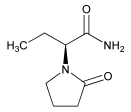
Add the following:

•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*].

» Levetiracetam contains not less than 98.0 percent and not more than 102.0 percent of $C_8H_{14}N_2O_2$, calculated on an anhydrous and solvent-free basis.

Packaging and storage—Preserve in well-closed containers, and store at room temperature.

USP Reference standards ⟨11⟩—*USP Levetiracetam RS. USP Levetiracetam Related Compound A RS. USP Levetiracetam Related Compound B RS. USP Levetiracetam Racemic Mixture RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak for levetiracetam in the chromatogram of the *Test solution* corresponds to the retention time of the levetiractem *S*-enantiomer in the chromatogram of the *System suitability solution*, as obtained in the test for *Limit of levetiracetam R-enantiomer.*

Water, *Method I* ⟨921⟩**:** not more than 0.5%.

Residue on ignition ⟨281⟩:not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:**not more than 20 ppm.

Limit of levetiracetam *R*-enantiomer—

Mobile phase—Prepare a filtered and degassed mixture of *n*-hexane and alcohol (4 : 1 v/v). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve an accurately weighed quantity of USP Levetiracetam Racemic Mixture RS, and dissolve in and dilute with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Levetiracetam RS, and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Test solution—Transfer about 200 mg of Levetiracetam, accurately weighed, to a 20-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector, and a 4.6-mm × 25-cm column that contains 10-µm packing L51. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the approximate relative retention times for levetiracetam *R*-enantiomer and levetiracetam *S*-enantiomer are 0.55 and about 1.0, respectively; and the resolution, *R,* between the *R*- and *S*-enantiomers is not less than 4.0. [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.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of levetiracetam *R*-enantiomer in the portion of Levetiracetam taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Levetiracetam RS in the *Standard solution;* C_U is the concentration, in mg per mL, of Levetiracetam in the *Test solution;* r_U is the peak response of levetiracetam *R*-enantiomer obtained from the *Test solution;* and r_S is the peak response of levetiracetam obtained from the *Standard solution*: not more than 0.8% is found.

Limit of levetiracetam related compound B [*(S)*-2-aminobutanamide hydrochloride]—[NOTE—Perform this test only if levetiracetamr related compound B is a known process impurity.]

Buffer—Dissolve about 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—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (17 : 3 v/v). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (17 : 3 v/v).

System suitability solution—Dissolve an accurately weighed quantity of USP Levetiracetam Related Compound B RS in *Diluent* to obtain a solution having a known concentration of about 2 mg per mL.

Standard solution—Quantitatively dilute a known volume of *System suitability solution* with *Diluent* to obtain a final solution having a known concentration of about 0.002 mg per mL of USP Levetiracetam Related Compound B RS.

Test solution—Dissolve an accurately weighed quantity of Levetiracetam in *Diluent* to obtain a final solution having a concentration of about 2.0 mg per mL.

Chromatographic system—The liquid chromatograph is equipped with a 200-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph about 10 µL of the *System suitability solution,* and record the peak responses as directed for *Procedure:* the approximate retention time for levetiracetam related compound B is about 9 minutes; the tailing factor for the levetiracetam related compound B peak is not more than 3.0; and the relative standard deviation for replicate injections is not more than 2.0%. [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.]

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of levetiracetam related compound B in the portion of Levetiracetam taken by the formula:

$$100(C_S / C_U)(r_S / r_U)(102.1/138.6)$$

in which C_S is the concentration, in mg per mL, of USP Levetiracetam Related Compound B RS in the *Standard solution;* C_U is the concentration, in mg per mL, of Levetiracetam in the *Test solution;* r_U is the peak response for levetiracetam related compound B, if present, in the *Test solution;* r_S is the peak response obtained for levetiracetam related compound B in the *Standard solution;* 102.1 is the molecular weight of levetiracetam related compound B free base; and 138.6 is the molecular weight of levetiracetam related compound B: not more than 0.10% is found. [NOTE—The amount of levetiracetam related compound B measured in this test is to be included in the total impurities in the test for *Related compounds.*]

Related compounds—

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

Standard solution—Dissolve an accurately weighed quantity of USP Levetiracetam RS in *Solution A,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.005 mg per mL.

Test solution—Transfer about 125 mg of Levetiracetam, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Solution A* to volume, and mix.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Levetiracetam taken by the formula:

$$100(1 / F)(C_S / C_U)(r_i / r_S)$$

in which F is the relative response factor (RRF) of each impurity obtained from *Table 1;* C_S is the concentration, in mg per mL, of USP Levetiracetam RS in the *Standard solution;* C_U is the concentration of Levetiracetam, in mg per mL, in the *Test solution;* r_i is the peak area for any impurity in the *Test solution;* and r_S is the peak area for levetiracetam in the *Standard solution.* [NOTE—Disregard any peak with a relative retention time of 0.19 or less.] Appropriate limits are given in *Table 1.*

Table 1

Compound	RRT	RRF	Limit NMT %
Pyridin-2-ol [1]	0.37	1.0	0.025
Levetiracetam acid[2]	0.62	1.2	0.3
Levetiracetam related compound A[3]	1.25	0.35	0.05
Any individual unspecified impurity	—	1.0	0.05
Total impurities	—	—	0.4

[1]Not included in the *Total impurities* limit.
[2]*(S)*-2-(2-Oxopyrrolidin-1-yl)butanoic acid. Included in the *Total impurities* limit.
[3]*(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.

Assay—

Buffer solution—Dissolve about 0.26 g of monobasic potassium phosphate in 1 L of water. Adjust with 2% aqueous potassium hydroxide (w/v) to a pH of 5.5.

Solution A—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (19 : 1 v/v).

Solution B—Use acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 5 mg of USP Levetiracetam RS into a 25-mL volumetric flask, and dissolve in 2.5 mL of 0.1 N potassium hydroxide. Let the mixture react at room temperature for about 15 minutes, and then neutralize by adding 2.5 mL of 0.1 N hydrochloric acid. Add about 2 mg of USP Levetiracetam Related Compound A RS, sonicate to dissolve, dilute with *Solution A* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Levetiracetam RS in *Solution A,* and dilute with *Solution A* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Levetiracetam in *Solution A,* and dilute with *Solution A* to obtain a solution having a nominal concentration of about 0.1 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector, and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 0.9 mL per minute. The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–3	100	0	isocratic
3–20	100→71	0→29	linear gradient

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are given in *Table 1;* the column efficiency is not less than 50,000 theoretical plates calculated for the levetiracetam peak; and the relative standard deviation for replicate injections is not more than 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.]

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the content, in percentage, of $C_8H_{14}N_2O_2$ in the portion of Levetiracetam taken by the formula:

$$[100(C_S / C_U)(r_U / r_S)] - \%\text{ of levetiracetam } R\text{-enantiomer}$$

in which C_S is the concentration, in mg per mL, of USP Levetiracetam RS in the *Standard preparation;* C_U is the nominal concentration, in mg per mL, of Levetiracetam in the *Assay preparation;* r_U and r_S are the peak responses for levetiracetam obtained from the *Assay preparation* and the *Standard preparation*, respectively; and the % of levetiracetam *R*-enantiomer is obtained from the test for *Limit of levetiracetam R-enantiomer.* ●(RB 1-Aug-2009)