

BRIEFING

**Lamivudine, Zidovudine, and Nevirapine Tablets.** A new USP Pending monograph for this drug product, based on validated methods, is proposed. The liquid chromatographic method in the *Assay* and in the test for *Dissolution* are based on analyses performed with the Inertsil ODS 3V brand of L1 column. In the *Assay*, the typical retention times for zidovudine, lamivudine, and nevirapine are 4, 7, and 10 min, respectively. In the test for *Dissolution*, the typical retention times for zidovudine, lamivudine, and nevirapine are 3, 5, and 7 min, respectively. The liquid chromatographic method in the test for *Organic impurities, Procedure 1* is based on analyses performed with the Inertsil ODS 3V brand of L1 column; the typical retention times for lamivudine and zidovudine are 5 and 21 min, respectively. The liquid chromatographic method in the test for *Organic Impurities, Procedure 2*, is based on analyses performed with the Supelcosil LC-ABZ brand of L60 column; the typical retention time for nevirapine is 14 min.

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Add the following:

**Lamivudine, Zidovudine, and Nevirapine Tablets**

Draft 1

**DEFINITION**

Lamivudine, Zidovudine, and Nevirapine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of lamivudine ( $C_8H_{11}N_3O_3S$ ), zidovudine ( $C_{10}H_{13}N_5O_4$ ), and nevirapine ( $C_{15}H_{14}N_4O$ ), respectively.

**IDENTIFICATION**

- The retention times of the major peaks from the *Sample solution* correspond to those from the *Standard solution*, as obtained in the *Assay*.

**ASSAY**

**PROCEDURE**

**Solution A:** 2.16 mg/mL of sodium 1-octanesulfonate adjusted with 10% phosphoric acid to a pH of 2.6

**Mobile phase:** Methanol and *Solution A* (2:3)

**Standard solution:** 0.15 mg/mL of USP Lamivudine RS, 0.3 mg/mL of USP Zidovudine RS, and 0.2 mg/mL of USP Nevirapine Anhydrous RS in methanol and *Mobile phase* (1:3). [NOTE—Dissolve first in methanol, using about 25% of the final volume, and sonicate. Dilute with *Mobile phase* to volume, sonicating if necessary.]

**Sample stock solution:** Equivalent to 0.6 mg/mL of lamivudine, 1.2 mg/mL of zidovudine, and 0.8 mg/mL of nevirapine in methanol from NLT 20 Tablets, finely crushed. [NOTE—Sonicate for 25 min with intermittent swirling.]

**Sample solution:** Equivalent to 0.15 mg/mL of lamivudine, 0.3 mg/mL of zidovudine, and 0.2 mg/mL of nevirapine in *Mobile phase* from the *Sample stock solution*

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 270 nm

**Column:** 4.6-mm × 15-cm; 5-μm packing L1

**Temperature:** 30°

**Flow rate:** 1 mL/min

**Injection size:** 10 μL

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Resolution:** NLT 2.0 between lamivudine and nevirapine

**Tailing factor:** NMT 2.0 for lamivudine, zidovudine, and nevirapine

**Relative standard deviation:** NMT 2.0% for lamivudine, zidovudine, and nevirapine

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of  $C_8H_{11}N_3O_3S$ ,  $C_{10}H_{13}N_5O_4$ , and  $C_{15}H_{14}N_4O$  in the portion of Tablets taken:

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

$r_U$  = response of lamivudine, zidovudine, or nevirapine from the *Sample solution*

$r_S$  = response of lamivudine, zidovudine, or nevirapine from the *Standard solution*

$C_S$  = concentration of USP Lamivudine RS, USP Zidovudine RS, or USP Nevirapine Anhydrous RS in the *Standard solution* (mg/mL)

$C_U$  = nominal concentration of lamivudine, zidovudine, or nevirapine in the *Sample solution* (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**DISSOLUTION (711)**

**Medium:** 0.1 N hydrochloric acid; 900 mL

**Apparatus 2:** 75 rpm

**Time:** 30 min

**Solution A:** 2.16 mg/mL of sodium 1-octanesulfonate, adjusted with dilute phosphoric acid to a pH of 2.6

**Mobile phase:** Methanol and *Solution A* (2:3)

**Standard solution:** 0.16 mg/mL of USP Lamivudine RS, 0.325 mg/mL of USP Zidovudine RS, and 0.225 mg/mL of USP Nevirapine Anhydrous RS in methanol and *Medium* (1:19). [NOTE—Dissolve first in methanol, using 5% of the final volume, and sonicate to dissolve. Dilute with *Medium* to volume, and sonicate if necessary.]

**Sample solution:** Pass a portion of the solution under test through a suitable filter.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 270 nm

**Column:** 4.6-mm × 15-cm; 5-μm packing L1

**Temperature:** 30°

**Flow rate:** 1.5 mL/min

**Injection size:** 10 μL

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Resolution:** NLT 2.0 between lamivudine and nevirapine

**Tailing factor:** NMT 2.0 for lamivudine, zidovudine, and nevirapine

**Relative standard deviation:** NMT 2.0% for lamivudine, zidovudine, and nevirapine

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of  $C_8H_{11}N_3O_3S$ ,  $C_{10}H_{13}N_5O_4$ , or  $C_{15}H_{14}N_4O$  dissolved:

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

$r_U$  = response of lamivudine, zidovudine, or nevirapine from the *Sample solution*

$r_S$  = response of lamivudine, zidovudine, or nevirapine from the *Standard solution*

- $C_s$  = concentration of USP Lamivudine RS, USP Zidovudine RS, or USP Nevirapine Anhydrous RS in the *Standard solution* (mg/mL)  
 $L$  = Tablet label claim for lamivudine, zidovudine, or nevirapine (mg)  
 $V$  = volume of *Medium* (mL), 900  
**Tolerances:** NLT 80% (Q) of the labeled amounts of lamivudine, zidovudine, and nevirapine are dissolved.  
 • **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

**IMPURITIES****Organic Impurities**• **PROCEDURE 1**

**Solution A:** 1.94 mg/mL of ammonium acetate adjusted with glacial acetic acid to a pH of 3.8

**Solution B:** Methanol

**Solution C:** Methanol and *Solution A* (1:9)

**Mobile phase:** See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	90	10
5	90	10
12.5	80	20
20	90	10
22.5	90	10
35	50	50
45	50	50
50	90	10
60	90	10

**Standard stock solution A:** 0.16 mg/mL of USP Lamivudine RS and 0.3 mg/mL of USP Zidovudine RS in methanol. [NOTE—Sonicate if necessary to dissolve.]

**Standard stock solution B:** 0.38 mg/mL of USP Salicylic Acid RS, 0.4 mg/mL of USP Zidovudine Related Compound B RS, 0.15 mg/mL of USP Zidovudine Related Compound C RS, and 0.4 mg/mL of USP Stavudine RS in methanol. [NOTE—Sonicate if necessary to dissolve.]

**Standard solution:** 3.2 µg/mL of lamivudine, 6 µg/mL of zidovudine from *Standard stock solution A* and 3.8 µg/mL of salicylic acid, 8 µg/mL of zidovudine related compound B, 15 µg/mL of zidovudine related compound C, and 8 µg/mL of stavudine from *Standard stock solution B* in *Solution C*

**System suitability solution:** 3.8 µg/mL of salicylic acid, 8 µg/mL of zidovudine related compound B, 15 µg/mL of zidovudine related compound C, 8 µg/mL of stavudine from *Standard stock solution B* and 1.5 mg/mL of USP Lamivudine RS, and 3 mg/mL of USP Zidovudine RS in *Solution C*. [NOTE—Sonicate if necessary to dissolve.]

**Sample solution:** Equivalent to 1.5 mg/mL of lamivudine and 3 mg/mL of zidovudine in *Solution C* from NLT 20 Tablets, finely crushed. [NOTE—Sonicate to obtain a uniform dispersion.]

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 277 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L1

**Temperature:** 35°

**Flow rate:** 1 mL/min

**Injection size:** 10 µL

**System suitability**

**Sample:** *Standard solution* and *System suitability solution*

**Resolution:** NLT 2.0 between zidovudine related compound C and lamivudine, *System suitability solution*; NLT 2.0 between zidovudine and zidovudine related compound B, *System suitability solution*

**Tailing factor:** NMT 2.0, lamivudine and zidovudine, *Standard solution*

**Relative standard deviation:** NMT 5.0% for each peak in the *Standard solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*  
 [NOTE—Zidovudine related compounds B and C, salicylic acid, and stavudine are determined by the following calculation formula.]

Calculate the percentage of each identified impurity in the portion of Tablets taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times F \times 100$$

$r_u$  = response of each identified impurity from the *Sample solution*

$r_s$  = response of each identified impurity from the *Standard solution*

$C_s$  = concentration of each identified impurity in the *Standard solution* (µg/mL)

$C_u$  = concentration of Tablets in the *Sample solution* (mg/mL)

$F$  = unit conversion factor (0.001 mg/µg)

Calculate the percentage of lamivudine-carboxylic acid in the portion of Tablets taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times F \times 100$$

$r_u$  = response of lamivudine-carboxylic acid from the *Sample solution*

$r_s$  = response of lamivudine from the *Standard solution*

$C_s$  = concentration of lamivudine in the *Standard solution* (µg/mL)

$C_u$  = concentration of Tablets in the *Sample solution* (mg/mL)

$F$  = unit conversion factor (0.001 mg/µg)

Calculate the percentage of each unspecified impurity in the portion of Tablets taken:

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

$r_T$  = response of each unspecified impurity from the *Sample solution*

$r_s$  = sum of all peak responses from the *Sample solution*

**Acceptance criteria**

**Individual impurities:** See *Impurity Table 1*.

**Total impurities:** NMT 2.5%

**Impurity Table 1**

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Lamivudine-carboxylic acid <sup>a</sup>	0.50	0.3
Zidovudine related compound C <sup>b</sup>	0.73	1.0
Lamivudine	1.0	—
Stavudine	1.8	0.3
Salicylic acid	3.3	0.1
Zidovudine	4.0	—
Zidovudine related compound B <sup>c</sup>	5.1	0.3
Any individual unspecified impurity	—	0.2

<sup>a</sup> (2*RS*,5*SR*) -5-(4-amino-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolane-2-carboxylic acid.

<sup>b</sup> Thymine.

<sup>c</sup> 3'-chloro-3'-deoxythymidine.

• **PROCEDURE 2**

**Solution A:** 2.88 mg/mL of monobasic ammonium phosphate adjusted with 1 N sodium hydroxide to a pH of 5.0

**Mobile phase:** Acetonitrile and *Solution A* (3:17)

**System suitability solution:** 1 mg/mL of USP Nevirapine Anhydrous RS and 1 µg/mL of USP Nevirapine Related compound B RS in acetonitrile and *Mobile phase* (1:9). [NOTE—Dissolve first in acetonitrile, using 10% of the final volume.]

Sonicate to dissolve. Dilute with *Mobile phase* to volume, sonicating if necessary.]

**Standard stock solution:** 1 mg/mL of USP Nevirapine Anhydrous RS in acetonitrile and *Mobile phase* (1:9). [NOTE—Dissolve first in acetonitrile, using 10% of the final volume. Sonicate to dissolve. Dilute with *Mobile phase* to volume, sonicating if necessary.]

**Standard solution:** 1 µg/mL of nevirapine in *Mobile phase* from *Standard stock solution*

**Sample solution:** Equivalent to 1 mg/mL of nevirapine in acetonitrile and *Mobile phase* (1:9) from NLT 20 Tablets, finely crushed. [NOTE—Dissolve first in acetonitrile, using 10% of the final volume. Sonicate for 10 min. Dilute with *Mobile phase* to volume, and sonicate for 15 min.]

#### Chromatographic system

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L60

**Temperature:** 35°

**Flow rate:** 1 mL/min

**Injection size:** 10 µL

#### System suitability

**Samples:** *System suitability solution* and *Standard solution*  
[NOTE—The relative retention times for nevirapine related compound B and nevirapine are 0.7 and 1.0, respectively.]

#### Suitability requirements

**Resolution:** NLT 1.5 between nevirapine and nevirapine related compound B, *System suitability solution*

**Tailing factor:** NMT 2.0, *Standard solution*

**Relative standard deviation:** NMT 5.0%, *Standard solution*

#### Analysis

**Samples:** *Standard solution* and *Sample solution*  
Calculate the percentage of each impurity in the portion of Tablets taken:

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

$r_U$  = response of each impurity from the *Sample solution*

$r_S$  = response of nevirapine from the *Standard solution*

$C_S$  = concentration of USP Nevirapine Anhydrous RS in the *Standard solution* (µg/mL)

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

$F$  = unit conversion factor (0.001 mg/µg)

#### Acceptance criteria

**Individual impurities:** NMT 0.1%

**Total impurities:** NMT 1.0%

**Total of impurities from Procedure 1 and Procedure 2:** NMT 3.0%

#### ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature.

• **USP REFERENCE STANDARDS** (11)

USP Lamivudine RS

USP Nevirapine Anhydrous RS

USP Nevirapine Related Compound B RS

USP Salicylic Acid RS

USP Stavudine RS

USP Zidovudine RS

USP Zidovudine Related Compound B RS

USP Zidovudine Related Compound C RS (1-Mar-2010)