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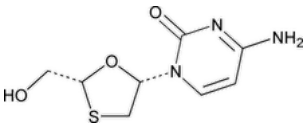
Lamivudine



$C_8H_{11}N_3O_3S$ 229.26
$C_8H_{11}N_3O_3S \cdot 0.2\ CH_3OH$ 235.66
$C_8H_{11}N_3O_3S \cdot 0.2\ H_2O$ 232.86

2(1*H*)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-, (2*R*-*cis*)-;
(−)-1-[(2*R*,5*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine CAS RN®: 134678-17-4; UNII: 2T8Q726O95.

DEFINITION

Lamivudine contains NLT 98.0% and NMT 102.0% of lamivudine ($C_8H_{11}N_3O_3S$), calculated on the anhydrous and solvent-free basis. If labeled as a methanol solvate, it contains NLT 98.0% and NMT 102.0% of lamivudine ($C_8H_{11}N_3O_3S$), calculated on the anhydrous, methanol-free, and solvent-free basis.

IDENTIFICATION

Change to read:

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

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *System suitability solution*, as obtained in the test for *Limit of Lamivudine Enantiomer*.

ASSAY

• **Procedure**

Buffer: Transfer about 1.9 g of ammonium acetate to a 1000-mL volumetric flask, dissolve in about 900 mL of water, adjust with acetic acid to a pH of 3.8 ± 0.2, and dilute with water to volume.

Mobile phase: Methanol and *Buffer* (5:95)

System suitability solution: 0.25 mg/mL of USP Lamivudine Resolution Mixture B RS in *Mobile phase*

Standard solution: 0.25 mg/mL of USP Lamivudine RS in *Mobile phase*

Sample solution: 0.25 mg/mL of Lamivudine in *Mobile phase*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 277 nm

Column: 4.6-mm × 25-cm; packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[Note—The relative retention times for lamivudine diastereomer and lamivudine are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between lamivudine and lamivudine diastereomer, *System suitability solution*

Relative standard deviation: NMT 2.0% for lamivudine, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of lamivudine ($C_8H_{11}N_3O_3S$) in the portion of Lamivudine taken:

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

r_U = peak response from the *Sample solution*

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r_S = peak response from the *Standard solution*

C_S = concentration of USP Lamivudine RS in the *Standard solution* (mg/mL)

C_U = concentration of Lamivudine in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

If labeled as a methanol solvate: 98.0%–102.0% on the anhydrous, methanol-free, and solvent-free basis

OTHER COMPONENTS

• **Content of Methanol** (if labeled as lamivudine methanol solvate)

Diluent: *N*,*N*-Dimethylformamide and *t*-butanol (500:1)

Standard solution: 0.625 mg/mL of methanol in diluent. Transfer 2.0 mL of this solution into a headspace vial, and immediately seal the vial.

Sample solution: Transfer 50 mg of Lamivudine to a headspace vial, add 2.0 mL of *Diluent*, and immediately seal the vial.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: GC headspace

Detector: Flame ionization

Column: 0.53-mm × 75-m, coated with a 3-µm film of phase G43

Temperatures

Injector: 180°

Detector: 250°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
40	—	40	13
40	40	240	12

Injection volume: 1.0 mL

Injection type: Split ratio, 15:1

Carrier gas: Helium

Flow rate: 6 mL/min

Headspace samplers

Oven: 95°

Loop: 175°

Transfer line: 175°

Equilibrium time: 10 min

System suitability

Sample: *Standard solution*

[Note—The relative retention times for methanol and *t*-butanol are 1.0 and 1.9, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for methanol

Column efficiency: NLT 25,000 for methanol

Relative standard deviation: NMT 5.0% for methanol

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of methanol in the portion of lamivudine methanol solvate taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of methanol to *t*-butanol from the *Sample solution*

R_S = peak response ratio of methanol to *t*-butanol from the *Standard solution*

C_S = concentration of methanol in the *Standard solution* (mg/mL)

C_U = concentration of Lamivudine (as methanol solvate) in the *Sample solution* (mg/mL)

Acceptance criteria: 2.0%–3.0%

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IMPURITIES

• **Limit of Lamivudine Enantiomer**

Buffer: 7.7 g/L of ammonium acetate in water

Mobile phase: Methanol and *Buffer* (5:95)

System suitability solution: 0.25 mg/mL of USP Lamivudine Resolution Mixture A RS in water

Sample solution: 0.25 mg/mL of Lamivudine in water

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 270 nm

Column: 4.6-mm × 25-cm; packing L45

Column temperature: 15°–30° (constant temperature)

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for lamivudine and the lamivudine enantiomer are 1.0 and 1.2, respectively.]

Suitability requirements

Resolution: NLT 1.5 between lamivudine and the lamivudine enantiomer

Analysis

Sample: *Sample solution*

Calculate the percentage of the lamivudine enantiomer in the portion of Lamivudine taken:

$$\text{Result} = [r_U/(r_U + r_S)] \times 100$$

r_U = peak response of the lamivudine enantiomer

r_S = peak response of lamivudine

Acceptance criteria: NMT 0.3%

• **Other Related Compounds**

Buffer, Mobile phase, System suitability solution, Standard solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Salicylic acid standard solution: 0.625 µg/mL of USP Salicylic Acid RS in *Mobile phase*

Sample solution: 0.25 mg/mL of Lamivudine in *Mobile phase*

Analysis

Samples: *Salicylic acid standard solution* and *Sample solution*

Calculate the percentage of salicylic acid in the portion of Lamivudine taken:

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

r_U = peak response of salicylic acid from the *Sample solution*

r_S = peak response of USP Salicylic Acid RS from the *Salicylic acid standard solution*

C_S = concentration of salicylic acid in the *Salicylic acid standard solution* (mg/mL)

C_U = concentration of Lamivudine in the *Sample solution* (mg/mL)

Calculate the percentage of other individual impurities in the portion of Lamivudine taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each impurity other than salicylic acid from the *Sample solution*

r_T = sum of the responses of all the peaks

Acceptance criteria: See *Table 2*.

Table 2

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Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Lamivudine-carboxylic acid[a]	0.4	0.3
Lamivudine-*trans* (lamivudine diastereomer)[b]	0.9	0.2
Lamivudine	1.0	—
Salicylic acid	2.7	0.1
Any other individual impurity	—	0.1
Total impurities	—	0.6

[a] (2*RS*,5*SR*)-5-(Cytosine-1-yl)-1,3-oxathiolane-2-carboxylic acid.

[b] 1−[(2*RS*,5*RS*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.

• **Residual Solvents**

Internal standard solution: Dilute 1 mL of 2-pentanone with dimethyl sulfoxide and water (1:1) to 100.0 mL.

Standard solution: Transfer 10 mL of the *Internal standard solution* to a 100-mL volumetric flask. Add 100 µL each of the following: dehydrated alcohol, isopropyl acetate, methanol, and triethylamine. Dilute with dimethyl sulfoxide and water (1:1) to volume.

Sample solution: Transfer 5 g of Lamivudine to a 100-mL volumetric flask, add 10 mL of the *Internal standard solution*, and dilute with dimethyl sulfoxide and water (1:1) to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 50-m, coated with a 5-µm film of phase G1

Temperatures

Injector: 150°

Detector: 250°

Column: See *Table 3*.

Table 3

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
70	—	70	3
70	30	200	6.5

Injection volume: 0.5 µL

Injection type: Split flow rate, 320 mL/min

Carrier gas: Hydrogen (at pressure 5 psig)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each residual solvent in the portion of Lamivudine taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of the respective analyte to the internal standard from the *Sample solution*

R_S = peak response ratio of the respective analyte to the internal standard from the *Standard solution*

C_S = concentration of the respective analyte in the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 4*.

Table 4

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Name	Acceptance Criteria, NMT (%)
Alcohol	0.2
Isopropyl acetate	0.2
Methanol	0.1
Triethylamine	0.1
Total residual solvents	0.3

SPECIFIC TESTS

• **Water Determination,** *Method Ic*⟨921⟩**:** NMT 2.0%

• **Light Absorption**

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: Vis

Sample solution: 50 mg/mL in water

Analytical wavelength: 440 nm

Cell: 4 cm

Acceptance criteria: Absorptivity NMT 0.0015

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed, light-resistant containers. Store at room temperature.

• **Labeling:** Where it is a methanol solvate form, the label so indicates.

• **USP Reference Standards** ⟨11⟩

USP Lamivudine RS

USP Lamivudine Resolution Mixture A RS

USP Lamivudine Resolution Mixture B RS

USP Salicylic Acid RS

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

Topic/Question	Contact	Expert Committee
LAMIVUDINE	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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