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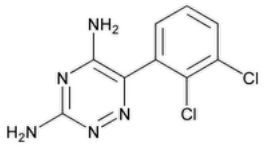
Lamotrigine



$C_9H_7Cl_2N_5$ 256.09

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

3,5-Diamino-6-(2,3-dichlorophenyl)-*as*-triazine CAS RN®: 84057-84-1; UNII: U3H27498KS.

DEFINITION

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

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020)

• **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%
- **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

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
LAMOTRIGINE	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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