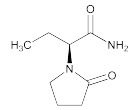
Levetiracetam



$C_8H_{14}N_2O_2$ 170.21

1-Pyrrolidineacetamide, α-ethyl-2-oxo-, (α*S*)-;
(–)-(*S*)-α-Ethyl-2-oxo-1-pyrrolidineacetamide [102767-28-2].

DEFINITION

Levetiracetam contains NLT 98.0% and NMT 102.0% of $C_8H_{14}N_2O_2$, calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197K⟩
- **B.** The retention time of the major peak for levetiracetam from the *Sample solution* corresponds to that of the levetiracetam *S*-enantiomer from the *System suitability solution*, as obtained in the test for *Limit of Levetiracetam R-Enantiomer*.

ASSAY

- **PROCEDURE**

Buffer: 2.7 g/L of monobasic potassium phosphate in water. Adjust with 2% aqueous potassium hydroxide (w/v) to a pH of 5.5.
Solution A: Acetonitrile and *Buffer* (1:19)
Solution B: Acetonitrile
Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
3	100	0
20	71	29

System suitability solution: 0.2 mg/mL of USP Levetiracetam RS and 0.08 mg/mL of USP Levetiracetam Related Compound A RS in *Solution A*. Prepare by first dissolving the required amount of USP Levetiracetam RS in a suitable volumetric flask. Add 10% of the flask 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. Add the required amount of USP Levetiracetam Related Compound A RS, sonicate to dissolve, dilute with *Solution A* to volume, and mix.
Standard solution: 0.1 mg/mL of USP Levetiracetam RS in *Solution A*
Sample solution: 0.1 mg/mL of Levetiracetam in *Solution A*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 205 nm
Column: 4.6-mm × 15-cm; packing L1
Flow rate: 0.9 mL/min
Injection size: 10 µL
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times are given in *Impurity Table 1*.]
Suitability requirements
Relative standard deviation: NMT 1.0%
[NOTE—If system suitability criteria cannot be met, it is recommended that the column temperature be maintained at 20° to stabilize the system.]
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of $C_8H_{14}N_2O_2$ in the portion of Levetiracetam taken:

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

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)
C_U = concentration of Levetiracetam in the *Sample solution* (mg/mL)
F = percentage of levetiracetam *R*-enantiomer from the test for *Limit of Levetiracetam R-Enantiomer*

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

Inorganic Impurities

- **RESIDUE ON IGNITION** ⟨281⟩**:** NMT 0.1%
- **HEAVY METALS,** *Method II* ⟨231⟩**:** 20 ppm

Organic Impurities

- **PROCEDURE 1: LIMIT OF LEVETIRACETAM RELATED COMPOUND B**

[NOTE—Perform this test only if levetiracetam related compound B is a known process impurity.]
Buffer: 1.22 g of sodium 1-decanesulfonate in 1 L of water containing about 1.3 mL of phosphoric acid. Adjust with 20% (w/v) potassium hydroxide to a pH of 3.0.
Mobile phase: Acetonitrile and *Buffer* (3:17)
System suitability solution: 2 mg/mL of USP Levetiracetam Related Compound B RS in *Mobile phase*
Standard solution: 0.002 mg/mL of USP Levetiracetam Related Compound B RS in *Mobile phase*
Sample solution: 2.0 mg/mL of Levetiracetam in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 200 nm
Column: 4.6-mm × 25-cm; packing L1
Flow rate: 1.0 mL/min
Injection size
System suitability: 10 µL
Analysis: 50 µL
System suitability
Sample: *System suitability solution*
[NOTE—The retention time for levetiracetam related compound B is 9 min.]
Suitability requirements
Tailing factor: NMT 3.0
[NOTE—If a significant tailing of the levetiracetam related compound B peak is observed (greater than 3.0), it is recommended that the column temperature be maintained at 27° to stabilize the system.]
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of levetiracetam related compound B in the portion of Levetiracetam taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of levetiracetam related compound B from the *Sample solution*
r_S = peak response of levetiracetam related compound B from the *Standard solution*
C_S = concentration of USP Levetiracetam Related Compound B RS in the *Standard solution* (mg/mL)
C_U = concentration of Levetiracetam in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of levetiracetam related compound B free base, 102.1
M_{r2} = molecular weight of levetiracetam related compound B, 138.6

Acceptance criteria: NMT 0.10%

[NOTE—The amount of levetiracetam related compound B measured is to be included in the total impurities in the test for *Organic Impurities, Procedure 2*.]

- **PROCEDURE 2**

Buffer, Solution A, Solution B, Mobile phase, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 0.005 mg/mL of USP Levetiracetam RS in *Solution A*

Sample solution: 5 mg/mL of Levetiracetam in *Solution A*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Levetiracetam 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 = concentration of Levetiracetam in the *Sample solution* (mg/mL)
F = relative response factor (see *Impurity Table 1*)

[NOTE—Disregard any peak with a relative retention time of 0.19 or less.]

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 0.4%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Pyridin-2-ol[a]	0.37	1.0	0.025
Levetiracetam acid[b]	0.62	1.2	0.3
Levetiracetam	1.00	—	—
Levetiracetam related compound A[c]	1.25	0.35	0.05
Any individual unspecified impurity	—	1.0	0.05

[a] Not included in the *Total impurities* limit.

[b] *(S)*-2-(2-Oxopyrrolidin-1-yl)butanoic acid. Included in the *Total impurities* limit.

[c] *(S)-N*-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide. Included in the *Total impurities* limit only if levetiracetam related compound B is a known process impurity.

SPECIFIC TESTS

- **WATER DETERMINATION,** *Method Ia* ⟨**921**⟩**:** NMT 0.5%
- **LIMIT OF LEVETIRACETAM *R*-ENANTIOMER**

Mobile phase: *n*-Hexane and dehydrated alcohol (4:1)

System suitability solution: 0.1 mg/mL of USP Levetiracetam Racemic Mixture RS in *Mobile phase*

Standard solution: 0.05 mg/mL of USP Levetiracetam RS in *Mobile phase*

Sample solution: 10 mg/mL of Levetiracetam 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: 1.0 mL/min
Injection size: 20 µL

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for levetiracetam *R*-enantiomer and levetiracetam *S*-enantiomer are 0.55 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 4.0 between the *R*- and *S*-enantiomers

[NOTE—If a loss of resolution (less than 4.0) is observed, it is recommended that the column temperature be maintained at 25° to stabilize the system.]

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of levetiracetam *R*-enantiomer in the portion of Levetiracetam taken:

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

r_U = peak response of levetiracetam *R*-enantiomer 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 = concentration of Levetiracetam in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.8%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at room temperature.
- **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Levetiracetam RS

USP Levetiracetam Racemic Mixture RS

A 1:1 mixture of levetiracetam *S*-enatiomer-(2*S*)-2-(2-oxopyrrolidin-1-yl)butanamide and levetiracetam *R*-enantiomer (2*R*)-2-(2-oxopyrrolidin-1-yl)butanamide.

USP Levetiracetam Related Compound A RS

(*S*)-*N*-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide.

$C_8H_{14}ClNO_3$ 207.65

USP Levetiracetam Related Compound B RS

(*S*)-2-Aminobutanamide hydrochloride.

$C_4H_{10}N_2O \cdot HCl$ 138.6

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**⟩
- **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.