Table 2 *(Continued)*

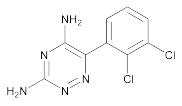
Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Lamivudine-(*S*-sulfoxide)[d]	0.20	1.0	—*
Lamivudine-(*R*-sulfoxide)[e]	0.22	1.0	—*
Zidovudine related compound C[f]	0.27	1.7	1.5
Lamivudine diastereomer[g]	0.50	1.0	0.2
Lamivudine	0.52	—	—
Zidovudine-(thymidine)[h]	0.60	1.0	—*
Lamivudine-(uracil derivative)[i]	0.70	1.0	—*
Lamivudine-(salicylic acid)[j]	0.80	1.0	—*
Zidovudine	1.00	—	—
Zidovudine related compound B[k]	1.10	1.0	—*
Individual unidentified impurity	—	1.0	0.1
Total lamivudine related impurities (the limit includes all lamivudine related impurities)	—	—	0.6
Total zidovudine related impurities (the limit includes individual unidentified impurities)	—	—	2.0

[a] 4-Aminopyrimidin-2(1*H*)-one.
[b] Pyrimidine-2,4(1*H*,3*H*)-dione.
[c] (2*R*,5*S*)-5-(4-Amino-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolane-2-carboxylic acid (2*R*,5*S*)-5-(cytosine-1-yl)-1,3-oxathiolane-2-carboxylic acid.
[d] 1-[(2*R*,3*S*,5*SS*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine *S*-oxide.
[e] 1-[(2*R*,3*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine *S*-oxide.
[f] 5-Methylpyrimidine-2,4(1*H*,3*H*)-dione.
[g] 1-[(2*S*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.
[h] [1-(2-Deoxy-β-D-ribofuranosyl)]thymine.
[i] (2*RS*,5*SR*)1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]uracil.
[j] 2-Hydroxybenzoic acid.
[k] 3′-Chloro-3′-deoxythymidine.
***** The individual impurity limit is not included because these are processes/other impurities monitored individually in the drug substances.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, protected from light, and store between 2° and 30°.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Lamivudine RS
  USP Lamivudine Resolution Mixture B RS
  USP Zidovudine RS

Lamotrigine



$C_9H_7Cl_2N_5$ 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].

DEFINITION

Lamotrigine contains NLT 98.0% and NMT 102.0% of $C_9H_7Cl_2N_5$, calculated on the dried basis.

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**

Diluent: Dilute 8.5 mL of hydrochloric acid with water to 1 L (0.1 M hydrochloric acid).
Buffer: 2.7 g/L of monobasic potassium phosphate in water
Solution A: Triethylamine and *Buffer* (1:150). Adjust with phosphoric acid to a pH of 2.0.
Solution B: Acetonitrile
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	76.5	23.5
4	76.5	23.5
14	20	80
15	76.5	23.5
19	76.5	23.5

Standard solution: 0.2 mg/mL of USP Lamotrigine RS prepared as follows. Transfer the required amount of USP Lamotrigine RS to a suitable volumetric flask, and add 5% of the final volume with methanol to facilitate dissolution. Dilute with *Diluent* to volume.
Sample solution: 0.2 mg/mL of Lamotrigine prepared as follows. Transfer the required amount of lamotrigine to a suitable volumetric flask, and add 5% of the final volume with methanol to facilitate dissolution. Dilute with *Diluent* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 270 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1 mL/min
Injection size: 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 1.5%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of lamotrigine ($C_9H_7Cl_2N_5$) in the portion of Lamotrigine taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Lamotrigine RS in the *Standard solution* (mg/mL)
C_U = concentration of Lamotrigine in the *Sample solution* (mg/mL)
Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** ⟨**281**⟩**:** NMT 0.1%
- **HEAVY METALS,** *Method II* ⟨**231**⟩**:** 10 ppm
- **LIMIT OF LAMOTRIGINE RELATED COMPOUND B**

Diluent, **Solution A**, and **Sample solution:** Prepare as directed in the *Assay*.

Mobile phase: Acetonitrile and *Solution A* (35:65)
System suitability stock solution: 0.2 mg/mL of USP Lamotrigine RS prepared as follows. Transfer the required amount of USP Lamotrigine RS to a suitable volumetric flask, and add 5% of the final volume with methanol to facilitate dissolution. Dilute with *Diluent* to volume.
Standard stock solution: 0.01 mg/mL of USP Lamotrigine Related Compound B RS prepared as follows. Transfer the required amount of USP Lamotrigine Related Compound B RS to a volumetric flask. Add 80% of the flask volume of methanol, and acidify with 1% of the flask volume of hydrochloric acid. Allow to cool, and dilute with methanol to volume. Dilute a portion of this solution with *Diluent.*
System suitability solution: 1 µg/mL of lamotrigine related compound B from the *Standard stock solution* in *System suitability stock solution*
Standard solution: 5 µg/mL of lamotrigine related compound B from the *Standard stock solution* in *Diluent*
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: 35°
Flow rate: 1 mL/min
Injection size: 10 µL
Run time: 2 times the retention time of lamotrigine related compound B
System suitability
Sample: *System suitability solution*
[NOTE—Identify the peaks in the *System suitability solution,* taking into account that lamotrigine is unretained, eluting at or near the solvent front.]
Suitability requirements
Tailing factor: NMT 2.0 for the lamotrigine related compound B peak
Relative standard deviation: NMT 5.0% for the lamotrigine related compound B peak
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of lamotrigine related compound B in the portion of Lamotrigine taken:

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

r_U = peak response for lamotrigine related compound B from the *Sample solution*
r_S = peak response for the lamotrigine related compound B from the *Standard solution*
C_S = concentration of USP Lamotrigine Related Compound B RS in the *Standard solution* (µg/mL)
C_U = concentration of Lamotrigine in the *Sample solution* (µg/mL)

Acceptance criteria: NMT 0.1% of lamotrigine related compound B. [NOTE—Lamotrigine related compound D, if present, will elute at a retention time of about 1.5 relative to lamotrigine related compound B. Disregard this peak as it is quantified in the test for *Organic Impurities*.]

- **ORGANIC IMPURITIES**

Diluent, Buffer, Solution A, Solution B, Mobile phase, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability stock solution: 0.2 mg/mL of USP Lamotrigine RS prepared as follows. Transfer the required amount of USP Lamotrigine RS to a suitable volumetric flask, and add 5% of the final volume with methanol to facilitate dissolution. Dilute with *Diluent* to volume.
Impurities stock solution: 0.1 mg/mL of each of USP Lamotrigine Related Compound C RS and USP Lamotrigine Related Compound D RS prepared as follows. Transfer suitable quantities of the Reference Standards to a suitable volumetric flask. Add an amount of methanol equal to 80% of the flask volume, and acidify with 1% of the flask volume of hydrochloric acid. Allow to cool. Dilute with methanol to volume.
System suitability solution: 0.5 µg/mL each of lamotrigine related compound C and lamotrigine related compound D from *Impurities stock solution* in *System suitability stock solution*
System suitability
Sample: *System suitability solution*
[NOTE—Refer to *Table 2* for relative retention times.]
Suitability requirements
Resolution: NLT 2.0 between lamotrigine and lamotrigine related compound C peaks
Analysis
Samples: *Diluent* and *Sample solution*
[NOTE—Disregard any peak that may be present in the chromatogram of the *Diluent* injection. Disregard any peak due to lamotrigine related compound B, because it is quantified in the test for *Limit of Lamotrigine Related Compound B*.]
Calculate the percentage of each impurity in the portion of Lamotrigine taken:

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

r_U = peak response for each impurity from the *Sample solution*
r_S = peak response for the lamotrigine peak from the *Sample solution*
F = relative response factor for each impurity from *Table 2*

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Lamotrigine	1.0	1.0	—
Lamotrigine related compound C[a]	1.5	1.0	0.1
Lamotrigine related compound B[b,c]	3.2	—	—
Lamotrigine related compound D[d]	3.7	0.8	0.2
Any individual, unspecified impurity	—	1.0	0.1
Total impurities, excluding lamotrigine related compound B	—	—	0.2

[a] 3-Amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5(4*H*)-one.
[b] 2,3-Dichlorobenzoic acid.
[c] Included only for identification.
[d] *N*-[5-Amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-3-yl]-2,3-dichlorobenzamide.

SPECIFIC TESTS

- **LOSS ON DRYING** ⟨**731**⟩**:** Dry a sample at 105° for 3 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at room temperature.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Lamotrigine RS
USP Lamotrigine Related Compound B RS
2,3-Dichlorobenzoic acid.
$C_7H_4Cl_2O_2$ 191.01

USP Lamotrigine Related Compound C RS
3-Amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-5(4*H*)-one.
$C_9H_6Cl_2N_4O$ 257.08
USP Lamotrigine Related Compound D RS
N-[5-Amino-6-(2,3-dichlorophenyl)-1,2,4-triazin-3-yl]-2,3-dichlorobenzamide.
$C_{16}H_9Cl_4N_5O$ 429.09

Lamotrigine Tablets

DEFINITION

Lamotrigine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$).

IDENTIFICATION

- **A. Ultraviolet Absorption** ⟨197U⟩
  Standard solution: 0.02 mg/mL of USP Lamotrigine RS in 0.01 N hydrochloric acid
  Sample solution: 0.02 mg/mL of lamotrigine from crushed powdered Tablets in 0.01 N hydrochloric acid
  Acceptance criteria: The spectra of the *Standard solution* and *Sample solution* exhibit maxima and minima at the same wavelengths.
- **B.** The retention time of the lamotrigine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **Procedure**
  Buffer: 0.8 g/L of ammonium acetate. Adjust with glacial acetic acid to a pH of 4.5.
  Mobile phase: Methanol and *Buffer* (60:40)
  Standard solution: 0.05 mg/mL of USP Lamotrigine RS in *Mobile phase*
  Sample solution: Transfer • an amount equivalent to 100 mg of lamotrigine from a portion of crushed Tablets (NLT 20) • (RB 1-May-2011) to a suitable volumetric flask to obtain a nominal concentration of lamotrigine of 1.0 mg/mL. Dissolve in 70% of the flask volume of *Mobile phase* by sonicating for 20 min. Dilute with *Mobile phase* to volume. Centrifuge the solution. Quantitatively dilute a suitable volume of centrifugate with *Mobile phase* to obtain a nominal concentration of 0.05 mg/mL of lamotrigine.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 210 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L1
  Flow rate: 1 mL/min
  Injection size: 10 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 2.0 for lamotrigine
  Relative standard deviation: NMT 2.0% for lamotrigine
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Lamotrigine RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of lamotrigine in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩
  Test 1
  Medium: 0.1 N hydrochloric acid; 900 mL
  Apparatus 2: 50 rpm
  Time: 30 min
  Determine the amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved by using one of the following methods.
  Spectrometric method
  Standard stock solution: 0.15 mg/mL of USP Lamotrigine RS in *Medium* prepared as follows. Dissolve a suitable quantity in 5% of the flask volume of methanol, then dilute with *Medium* to volume.
  Standard solution: ▲Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of 0.028 µg/mL.▲*USP35*
  Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute with *Medium* ▲according to *Table 1*.

Table 1

Tablet Label Claim (mg)	Volume of Sample (mL)	Volume of Volumetric Flask	Final Concentration (mg/mL)
25	—	—	0.028
100	5.0	20	0.029
150	4.0	25	0.027
200	3.0	25	0.027

▲*USP35*

Instrumental conditions
(See *Spectrophotometry and Light-Scattering* ⟨851⟩.)
Mode: UV
Analytical wavelength: 267 nm
Blank: *Medium*
Analysis
Calculate the percentage of the labeled amount of lamotrigine ($C_9H_7Cl_2N_5$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times {}^{\blacktriangle}D \times {}_{\blacktriangle USP35}V \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
${}^{\blacktriangle}D$ = dilution factor of the *Sample solution*▲*USP35*
V = volume of *Medium*, 900 mL

Chromatographic method
Buffer and **Mobile phase:** Prepare as directed in the *Assay*.
Standard stock solution: 0.5 mg/mL of USP Lamotrigine RS in *Medium*, prepared as follows. Dissolve a suitable quantity in 15% of the flask volume of methanol, then dilute with *Medium* to volume.
Standard solution: (*L*/1000) mg/mL of USP Lamotrigine RS from the *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Tablet
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)