Levetiracetam Tablets

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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 Levetiracetam Tablets monograph.

The purpose of this revision is to add *Dissolution Test 5* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s).

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 Sujatha Ramakrishna, Senior Principal Scientist (301-816-8349 or sxr@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

Levetiracetam Tablets

DEFINITION

Levetiracetam Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$).

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 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 acetone 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 acetone. 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 acetone 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*.)

  Mode: LC

  Detector: UV 220 nm

  Column: 4.6-mm × 25-cm; 4-µm packing L1

  Flow rate: 2 mL/min

  Injection volume: 10 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 of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) in the portion of Tablets 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 USP Levetiracetam RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

Test 1

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: See *Table 1*.

Table 1

Tablet Strength (mg/Tablet)	Time (min)
250	15
500	15
750	15
1000	30

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 though 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

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 ($C_8H_{14}N_2O_2$) dissolved:

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

r_U = 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)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 70% (Q) of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) in 15 min for Tablets labeled to contain 250, 500, or 750 mg; NLT 80% (Q) of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) in 30 min for Tablets labeled to contain 1000 mg

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

Medium: Water; 900 mL, deaerate, if necessary

Apparatus 2: 50 rpm

Time: 15 min

Buffer: 1.36 g/L of monobasic potassium phosphate, adjusted with 10% potassium hydroxide to a pH of 5.0

Mobile phase: Acetonitrile and *Buffer* (10:90)

Standard solution: 54 µg/mL of USP Levetiracetam RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter. Dilute an aliquot with *Medium* 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 × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times D \times V \times 100$$

r_U = 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)

L = label claim (mg/Tablet)

D = dilution factor of the *Sample solution*

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) is dissolved.

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

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Buffer, Mobile phase, Standard solution, Sample solution, Chromatographic system, System suitability, and **Analysis:** Proceed as directed for *Test 1*.

Tolerances: NLT 80% (Q) of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) is dissolved.

Test 4: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 4*.

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 ($C_8H_{14}N_2O_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (1/L) \times 100$$

r_U = 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

D = dilution factor of the *Sample solution*

L = label claim (mg/Tablet)

Tolerances: NLT 85% (Q) of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) is dissolved.

▲**Test 5:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 5*.

Medium: 0.1 N hydrochloric acid VS, deaerated; 500 mL

Apparatus 2: 50 rpm

Time: 30 min

Buffer: 1.36 g/L of monobasic potassium phosphate, adjusted with 10% w/v potassium hydroxide solution to a pH of 5.0

Mobile phase: Acetonitrile and *Buffer* (10:90)

Standard solution: (L/500) mg/mL in *Medium*, where L is the label claim in mg/Tablet. Sonication may be necessary for complete dissolution.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.22-µm pore size and discard the first few milliliters.

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: 1.5 mL/min

Temperatures

Autosampler: 10°

Column: 30°

Injection volume: 5 µL

Run time: NLT 1.6 times the retention of the levetiracetam

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) dissolved:

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

r_U = peak response of levetiracetam 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)

L = label claim (mg/Tablet)

V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (Q) of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$) is dissolved. ▲ (TBD)

- **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:

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

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of 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 (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Levetiracetam related compound B[a]	0.54	—	—
Levetiracetam	1.0	—	—
Levetiracetam related compound A[a,b]	1.7	—	—
Levetiracetam acid[c]	2.1	0.79	0.3
Any individual unspecified degradation product	—	1.0	0.1
Total impurities	—	—	0.6

[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.

  $C_4H_{10}N_2O \cdot HCl$ 138.60

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Not Applicable

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