Levetiracetam Tablets

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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 ($C_8H_{14}N_2O_2$).

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 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. • (RB 1-Mar-2018)

• **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	—	—

[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.

Table 2 *(Continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
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