In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Lacosamide monograph.

On the basis of supporting data received from a manufacturer with tentative FDA approval, the Expert Committee proposes to widen the acceptance criteria of the Limit of Lacosamide S-Enantiomer, Total Impurities in the Organic Impurities and Water Determination tests to accommodate drug products with acceptance criteria wider than the existing monograph.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.¹

Should you have any questions, please contact Claire Chisolm, Senior Scientist II (301-230-3215 or cnc@usp.org).

¹ This text is not the official version of a USP–NF monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the USP–NF for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product’s final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the Pharmacopeial Forum must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.
Lacosamide

\[
\begin{align*}
\text{C}_{13}\text{H}_{18}\text{N}_{2}\text{O}_3 & \quad 250.30 \\
\text{Propanamide, 2-} & \text{-(acetylamino)-3-methoxy-}\text{-N-(phenylmethyl)-, (2R)-;} \\
& \text{(+)-(R)-2-(Acetylamino)-N-benzyl-3-methoxypropanamide. \quad [175481-36-4].}
\end{align*}
\]

**DEFINITION**
Lacosamide contains NLT 98.0% and NMT 102.0% of lacosamide (C_{13}H_{18}N_{2}O_{3}).

**IDENTIFICATION**
- **A. Spectroscopic Identification Tests** (197), *Infrared Spectroscopy*: 197K or 197A
- **B.** The retention time of the major peak of the Sample solution corresponds to that of the System suitability solution, as obtained in the test for Limit of Lacosamide S-Enantiomer.

**ASSAY**
- **Procedure**
  - **Solution A:** To each liter of water add 1 mL of trifluoroacetic acid.
  - **Solution B:** Acetonitrile and methanol (50:50). To each liter add 0.3 mL of trifluoroacetic acid.
  - **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>89</td>
<td>11</td>
</tr>
<tr>
<td>12.2</td>
<td>69</td>
<td>31</td>
</tr>
<tr>
<td>17.5</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>18.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>19.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>19.1</td>
<td>89</td>
<td>11</td>
</tr>
<tr>
<td>24.0</td>
<td>89</td>
<td>11</td>
</tr>
</tbody>
</table>
System suitability solution: 5 mg/mL of USP Lacosamide RS and 10 µg/mL each of USP Lacosamide Related Compound B RS and N-benzylacetamide prepared as follows. Weigh an appropriate amount of USP Lacosamide RS, USP Lacosamide Related Compound B RS, and N-benzylacetamide into a suitable volumetric flask. Dissolve in 10% of the flask volume of methanol. Dilute with water to volume.

Standard solution: 5 mg/mL of USP Lacosamide RS prepared as follows. Weigh an appropriate amount of USP Lacosamide RS into a suitable volumetric flask. Dissolve in 10% of the flask volume of methanol. Dilute with water to volume.

Sample solution: 5 mg/mL of Lacosamide prepared as follows. Weigh an appropriate amount of Lacosamide into a suitable volumetric flask. Dissolve in 10% of the flask volume of methanol. Dilute with water to volume.

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

Mode: LC
Detector: UV 258 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L7
Autosampler temperature: 10°
Flow rate: 1.2 mL/min
Injection volume: 20 µL

System suitability
Samples: System suitability solution and Standard solution
[Note—See Table 2 for relative retention times.]
Suitability requirements
Resolution: NLT 2.0 between N-benzylacetamide and lacosamide; NLT 4.5 between lacosamide and lacosamide related compound B, System suitability solution
Tailing factor: NMT 2.5, Standard solution
Relative standard deviation: NMT 0.73%, Standard solution

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of lacosamide (C₁₃H₁₈N₂O₃) in the portion of Lacosamide taken:

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

⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻permalinkation

IMPURITIES

- Residue on Ignition (281): NMT 0.1%

Change to read:

- Limit of Lacosamide S-Enantiomer

Mobile phase: Heptane, isopropyl alcohol, and water (90: 10: 0.3)
System suitability solution: 1 mg/mL of USP Lacosamide RS and 5 µg/mL of USP Lacosamide S-Enantiomer RS in Mobile phase
Sample solution: 1 mg/mL of Lacosamide in Mobile phase
Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 215 nm
Column: 4.6-mm x 25-cm; 10-µm packing L51
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: NLT 1.7 times the retention time of lacosamide

System suitability
Sample: System suitability solution
[Note—The relative retention times for lacosamide S-enantiomer and lacosamide are 0.75 and 1.0, respectively.]

Suitability requirements
Resolution: NLT 3.0 between lacosamide S-enantiomer and lacosamide
Signal-to-noise ratio: NLT 10 for S-enantiomer

Analysis
Sample: Sample solution
Calculate the percentage of S-enantiomer in the portion of Lacosamide taken:

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

\[ r_U = \text{peak response of S-enantiomer} \]
\[ r_T = \text{sum of the peak responses of lacosamide and S-enantiomer} \]

Acceptance criteria: NMT ▲0.50% ▲(TBD)

Change to read:

- Organic Impurities
  Solution A, Solution B, Mobile phase, System suitability solution, Sample solution, and Chromatographic system: Proceed as directed in the Assay.

  Diluent: Methanol and water (10:90)

  Sensitivity solution: 2.5 µg/mL of USP Lacosamide RS in Diluent

  Standard solution: 0.005 mg/mL of USP Lacosamide RS in Diluent

System suitability
Samples: System suitability solution, Sensitivity solution, and Standard solution
[Note—See Table 2 for relative retention times.]

Suitability requirements
Resolution: NLT 2.0 between N-benzylacetamide and lacosamide; NLT 4.5 between lacosamide and lacosamide related compound B, System suitability solution

Relative standard deviation: NMT 5.0%, Standard solution

Signal-to-noise ratio: NLT 10, Sensitivity solution

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

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

\[ r_U = \text{peak response of each impurity from the Sample solution} \]
\( r_S \) = peak response of lacosamide from the Standard solution
\( C_S \) = concentration of USP Lacosamide RS in the Standard solution (mg/mL)
\( C_U \) = concentration of Lacosamide in the Sample solution (mg/mL)
\( F \) = relative response factor (see Table 2)

**Acceptance criteria:** See Table 2. The reporting threshold is 0.05%.

<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>Lacosamide related compound F(^b)</td>
<td>0.68</td>
<td>1.0</td>
<td>0.15</td>
</tr>
<tr>
<td>( N )-Benzyllactamamide</td>
<td>0.92</td>
<td>1.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Lacosamide related compound B</td>
<td>1.15</td>
<td>1.0</td>
<td>0.15</td>
</tr>
<tr>
<td>( N )-Methyl lacosamide(^b)</td>
<td>1.32</td>
<td>1.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Ureidolacosamide(^c)</td>
<td>1.53</td>
<td>1.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Any individual unspecified impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>▲1.0▲ (TBD)</td>
</tr>
</tbody>
</table>

\( ^a \) 2-Acetamido-\( N \)-benzyl-3-hydroxypropanamide.

\( ^b \) (\( R \))-\( N \)-Benzyll-3-methoxy-2-(\( N \)-methylacetamido)propanamide.

\( ^c \) (\( R \))-\( N \)-Benzyll-2-(3-benzylureido)-3-methoxypropanamide.

**SPECIFIC TESTS**

* change to read:

- **Water Determination (921), Method I:** NMT ▲0.5%.▲ (TBD)
  
  [NOTE—Method Ia or Method Ic may be used.]

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in well-closed containers, and store at controlled room temperature.
- **USP Reference Standards (11).**

  - **USP Lacosamide RS**
  - **USP Lacosamide Related Compound B RS**
  - 2-Acetamido-3-(benzylamino)-3-oxopropyl acetate.
    
    \[ \text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_4 \]
    
    278.31

  - **USP Lacosamide S-Enantiomer RS**

    (S)-2-(Acetylamino)-\( N \)-benzyl-3-methoxypropanamide.
C_{13}H_{18}N_{2}O_{3}  
250.29

Page Information:
Not Applicable

Current DocID:
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