

BRIEFING

Tenofovir Disoproxil Fumarate Tablets. This monograph was posted on the USP Website as a draft USP Pending Monograph on February 25, 2011, and has been available for public comment for more than 90 days. No comments were received. The SM1 Expert Committee reviewed the draft and approved the monograph as an Authorized USP Pending Monograph. The liquid chromatographic procedures in the *Assay* and the test for *Organic Impurities* were validated with the YMC-Pack ODS-AQ brand of L1 column, in which tenofovir disoproxil elutes at about 6 min with the isocratic conditions used in the *Assay* and about 21 min with the gradient conditions used in the test for *Organic Impurities*.

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Tenofovir Disoproxil Fumarate Tablets

v.1 Authorized September 1, 2011

DEFINITION

Tenofovir Disoproxil Fumarate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B. ULTRAVIOLET ABSORPTION (197U)**
Wavelength range: 220–320 nm
Acceptance criteria: The spectrum of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the test for *Dissolution*.

ASSAY

- **PROCEDURE**
Buffer: 1 mL/L of triethylamine in water. Adjust with phosphoric acid or triethylamine to a pH of 6.0.
Mobile phase: Acetonitrile and Buffer (45:55)
Diluent 1: 0.01 M hydrochloric acid
Diluent 2: Acetonitrile and water (10:90)
Standard stock solution: 0.6 mg/mL of USP Tenofovir Disoproxil Fumarate RS in Diluent 1
Standard solution: 0.06 mg/mL of USP Tenofovir Disoproxil Fumarate RS in Diluent 2 from the *Standard stock solution*
Sample stock solution: 3 mg/mL of tenofovir disoproxil fumarate in Diluent 1 prepared as follows. Dissolve Tablets (NLT 5) equivalent to 1500 mg of tenofovir disoproxil fumarate in Diluent 1 using 70% of the final volume by sonicating for 20 min with intermittent shaking. Cool the solution to room temperature, and dilute with Diluent 1 to volume.
Sample solution: 0.06 mg/mL of tenofovir disoproxil fumarate in Diluent 2 prepared from the *Sample stock solution*. Pass a portion of this solution through a suitable filter.
Chromatographic system
(See *Chromatography (621)*, *System Suitability*.)

Mode: LC
Detector: UV 260 nm
Column: 4.6-mm × 25-cm; 5-μm packing L1
Column temperature: 30°
Flow rate: 1 mL/min
Injection size: 10 μL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$) 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 Tenofovir Disoproxil Fumarate RS in the *Standard solution* (mg/mL)
 C_U = nominal concentration of tenofovir disoproxil fumarate 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: 50 rpm
Time: 30 min
Standard solution: 0.033 mg/mL of USP Tenofovir Disoproxil Fumarate RS in *Medium*
Sample solution: Pass a portion of the solution under test through a filter of 0.45-μm pore size. Dilute with *Medium* to obtain a concentration similar to the *Standard solution*.
Instrumental conditions
(See *Spectrophotometry and Light-Scattering (851)*.)
Analytical wavelength: 260 nm
Cell path length: 1 cm
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$) dissolved:

$$\text{Result} = [(A_U \times C_S \times D \times V)/(A_S \times L)] \times 100$$

A_U = absorbance of the *Sample solution*
 C_S = concentration of USP Tenofovir Disoproxil Fumarate RS in the *Standard solution* (mg/mL)
 D = dilution factor
 V = volume of *Medium*, 900 mL
 A_S = absorbance of the *Standard solution*
 L = label claim (mg/Tablet)
Tolerances: NLT 80% (Q) of the labeled amount of tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements for *Weight Variation*. The acceptance value (AV) is NMT 15.0.

IMPURITIES

- **ORGANIC IMPURITIES**
Buffer: 0.01 M dibasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 5.5.
Solution A: Methanol, tertiary butyl alcohol, and Buffer (11:1:28)
Solution B: Methanol, tertiary butyl alcohol, and Buffer (27:1:12)

2 / Tenofovir

Mobile phase: See Table 1.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
2	100	0
30	0	100
45	0	100
50	100	0
60	100	0

System suitability solution: 0.75 µg/mL of USP Tenofovir RS and USP Adenine RS in *Solution A*

Standard solution: 0.5 µg/mL of USP Tenofovir Disoproxil Fumarate RS in *Solution A*

Sample solution: 500 µg/mL of tenofovir disoproxil fumarate in *Solution A* prepared as follows. Dissolve Tablets (NLT 20) equivalent to 250 mg of tenofovir disoproxil fumarate in *Solution A* using 70% of the final volume by sonicating for 10 min. Cool the solution to room temperature, and dilute with *Solution A* to volume. Pass a portion of this solution through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 35°

Sample temperature: 4°

Flow rate: 1 mL/min

Injection size: 10 µL

System suitability

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

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

Resolution: NLT 1.5 between tenofovir and adenine, *System suitability solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—The tenofovir disoproxil ethyl ester peak may elute as a split peak; consider it a single peak.]

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

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times (1/F) \times 100$$

r_u = peak response of each impurity from the *Sample solution*

r_s = peak response from the *Standard solution*

C_s = concentration of USP Tenofovir Disoproxil Fumarate RS in the *Standard solution* (µg/mL)

C_u = nominal concentration of tenofovir disoproxil fumarate in the *Sample solution* (µg/mL)

F = relative response factor (see Table 2)

Acceptance criteria: See Table 2.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Fumaric acid ^a	0.12	—	—
Tenofovir ^b	0.14	2.1	0.2
Adenine ^c	0.16	4.4	0.2
Tenofovir isoproxil monoester ^d	0.24	1.5	3.0
Tenofovir disoproxil ethyl ester ^a	0.80	—	—
Tenofovir isopropyl isoproxil ^a	0.82	—	—
Tenofovir disoproxil	1.00	—	—
Tenofovir disoproxil carbamate ^a	1.40	—	—
Tenofovir disoproxil dimer ^e	1.76	1.0	0.75
Any individual unspecified impurity	—	1.0	0.2
Total impurities	—	—	4.0

^a Process impurity. Do not quantify.

^b (R)-(1-(6-Amino-9H-purin-9-yl)propan-2-yloxy)methylphosphonic acid.

^c 9H-Purin-6-amine.

^d (((R)-1-(6-Amino-9H-purin-9-yl)propan-2-yloxy)methyl)(hydroxy)phosphoryloxy)methyl isopropyl carbonate.

^e Tetra(isopropoxycarbonyloxymethyl) (2S)-1,1'-[6,6'-methylenebis(azanediyl)bis(9H-purine-9,6-diyl)]bis(propane-2,1-diyl)bis(oxy)bis(methylene)diphosphonate.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Store at controlled room temperature.

• **USP REFERENCE STANDARDS <11>**

USP Adenine RS

1H-Purin-6-amine.

C₅H₅N₅ 135.13

USP Tenofovir RS

(R)-[[2-(6-Amino-9H-purin-9-yl)-1-

methylethoxy)methyl]phosphonic acid monohydrate.

C₉H₁₄N₅O₄P · H₂O 305.23

USP Tenofovir Disoproxil Fumarate RS