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World Health Organization

WHO Drug Information

WHO Drug Information provides an overview of topics relating to medicines development, regulation, quality and safety. The journal also publishes and reports on guidance documents and includes lists of International Nonproprietary Names for Pharmaceutical Substances (INN), ATC/DDD classification and monographs for The International Pharmacopoeia. It presents and describes WHO policies and activities while reflecting on technical and pharmaceutical topics of international and regional interest.

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International Nonproprietary Names (INN)

Abbreviations and websites

CHMP	Committee for Medicinal Products for Human Use (EMA)
EMA	European Medicines Agency (www.ema.europa.eu)
EU	European Union
FDA	U.S. Food and Drug Administration (www.fda.gov)
Health Canada	Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
HPRA	Health Products Regulatory Authority, Ireland(www.hpra.ie)
HSA	Health Sciences Authority, Singapore (www.hsa.gov.sg)
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (www.ich.org)
IGDRP	International Generic Drug Regulators Programme (https://www.igdrp.com)
INN	International Nonproprietary Names
MHLW	Ministry of Health, Labour and Welfare, Japan
MHRA	Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe	New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
Ph. Int	*The International Pharmacopoeia* (http://apps.who.int/phint/)
PMDA	Pharmaceuticals and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic	Swiss Agency for Therapeutic Products(www.swissmedic.ch)
TGA	Therapeutic Goods Administration, Australia (www.tga.gov.au)
WHO	World Health Organization (www.who.int)
WHO MHP	WHO Access to Medicines and Health Products Division (www.who.int/medicines/en/)
WHO RPQ	WHO Regulation and Prequalification Department
WHO PQT	WHO Prequalification Unit (https://www.who.int/topics/prequalification/en/)
WHO HPS	WHO Health Product Policy and Standards Department

Note: The online version of this issue is available at
https://www.who.int/our-work/access-to-medicines-and-health-products/who-drug-information

TENOFOVIR DISOPROXIL FUMARATE

(TENOFOVIRI DISOPROXILI FUMARAS)

DRAFT FOR COMMENTS

Comments on this draft working document have been sent to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int) by **29 April 2022**.

Our working documents are sent out electronically and are placed on the WHO Medicines website (*https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/current-projects*) for comments under the "Working documents in public consultation" link.

*[**Note from the Secretariat**. It is proposed to revise the monograph on Tenofovir disoproxil fumarate:*

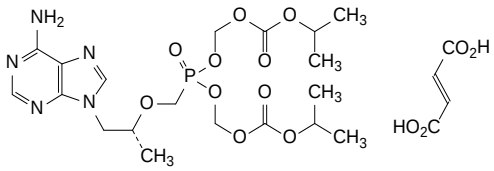
- *by adding a test for tenofovir disoproxil enantiomer (impurity G);*
- *by revising the test for related substances; and*
- *by including further changes.*

The proposal is based on laboratory investigations and on information found in other pharmacopoeias, the scientific literature or submitted by manufacturers.]

TENOFOVIR DISOPROXIL FUMARATE

(TENOFOVIRI DISOPROXILI FUMARAS)

Graphic formula



Molecular formula. $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$

Relative molecular mass. 635.5.

Chemical names. 1,1'-bis(propan-2-yl) 1,1'-[({[(2*R*)-1-(6-amino-9*H*-purin-9-yl)-1-propan-2-yloxy]methyl}phosphonoyldioxy)dimethyl] dicarbonate (ester) hydrogen (2*E*)-but-2-enedioate (salt); bis(1-methylethyl) 5-{[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl}-5-oxo-2,4,6,8-tetraoxa-5-λ^5-phosphanonanedioate (ester) hydrogen (2*E*)-but-2-enedioate (salt); bis({[(1-methylethoxy)carbonyl]oxy}methyl) {[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl}phosphonate (ester) hydrogen (2*E*)-but-2-enedioate (salt); CAS Reg. No. 202138 50 9

Description. White to almost-white, crystalline powder.

Solubility. Slightly soluble in water R, soluble in methanol R, very slightly soluble in dichloromethane R.

Category. Antiretroviral (Nucleotide Reverse Transcriptase Inhibitor).

Storage. Tenofovir disoproxil fumarate should be kept in a tightly closed container, protected from light and stored at a temperature between 2–8 °C.

Additional information. Tenofovir disoproxil fumarate may exhibit polymorphism.

Requirements

Definition. Tenofovir disoproxil fumarate contains not less than 98.5% and not more than 101.0% of tenofovir disoproxil fumarate ($C_{19}H_{30}N_5O_{10}P.C_4H_4O_4$), calculated with reference to the anhydrous substance.

Manufacture. The production method is validated to ensure that the substance, if tested, would comply with a limit of not more than 5 ppm for the mutagenic impurity 9-propenyladenine using a suitable method.

Identity tests

- Either tests A and C or tests E and C together with tests B or D may be applied.

A. Carry out the examination as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from tenofovir disoproxil fumarate RS or with the reference spectrum of tenofovir disoproxil fumarate.

If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and tenofovir disoproxil fumarate RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from tenofovir disoproxil fumarate RS.

B. Carry out the test as described under *1.14.1 Thin-layer chromatography* using silica gel R6 as the coating substance and a mixture of 67 volumes of dichloromethane R, 20 volumes of acetonitrile R, 10 volumes of methanol R and 3 volumes of ammonia (~260 g/L) TS as the mobile phase. Apply separately to the plate, 5 µL of each of two solutions in methanol containing (A) 10 mg of the test substance per mL and (B) 10 mg of tenofovir disoproxil fumarate RS per mL. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of air. Examine the plate in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

C. Carry out test C.1 or test C.2.

C.1 Determine the specific optical rotation (*1.4*) using a freshly prepared 10.0 mg/mL solution of the test substance in hydrochloric acid (0.1 mol/L) VS. Perform the test without delay and calculate with reference to the anhydrous substance; $[\alpha]_D^{20}$= -15 to -20.

C.2 Carry out the test as described under *1.14.4 High-performance liquid chromatography* using the conditions and solution (1) given under "Impurity G". Prepare the following solutions using a mixture of 9 volumes of dehydrated ethanol R and 1 volume of acetonitrile (v/v) as the diluent. For solution (1), dissolve 2 mg of the test substance in 20 mL. For solution (2), dissolve 2 mg of tenofovir disoproxil fumarate for enantiomer identification RS (containing tenofovir disoproxil fumarate and impurity G) in 20 mL. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to tenofovir disoproxil in the chromatogram obtained with solution (2).

D. The absorption spectrum (*1.6*) of a 25 µg/mL solution of the test substance in water R, when observed between 220 nm and 320 nm, exhibits a maximum at about 261 nm. Alternatively, in combination with identity test C.2, where a diode array detector is available, record the UV spectra of the principal peaks in the chromatograms 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).

E. Carry out the test as described under *1.14.1 Thin-layer chromatography* using silica gel R6 as the coating substance and a mixture of 50 volumes of heptane R, 30 volumes of glacial acetic acid R and 20 volumes of dichloromethane R as the mobile phase. Apply separately to the plate, 5 µL of each of the following two solutions in ethanol R. For solution (A), use 10 mg of the test substance per mL and for solution (B), use 2 mg of fumaric acid R per mL. Develop the plate in an unsaturated tank over a path of 10 cm. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air or in a current of air. Examine the chromatogram in ultraviolet light (254 nm).

One of the principal spots obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

Fumaric acid. Dissolve 0.250 g in 50 mL of water R and titrate with sodium hydroxide (0.1 mol/L) VS. Determine the end-point potentiometrically as described under *2.6 Non-aqueous titration*, Method A. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent 5.804 mg of fumaric acid ($C_4H_4O_4$). The fumaric acid content is between 17.5%-19.0% on the anhydrous basis.

Water. Determine as described under *2.8 Determination of water by the Karl Fischer method*, Method A. Use about 1.0 g of the substance; the water content is not more than 10 mg/g.

Heavy metals. Use 1.0 g in 30 mL of methanol R for the preparation of the test solution as described under *2.2.3 Limit test for heavy metals*, Procedure 2; determine the heavy metals content according to Method A; not more than 20 µg/g.

Sulfated ash (*2.3*). Not more than 2.0 mg/g.

Impurity G. Carry out the test as described under *1.14.4 High-performance liquid chromatography* using a stainless steel column (15 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with amylose *tris* (3,5-dimethylphenyl carbamate) (5 µm).[1] As the mobile phase, use a mixture of 900 volumes of dehydrated ethanol R, 100 volumes of acetonitrile R and 1 volume of diethylamine 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 35 °C. Prepare the following solutions using a mixture of 9 volumes of dehydrated ethanol R and 1 volume of acetonitrile (v/v) as the diluent. For solution (1), dissolve 40.0 mg of the test substance in 100.0 mL. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3), dilute 1.0 mL of solution (2) to 10.0 mL. For solution (4), use a solution containing 0.1 mg of tenofovir disoproxil fumarate for enantiomer identification RS (containing tenofovir disoproxil and the impurity G) per mL.

Inject 10 µL of solutions (3) and (4). Record the chromatograms for about 3 times the retention of tenofovir disoproxil.

Use the chromatogram obtained with solution (4) and the chromatogram supplied with tenofovir disoproxil fumarate for enantiomer identification RS to identify the peak due to the impurity G. Impurity G is eluted at the relative retention of 1.6 with reference to tenofovir disoproxil (retention time about 3.5 minutes)