

BRIEFING

Levetiracetam. This monograph proposal was published on the USP Website as a draft USP Pending Standard for public comments. The MD-PP expert committee has reviewed all the comments that were received and has approved the monograph as an Authorized USP Pending Standard.

Comment 1: It was suggested that the name of the impurity, currently listed as pyrrolidine-*N*-butyric acid, does not reflect the actual chemical structure.

Response: The impurity name has been revised with a simpler common name and the correct chemical name has been added in the footnote.

Comment 2: It was suggested that the limit for related compound A should be 0.05%, based on the total daily dose.

Response: Comment incorporated.

Comment 3: It was requested to add a *Note* in the test for *Related compounds* to allow the analyst to disregard the peak due to levetiracetam related compound B, which elutes at a relative retention time (RRT) of 0.19.

Response: Comment incorporated with a *Note*.

Comment 4: It was requested that in the test for *Limit of levetiracetam related compound B* the limit should be increased to 0.10% to be consistent with the tentatively approved ANDA.

Response: Comment incorporated.

Comment 5: It was suggested that Levetiracetam has known polymorphs, and therefore the polymorph equalization procedure for IR should be included.

Response: The comment was not incorporated because of a lack of sufficient data on other polymorphs.

Comment 6: A comment was made that questioned the rationale behind the “solvent-free” basis while no test or limit has been given for residual solvents.

Response: The comment was not incorporated because the levels of all the residual solvents used in the process are below the limits specified in general test chapter *Residual Solvents* (467), and therefore the test method or limits are not included. “Solvent-free” basis” is necessary to ensure that the sum of all the residual solvents does not impact the *Assay*.

Comment 7: It was requested that there be a 10-fold lowering of the concentration of the *Test solution* in the test for *Limit of D-levetiracetam*.

Response: The comment was not incorporated because of a lack of supporting data.

Comment 8: It was requested to lower the limit for the *Heavy metals* test from 200 ppm to 10 ppm based on total daily intake.

Response: The comment was not incorporated because of a lack of supporting data.

Comment 9: It was suggested that a derivatization–detection scheme be used in the test for *Limit of levetiracetam related compound B*.

Response: The comment was not incorporated because of a lack of supporting data.

The proposed method in the test for *Limit of D-levetiracetam* is based on analyses performed using a Chiral Pak AD brand of 10- μ m L51 column. The typical retention time for L-levetiracetam is about 13 minutes. The proposed method in the test for *Limit of levetiracetam related compound B* is based on analyses performed using an Xterra RP18 brand of 5- μ m L1 column in which the typical retention time for levetiracetam related compound B is about 9 minutes. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses

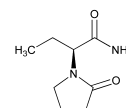
performed using a YMC-Pack AQ brand of 3- μ m L1 column in which the typical retention time for levetiracetam is about 10.5 minutes.

(MD-PP: R. Ravichandran) RTS—C42827

Add the following:

■Levetiracetam

v. 1 Authorized March 27, 2008



C₈H₁₄N₂O₂ 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 C₈H₁₄N₂O₂, 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 *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

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Water, Method I (921): not more than 0.5%.

Residue on ignition (281): not more than 0.1%.

$$100(C_s/C_v)(r_u/r_s)$$

Heavy metals, Method II (231): not more than 20 ppm.

Limit of D-levetiracetam—

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 L-levetiracetam and D-levetiracetam are 1.0 and about 0.55, respectively; the resolution, *R*, between L-levetiracetam and D-levetiracetam 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 D-levetiracetam in the portion of Levetiracetam taken by the formula:

in which *C_s* is the concentration, in mg per mL, of USP Levetiracetam RS in the *Standard solution*; *C_v* is the concentration, in mg per mL, of Levetiracetam in the *Test solution*; *r_v* is the peak response of D-levetiracetam obtained from the *Test solution*; and *r_s* is the peak response of levetiracetam obtained from the *Standard solution*: not more than 0.50% is found.

Limit of levetiracetam related compound B ((S)-2-aminobutanamide)—

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 levetir-

acetam 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:

$$100(C_s/C_v)(r_s/r_v)(102.1/138.6)$$

in which C_s is the concentration, in mg per mL, of USP Levetiracetam Related Compound B RS in the *Standard solution*; C_v is the concentration, in mg per mL, of Levetiracetam in the *Test solution*; r_v 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 hydrochloride: not more than 0.10% is found.

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:

$$100(1/F)(C_s/C_T)(r_i/r_s)$$

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_T 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
			%
Levetiracetam acid ¹	0.62	1.2	0.10
Levetiracetam related compound A ²	1.25	0.35	0.05
Any individual unspecified impurity	—	1.0	0.05
Total*	—	—	0.40

¹ (S)-2-(2-Oxopyrrolidin-1-yl)butanoic acid.

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

* Includes levetiracetam related compound B.

Assay—

Buffer solution—Dissolve about 0.26 g of monobasic potassium phosphate in 1 L of water. Adjust with aqueous potassium hydroxide 2% (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).

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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 solution. Let the mixture react at room temperature for about 15 minutes, and then neutralize by an addition of 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)	<i>Solution A</i> (%)	<i>Solution B</i> (%)	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 fewer 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 C₈H₁₄N₂O₂ in the portion of Levetiracetam taken by the formula:

$$[100(C_s / C_v)(r_v / r_s)] - \%D\text{-levetiracetam}$$

in which C_s is the concentration, in mg per mL, of USP Levetiracetam RS in the *Standard preparation*; C_v is the nominal concentration, in mg per mL, of Levetiracetam in the *Assay preparation*; r_v is the peak response for levetiracetam obtained from the *Assay preparation*; r_s is the peak response for levetiracetam obtained from the *Standard preparation*; and the %D-levetiracetam is obtained from the test for *Limit of D-levetiracetam*. ■