times specified, conform to Dissolution (711), Acceptance Table 2.

• Uniformity of Dosage Units (905): Meet the requirements

IMPURITIES

Change to read:

• Organic Impurities

Solution A: Dilute 2 mL of phosphoric acid with water to 1 L.

Diluent: Acetonitrile and Solution A (5:95)

Buffer: 1.4 g/L of anhydrous dibasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and Buffer (5:95). To each L of the mixture, add 1 g of sodium 1-hexanesulfonate monohydrate.

System suitability solution: 0.3 mg/mL of USP Levetiracetam 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. Dilute with Diluent to volume. [Note—This solution contains levetiracetam and levetiracetam acid.]

Standard solution: 12.5 µg/mL of USP Levetiracetam RS in water. Sonication may be used to aid in dissolution. Pass a
portion of the solution through a suitable filter of 0.2-µm pore size.

Sample solution: Nominally equivalent to 2.5 mg/mL of levetiracetam in water, from a portion of crushed Tablets (NLT 20) prepared as follows. Transfer the weighed amount of crushed Tablet powder to a volumetric flask containing water to fill 80% of final volume. Sonicate in cold water for 10 min. Equilibrate to room temperature. Dilute with water to volume. Pass a portion through a suitable filter of 0.2-µm pore size.

Alternatively, the Sample solution having a nominal concentration of 2–3 mg/mL of levetiracetam may be prepared as follows. Finely grind NLT 10 Tablets, and transfer an amount equivalent to one Tablet to a suitable volumetric flask. Add NLT 30 mL of acetonitrile. Sonicate for 10 min, and shake using a mechanical shaker for 10 min. Add NLT 30 mL of water, and shake for 15 min using a mechanical shaker. Allow the resulting mixture to equilibrate to room temperature. Add NMT 25% of the final flask volume of acetonitrile. Dilute with water to volume. Centrifuge for 15 min, and pass a portion through a suitable filter of 0.45-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 205 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Temperatures
Column: 30°
Autosampler: 10°
Flow rate: 2 mL/min
Injection volume: 20 µL
Run time: 5 times the retention time of levetiracetam

System suitability
Samples: System suitability solution and Standard solution
Suitability requirements
Resolution: NLT 1.5 between levetiracetam and levetiracetam acid peaks, 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 any unspecified degradation product in the portion of Tablets taken:

Result = \( \left( \frac{r_i}{r_s} \right) \times \left( \frac{C_s}{C_i} \right) \times 100 \)

- \( r_i \): peak response of each impurity from the Sample solution
- \( r_s \): peak response of USP Levetiracetam RS from the Standard solution
- \( C_s \): concentration of USP Levetiracetam RS in the Standard solution (mg/mL)
- \( C_i \): nominal concentration of levetiracetam in the Sample solution (mg/mL)

Acceptance criteria: See Table 11.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam related compound B(^a) (\text{b} )</td>
<td>0.40</td>
<td>—</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Levetiracetam acid(^c)</td>
<td>1.3</td>
<td>0.30</td>
</tr>
<tr>
<td>Levetiracetam related compound A(^d)</td>
<td>1.9</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>0.10</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

\(^a\) (S)-2-Aminobutanamide.
\(^b\) Process impurities controlled in the drug substance. Included for identification purposes only. Not reported for the drug product, and not included in total impurities.
\(^c\) (S)-2-(2-Oxopyrrolidin-1-yl)butanoic acid.
\(^d\) (S)-N-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide.

ADDITIONAL REQUIREMENTS
• PACKAGING AND STORAGE: Preserve in well-closed 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