

BRIEFING

Lamotrigine. 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. The following is a summary of the comments received and the Expert Committee's responses.

Comment 1: Commenter indicated that the run time in *Limit of Related compound B* is inconsistent with the retention time of lamotrigine related compound B.

Response 1: Comment was incorporated by deleting the run time.

Comment 2: Commenter indicated that the *Assay* calls for "Solution B: acetonitrile" while it is not used anywhere.

Response 2: Comment was incorporated by deleting the subsection *Solution B*.

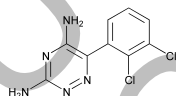
The test for *Related compounds* and the *Assay* are based on analyses performed using the Inertsil ODS2 brand of L1 column, in which the typical retention time for lamotrigine is about 10 minutes. The proposed HPLC test for *Limit of lamotrigine related compound B* is based on analyses performed using the Inertsil ODS2 C18 brand of L1 column. The typical retention time for lamotrigine related compound B is about 15 minutes.

(MD-PP: R. Ravichandran) RTS—C43562

Add the following:

■ **Lamotrigine**

v.1 Authorized November 1, 2007



C₉H₇Cl₂N₅ 256.09

1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl).

3,5-Diamino-6-(2,3-dichlorophenyl)-*as*-triazine

[84057-84-1].

» Lamotrigine contains not less than 98.0 percent and not more than 102.0 percent of C₉H₇Cl₂N₅, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store at room temperature.

USP Reference standards <11>—*USP Lamotrigine RS*. *USP Lamotrigine Related Compound A RS*. *USP Lamotrigine Related Compound B RS*.

Identification—

A: *Infrared Absorption* <197K>.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

Loss on drying <731>—Dry it at 105° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition <281>: not more than 0.1%.

Heavy metals, Method II <231>: 0.001%.

Limit of lamotrigine related compound B—[NOTE—Lamotrigine related compound B is 2,3-dichlorobenzoic acid.]

Buffer solution—Proceed as directed in the *Assay*.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (1:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* <621>).

Standard solution—Prepare a solution having a known concentration of about 1.6 µg per mL of USP Lamotrigine Related Compound B RS in *Mobile phase*.

Test solution—Transfer 80 mg of Lamotrigine, accurately weighed, to a 50-mL volumetric flask. Dissolve in about 15 mL of methanol, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard solution*, and record the chromatogram as directed for *Procedure*: the column efficiency is not less than 6000 theoretical plates; the signal-to-noise (S/N) ratio for lamotrigine related compound B is not less than 20; and the tailing factor for lamotrigine related compound B is not more than

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2.0. [NOTE—For identification purposes only, the retention time of lamotrigine related compound B is approximately 15 minutes].

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the chromatograms. Measure the peak area of the lamotrigine related compound B peak in the *Standard solution* and in the *Test solution*. Calculate the percentage of lamotrigine related compound B in the portion of Lamotrigine taken by the formula:

$$100(C_s/C_T)(r_U/r_S)$$

in which C_s is the concentration, in mg per mL, of USP Lamotrigine Related Compound B RS in the *Standard solution*; C_T is the concentration, in mg per mL, of Lamotrigine in the *Test solution*; and r_U and r_S are the peak responses for lamotrigine related compound B obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.1% of lamotrigine related compound B is found.

Related compounds—[NOTE—Lamotrigine related compound A is 2,4-dichlorolamotrigine.]

Mobile phase—Proceed as directed in the *Assay*.

Resolution solution—Dissolve accurately weighed quantities of USP Lamotrigine RS and USP Lamotrigine Related Compound A RS in *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL and 0.04 mg per mL, respectively.

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* (621))—Proceed as directed in the *Assay*. Chromatograph about 10 µL of the *Resolution solution*, and record the peak areas as directed for *Procedure*: the relative retention times are 1.0 and 1.1 for lamotrigine and lamotrigine related compound A, respectively; the resolution, R , between lamotrigine and lamotrigine related compound A is not less than 1.5; and the tailing factor for the lamotrigine peak is not more than 2.0.

Procedure—Inject about 10 µL of the *Test solution* into the chromatograph, and allow the chromatogram to run four times longer than the retention time for lamotrigine. Measure the area responses for all the peaks in the *Test solution*. Calculate the percentage of each impurity in the portion of Lamotrigine taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the individual peak response for the lamotrigine related compounds, and r_s is the sum of the responses of all the peaks in the chromatogram obtained from the *Test solution*: not more than 0.1% of lamotrigine related compound A is found; not more than 0.1% of any other individual unidentified impurity is found; and not more than 0.2% of total impurities, excluding lamotrigine related compound B, is found.

Assay—

Buffer solution—Transfer 14 mL of triethylamine to a 1-L volumetric flask. Dilute with water to volume, and mix. Adjust with phosphoric acid to a pH of 2.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (3:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

Standard preparation—Transfer 25 mg, accurately weighed, of USP Lamotrigine RS to a 25-mL volumetric flask. Dissolve in 5 mL of methanol, and dilute with *Mobile phase* to volume.

Assay preparation—Transfer 50 mg, accurately weighed, of Lamotrigine to a 50-mL volumetric flask. Dissolve in 5 mL of methanol, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 250-nm detector and a 4.6-mm × 25-cm column containing 5-µm L1 packing. The flow rate is about 0.8 mL per minute, and the column temperature is maintained at 40°. Chromatograph the *Standard preparation*, and record the peak areas as directed

for *Procedure*: the tailing factor for the lamotrigine peak is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 μ L) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the lamotrigine peak. Calculate the percentage of $C_9H_7Cl_2N_5$ in the portion of Lamotrigine 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 Lamotrigine RS in the *Standard preparation*; C_u is the concentration, in mg per mL, of Lamotrigine in the *Assay preparation*; and r_u and r_s are the lamotrigine peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■

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