Levetiracetam Oral Solution

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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Levetiracetam Oral Solution monograph. The purpose for the revision is to widen the upper limit of pH range from 6.3 to 7.0 to be consistent with the FDA-approved specification.

The Levetiracetam Oral Solution Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Ren-Hwa Yeh, Senior Scientific Liaison (301-998-6818 or rhy@usp.org).

Levetiracetam Oral Solution

DEFINITION

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

IDENTIFICATION

• **A.** The retention time of the major peak in the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **PROCEDURE**

Solution A: Dilute 1 mL of phosphoric acid with water to 1 L.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	92	8
6	92	8
7	40	60
10	40	60
11	92	8
15	92	8

Standard solution: 1.0 mg/mL of USP Levetiracetam RS in *Solution A*

Sample solution: Nominally 1.0 mg/mL of levetiracetam prepared as follows. Transfer a suitable volume of the Oral Solution to a suitable volumetric flask to obtain 1.0 mg/mL final concentration of levetiracetam. Add 60% of the flask volume of *Solution A*, and sonicate at room temperature for 5 min with intermittent shaking. Allow the solution to cool, and dilute with *Solution A* to volume. Pass a portion of the solution under test through a suitable filter.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 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 Oral Solution taken:

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

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)

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

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• **ORGANIC IMPURITIES**

Solution A: Dilute 2 mL of phosphoric acid with water to 1 L.

Solution B: Acetonitrile

Diluent: Acetonitrile and *Solution A* (5:95)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
7	95	5
20	90	10
30	75	25
35	50	50
40	50	50
41	100	0
50	100	0

System suitability solution: 0.2 mg/mL of USP Levetiracetam RS and 0.1 mg/mL of USP Levetiracetam Related Compound A RS in *Diluent* prepared as follows. Dissolve the required amount of USP Levetiracetam RS in 10% of the final 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, and dilute with *Diluent* to volume. [NOTE—This solution contains levetiracetam, levetiracetam acid, and levetiracetam related compound A.]

Standard solution: 3 µg/mL of USP Levetiracetam RS in *Solution A*

Sample solution: Nominally 2 mg/mL of levetiracetam prepared as follows. Transfer a suitable volume of the Oral Solution to a suitable volumetric flask. Add 60% of the flask volume of *Solution A*, and sonicate at room temperature for 5 min with intermittent shaking. Allow the solution to cool, and dilute with *Solution A* to volume. Pass a portion of the solution through a suitable filter.

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: 45°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between levetiracetam related compound A and levetiracetam acid, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Oral Solution taken:

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

r_U = peak response of the 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 for each impurity (see *Table 3*)

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Levetiracetam	1.00	—	—
Levetiracetam related compound A[a, b]	1.38	—	—
Levetiracetam acid[c]	1.46	0.92	0.3
Any individual unspecified degradation product	—	1.0	0.10
Total impurities	—	—	1.0

[a] (*S*)-*N*-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide.
[b] This is a process impurity and included for peak identification purposes only.
[c] (*S*)-2-(2-Oxopyrrolidin-1-yl)butanoic acid.

SPECIFIC TESTS

Change to read:

- **pH** ⟨791⟩**:** 4.8–▲7.0▲ (RB 1-Dec-2019)
- **Microbial Enumeration Tests** ⟨61⟩ and **Tests for Specified Microorganisms** ⟨62⟩**:** The total aerobic microbial count does not exceed 10^2 cfu/mL. The total yeasts and molds count does not exceed 10^1 cfu/mL. It meets the requirement of the test for absence of *Escherichia coli*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in light-resistant containers. Store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩
  USP Levetiracetam RS
  USP Levetiracetam Related Compound A RS
  (*S*)-*N*-(1-Amino-1-oxobutan-2-yl)-4-chlorobutanamide.
  $C_8H_{15}ClN_2O_2$ 206.67