Tenofovir disoproxil tablets (Tenofoviri disoproxili compressi)

2025-01

Category. Antiretroviral (Nucleoside/Nucleotide reverse transcriptase inhibitor).

Storage. Tenofovir disoproxil tablets should be kept in a tightly closed container.

Additional information. Strength in the current WHO Model List of Essential Medicines: 300 mg Tenofovir disoproxil fumarate. 300 mg of tenofovir disoproxil fumarate is equivalent to approximately 245 mg of tenofovir disoproxil.

Requirements

Comply with the monograph for *Tablets*.

Definition. Tenofovir disoproxil tablets contain Tenofovir disoproxil fumarate. They contain not less than 90.0% and not more than 110.0% of the amount of tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P$) stated on the label.

Manufacture. The manufacturing process and the product packaging are designed and controlled so as to minimize the moisture content of the tablets.

Identity tests

Any two of tests A, B or C may be performed.

Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions and solutions given under "Assay". The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the corresponding peak due to tenofovir disoproxil in the chromatograms obtained with solution (2).

Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R6 as the coating substance and a freshly prepared mixture of ethyl acetate R, water R, anhydrous formic acidR and glacial acetic acid R (71:14:7:7 *V/V/V/V*) as the mobile phase. Apply separately to the plate 5 µL of each of the following 2 solutions in a mixture of methanol R and formic acid (~1080 g/L) TS (9:1 *V/V*). For solution (A), disperse a quantity of the powdered tablets, nominally containing 10 mg of tenofovir disoproxil, in 2 mL, sonicate for 5 minutes and filter. For solution (B), use a solution containing 6 mg of tenofovir disoproxil fumarate RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of air and examine the chromatogram under ultraviolet light (254 nm and 365 nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the corresponding spots due to tenofovir disoproxil obtained with solution (B).

Disperse a quantity of the powdered tablets, nominally containing 5 mg of tenofovir disoproxil, in 250 mL water R, filter and use the filtrate. The absorption spectrum (*1.6*) of the solution, when observed between 220 nm and 320 nm, exhibits a maximum at about 261 nm.

Alternatively, and in combination with identity test A, where a diode array detector is available, record the UV spectra of the principal peaks with a diode array detector in the range of 220 nm to 320 nm. The UV spectrum of the principal peak in the chromatogram obtained with solution (1) corresponds to the UV spectrum of the peak due to tenofovir disoproxil in the chromatogram obtained with solution (2).

Dissolution. Carry out the test described under *5.5 Dissolution test for oral dosage forms*, using as the dissolution medium 900 mL of hydrochloric acid (0.1 mol/L) VS and rotating the paddle at 50 revolutions per minute. At 30 minutes, withdraw a sample of 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature and dilute 5.0 mL of the sample solution to 50.0 mL with the dissolution medium.

Measure the absorbance (*1.6*) of a 1 cm layer of the resulting solution at the maximum of about 260 nm. For each of the tablets tested, calculate the total amount of tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P$) in the medium using the absorptivity value of 22.3 ($A^{1\%}_{1\ cm}$ = 223) for tenofovir disoproxil fumarate. Each mg of tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$) is equivalent to 0.817 mg of tenofovir disoproxil ($C_{19}H_{30}N_5O_{10}P$).

Evaluate the results as described under *5.5 Dissolution test for oral dosage forms*, Acceptance criteria. The amount of tenofovir disoproxil ($C_{19}H_{30}N_5O_{10}P$) released is not less than 80% (Q) of the amount declared on the label .

Tests for related substances. Perform the test in subdued light using low-actinic glassware. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).

Use the following conditions for gradient elution:

mobile phase A: acetate buffer pH 4.2; and

mobile phase B: acetonitrile R.

Prepare the acetate buffer pH 4.2 by dissolving 9.64 g of ammonium acetate R in 900 mL of water R, adjust the pH to 4.2 with glacial acetic acid R and dilute to 1000 mL with water R.

Time (minutes)	Mobile phase A (% *V*/*V*)	Mobile phase B (% *V*/*V*)	Comments
0–2	100	0	Isocratic
2–17	100 to 95	0 to 5	Linear gradient
17–47	95 to 60	5 to 40	Linear gradient
47–62	60 to 25	40 to 75	Linear gradient
62–63	25 to 100	75 to 0	Return to initial composition
63–75	100	0	Re-equilibration

Operate with a flow rate of 1.0 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 260 nm. Maintain the column temperature at 25 °C and the autosampler temperature between 2 °C and 6 °C.

Prepare the following solutions using water R as diluent.

For solution (1), transfer a quantity of the powdered tablets, nominally equivalent to 184 mg of tenofovir disoproxil, to a 250 mL volumetric flask. Add about 175 mL of diluent and sonicate at room temperature for about 30 minutes with intermittent shaking. Allow to cool to room temperature, dilute to volume and filter.

For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL.

For solution (3), dilute 10.0 mL of solution (2) to 100.0 mL.

For solution (4), dissolve the content of a vial of tenofovir disoproxil fumarate for system suitability RS (containing tenofovir disoproxil fumarate and impurity H) in 0.5 mL of water R.

For solution (5)(used to generate tenofovir disoproxil impurity A), dissolve 10 mg of tenofovir disoproxil fumarate RS in 10 mL. Heat the solution carefully in a boiling water-bath for 20 minutes. Cool to room temperature and dilute 1 mL of the solution to 10 mL.

For solution (6), use a solution containing 0.2 mg of fumaric acid R per mL.

For solution (7), dissolve or disperse a suitable amount of each of the excipients stated on the label in 10 mL, dilute to 100.0 mL and filter. Adjust the weight of the excipient so that its concentration resembles the concentration of the excipient in solution (1), provided this information is available.

Inject 10 µL each of solutions (1), (2), (3), (4), (5), (6) and (7).

Use the chromatogram obtained with solution (4) and the chromatogram supplied with tenofovir disoproxil fumarate for system suitability RS to identify the peak due to the tenofovir disoproxil impurity H in the chromatogram obtained with solution (1), if present.

Use the chromatogram obtained with solution (5) to identify the peak due to the tenofovir disoproxil impurity A in the chromatogram obtained with solution (1), if present.

Use the chromatogram obtained with solution (6) to identify the peak due to fumaric acid in the chromatogram obtained with solution (1). The peak due to fumaric acid is eluted at about 2.5 minutes and may appear as a single or a split peak.

Use the chromatogram obtained with solution (7) to identify the peaks due to excipients.

The impurities, if present, are eluted at the following relative retentions with reference to tenofovir disoproxil (retention time about 48 minutes):

Impurity	Relative retention	Impurity Classification

Tenofovir disoproxil impurity R	0.30	
Tenofovir disoproxil impurity N	0.33	Synthesis/Degradation
Tenofovir disoproxil impurity A	0.63	Synthesis/Degradation
Tenofovir disoproxil impurity F	0.73	Degradation
Tenofovir disoproxil impurity E	0.76	Synthesis/Degradation
Tenofovir disoproxil impurity B	0.80 and 0.81	Synthesis
Tenofovir disoproxil impurity L	0.87	Synthesis
Tenofovir disoproxil impurity C	0.88	Synthesis
Tenofovir disoproxil impurity D	0.90	Synthesis
Tenofovir disoproxil impurity M	0.94	Synthesis
Tenofovir disoproxil impurity P	0.96	Synthesis
Tenofovir disoproxil impurity O	0.97	Synthesis
Tenofovir disoproxil impurity I	0.98	Synthesis/Degradation
Tenofovir disoproxil impurity H	1.01	Synthesis
Tenofovir disoproxil impurity Q	1.10	Synthesis/Degradation
Tenofovir disoproxil impurity J	1.19	Synthesis/Degradation

Note: Tenofovir disoproxil impurities B and C may appear as single or split peaks. If they appear as split peaks, use the sum of the two peaks in the calculation of the concentration. ("Synthesis" stands for synthesis-related impurity; "Degradation" for degradation product.)

The test is not valid unless:

in the chromatogram obtained with solution (3), the signal-to-noise ratio of the peak due to tenofovir disoproxil is at least 20; and

in the chromatogram obtained with solution (4), the resolution between the peaks due to tenofovir disoproxil and tenofovir disoproxil impurity H is at least 1.2.

*[**Note from the Secretariat.** It is intended to use the peak-to-valley ratio in the verification of the system suitability once the International Chemical Reference Substance on tenofovir disoproxil for system suitability has been established.]*

In the chromatogram obtained with solution (1):

the area of any peak corresponding to tenofovir disoproxil impurity A, when multiplied by a correction factor of 0.7, is not greater than five times the area of the peak due to tenofovir disoproxil in the chromatogram obtained with solution (2) (5.0%);

the area of any peak corresponding to either tenofovir disoproxil impurity F, I or J, is not greater than 0.75 times the area of the peak due to tenofovir disoproxil in the chromatogram obtained with solution (2) (0.75%);

the area of any peak corresponding to tenofovir disoproxil impurity D is not greater than 3 times the area of the peak due to tenofovir disoproxil in the chromatogram obtained with solution (3) (0.3%);

the area of any peak corresponding to tenofovir disoproxil impurity N, when multiplied by a correction factor of 0.5, is not greater than two times the area of the peak due to tenofovir disoproxil in the chromatogram obtained with solution (3) (0.2%); and

the area of any other impurity peak, corresponding to any other degradation product, is not greater than two times the area of the peak due to tenofovir disoproxil in the chromatogram obtained with solution (3) (0.2 %).

The sum of the areas of all impurity peaks, including the corrected areas of any peaks corresponding to tenofovir impurities N and A is not greater than 5 times the area of the peak due to tenofovir disoproxil in the chromatogram obtained with

solution (2) (5.0%). Disregard any peak with an area or a corrected area of less than 0.5 times the area of the peak due to tenofovir disoproxil in the chromatogram obtained with solution (3) (0.05%) and any peak due to fumaric acid.

Assay. Perform the test in subdued light using low-actinic glassware. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).

As the mobile phase use a mixture of a sodium dihydrogen phosphate buffer pH 2.3 and acetonitrile for chromatography R (60:40 *V/V*).

Prepare the sodium dihydrogen phosphate buffer pH 2.3 by dissolving 6.9 g of sodium dihydrogen phosphate R in 900 ml of water R, adding 1.0 mL of triethylamine R, adjusting the pH to 2.3 with phosphoric acid (~105 g/l) TS, and diluting to 1000 ml with water R.

Operate at a flow rate of 1.0 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 260 nm. Maintain the column temperature at 30 °C.

Prepare the following solution. For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, nominally equivalent to 245.0 mg of tenofovir disoproxil, to a 100 mL volumetric flask. Add about 80 mL of hydrochloric acid (~0.365 g/L) TS, sonicate for about 15 minutes with intermittent shaking, allow to cool to room temperature, dilute to volume with the same solvent and filter. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase. For solution (2), dissolve 75.0 mg of tenofovir disoproxil fumarate RS in hydrochloric acid (~0.365 g/L) TS and dilute to 25.0 mL with the same solvent. Dilute 5.0 mL of this solution to 100.0 mL with the mobile phase.

Inject 20 µL each of solutions (1) and (2).

Measure the areas of the peaks corresponding to tenofovir disoproxil obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of tenofovir disoproxil ($C_{19}H_{30}N_5O_{10}P$) in the tablets using the declared content of tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$) in tenofovir disoproxil fumarate RS. Each mg of tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$) corresponds to 0.817 mg of tenofovir disoproxil ($C_{19}H_{30}N_5O_{10}P$).

Impurities. The impurities limited by the requirements of this monograph include those listed in the monographs on Tenofovir disoproxil fumarate, excluding tenofovir disoproxil impurity G.