Lacosamide

Type of Posting	Notice of Intent to Revise
Posting Date	28-May-2021
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 4

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]

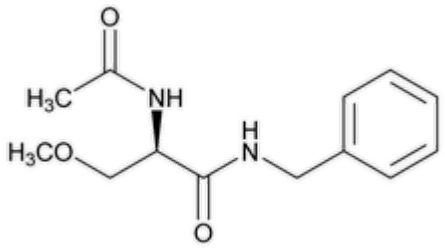
Should you have any questions, please contact Claire Chisolm, Senior Scientist II (301-230-3215 or cnc@usp.org).

[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*.

Notice of Intent to Revise
Official: To Be Determined

Lacosamide



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$C_{13}H_{18}N_2O_3$ 250.30
Propanamide, 2-(acetylamino)-3-methoxy-*N*-(phenylmethyl)-, (2*R*)-;
(+)-(*R*)-2-(Acetylamino)-*N*-benzyl-3-methoxypropanamide. [175481-36-4].

DEFINITION
Lacosamide contains NLT 98.0% and NMT 102.0% of lacosamide ($C_{13}H_{18}N_2O_3$).

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

Time (min)	Solution A (%)	Solution B (%)
0	89	11
12.2	69	31
17.5	23	77
18.0	0	100
19.0	0	100
19.1	89	11
24.0	89	11

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 ($C_{13}H_{18}N_2O_3$) in the portion of Lacosamide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the USP Lacosamide RS in the *Standard solution* (mg/mL)

C_U = concentration of Lacosamide in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0%

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 × 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:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of *S*-enantiomer

r_T = 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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = 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 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Lacosamide related compound F[a]	0.68	1.0	0.15
N-Benzylacetamide	0.92	1.4	0.15
Lacosamide	1.0	1.0	—
Lacosamide related compound B	1.15	1.0	0.15
N-Methyl lacosamide[b]	1.32	1.0	0.15
Ureidolacosamide[c]	1.53	1.4	0.15
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	▲1.0▲ (TBD)

[a] 2-Acetamido-*N*-benzyl-3-hydroxypropanamide.

[b] (*R*)-*N*-Benzyl-3-methoxy-2-(*N*-methylacetamido)propanamide.

[c] (*R*)-*N*-Benzyl-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.

$C_{14}H_{18}N_2O_4$ 278.31

USP Lacosamide *S*-Enantiomer RS

(*S*)-2-(Acetylamino)-*N*-benzyl-3-methoxypropanamide.

$C_{13}H_{18}N_2O_3$	250.29

Page Information:

Not Applicable

Current DocID: