THEUNITEDREPUBLICOFTANZANIA

MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE (EMTRICITABINE 200MG AND TENOFOVIR DISOPROXIL FUMARATE 300MG) FILM COATED TABLETS

Version number 01
3rd January, 2023

TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Swaswa Road, P. O. Box 1253, Dodoma – Tanzania, Telephone: +255 (26) 2961989/2061990/+255 (22) 2450512/2450751/2452108, Email: info@tmda.og.tz, Website: **www.tmda.go.tz**
Toll free: 0800110084

1. Introduction

Emtricitabine and Tenofovir Disoproxil Fumarate is a generic medicine of Truvada® (Gilead Sciences). Emtricitabine and Tenofovir Disoproxil Fumarate is an Antiviral medicine belonging to Nucleoside and nucleotide reverse transcriptase inhibitor group.

Emtricitabine is a synthetic nucleoside analogue of cytidine with activity that is specific to HIV-1, HIV-2 and HBV. Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate, which competitively inhibits HIV-1 reverse transcriptase, resulting in DNA chain termination. Emtricitabine is a weak inhibitor of mammalian DNA polymerase α, β and ε and mitochondrial DNA polymerase γ

Tenofovir disoproxil fumarate is the fumarate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate has an intracellular half-life of 10 hours in activated and 50 hours in resting peripheral blood mononuclear cells (PBMCs). Tenofovir diphosphate inhibits HIV-1 reverse transcriptase and the HBV polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of cellular polymerases α, β, and γ. At concentrations of up to 300 μmol/l, tenofovir has also shown no effect on the synthesis of mitochondrial DNA or the production of lactic acid in in vitro assays.

Emtricitabine and Tenofovir Disoproxil Fumarate is approved in Tanzania for use in adults and adolescents over 10 years of age and weighing at least 30 kg

1.1. Product details

Registration number	TAN 21 HM 0258
Brand name	Emtricitabine and Tenofovir Disoproxil Fumarate
Generic name, strength and form	Emtricitabine 200 mg and Tenofovir Disoproxil Fumarate 300 mg
ATC classification	Emtricitabine: J05AF09 Tenofovir Disoproxil Fumarate: J05AF07 Emtricitabine and Tenofovir Disoproxil Fumarate; J05AR03
Distribution category	POM
Country of origin	India
Associated product	

Marketing Authorization Holder	Sun Pharmaceutical Industries Limited Village Ganguwala, Paonta Sahib District Sirmour Himachal Pradesh- 173025 **INDIA.** E-Mail: anurag.agrawal@sunpharma.com
Local Technical Representative	Phillips Disitributors Limited Plot No 111, Nyerere Road, Vingunguti Industrial Area P.O.Box 737, **DAR ES SALAAM.** E-Mail: info@phillipstanzania.com

1.2. Assessment procedure

The application for registration of Emtricitabine and Tenofovir Disoproxil Fumarate was submitted on 11th March 2021. The product underwent abridged assessment. Assessment was completed in one rounds of evaluation. Emtricitabine and Tenofovir Disoproxil Fumarate was registered on 3rd June, 2021

1.3. Information for users

Visual description of the finished product	White to off-white, capsule shaped film coated tablets debossed with 'RF14' on one side and plain on the other side
Primary packing material	HDPE Bottle
Secondary packing materials	Carton box
Shelf-life and storage condition	36 months Do not store above 30°C, protected from moisture
Route of administration	Oral
Therapeutic indications	Emtricitabine & Tenofovir Disoproxil Fumarate Tablets 200/300 mg is indicated for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents over 10 years of age and weighing at least 30 kg

2. Labelling and product information

Summary of product characteristics

The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet

The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM that is intended for long term use the package insert contains full prescribing information as per SmPC

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name: Emtricitabine and Tenofovir Disoproxil Fumarate

Composition: Emtricitabine and Tenofovir Disoproxil Fumarate, Microcrystalline Cellulose, Anhydrous Lactose, Pregelatinised Starch, Magnesium Stearate, Microcrystalline Cellulose, Croscarmellose Sodium and Opadry II 31K58902 white

Pack size: 30's ,90's

Manufacturing details: <batch number, manufacturing date, expiry date>

Storage conditions: Do not store above 30°C, protected from moisture

Manufacturer address: Sun Pharmaceutical Industries Limited, Village Ganguwala, Paonta Sahib District Sirmour, Himachal Pradesh- 173025 India

Unique identifier: NA

Special warnings/precautions or instructions for use: <include warnings or IFU if applicable>

The details of the primary pack include:

Brand name and strength: Emtricitabine 200 mg and Tenofovir Disoproxil Fumarate 300 mg

Manufacturing details: <batch number, manufacturing date, expiry date>

Name of manufacturer: Sun Pharmaceutical Industries Limited

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Describe any approved deviation to the requirements and the justification for the deviation.

Mock labels are appended as annex I

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

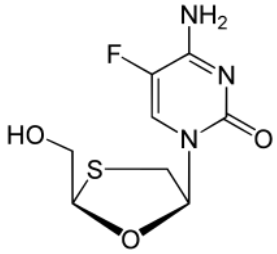
Information on quality of the API was submitted in form of <CEP/APIMF/DMF/Full details/WHO Prequalification proof>.

General properties

Emtricitabine

Emtricitabine API is compendia in International Pharmacopeia.
Molecular formula: $C_8H_{10}FN_3O_3S$
Chemical name: 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1H)-one; 5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine; (-)-2',3'-dideoxy-5-fluoro-3'-thiacytidine

Structure:



Emtricitabine is described as white to almost white crystalline powder. Emtricitabine (up to 200 mg oral dose) is classified as BCS class 1 molecule which is highly soluble API according to BCS. Emtricitabine has two chiral centres. The desired stereochemistry is built into the key intermediate in the multi-step synthesis process, with L-menthol as the starting material for synthesis. Emtricitabine is known to exhibit polymorphism. Form I is consistently produced by Hetero Labs Limited.

Manufacture
The API manufacturing site, Hetero Labs Limited, (Unit-1) S. No. 10, I.D.A., Block E and D, Gaddapotharam Village, Jinnaram Mandal, Medak District, Andhra Pradesh, India

was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by WHO PQ. Emtricitabine API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per International Ph, in-house standards and ICHQ3A. The parameters monitored during quality control are: description, identification, solubility, polymorphism (XRD), loss on drying, sulphated ash, related substances, assay and residual solvents. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Emtricitabine API is 60 months when packed in < polythene bags in HDPE drum and stored at 30±2°C/75±5% RH.

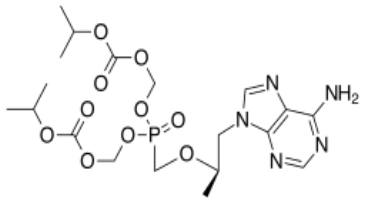
Tenofovir Disoproxil Fumarate

Tenofovir Disoproxil Fumarate API is compendia in International Pharmacopeia.

Molecular formula: C19H30N5O10P.C4H4O4

Chemical name: [[(1R)-2-(6–Amino-9H–purin -9-yl)-1-methylethoxy] methyl]phosphonic acid disoproxil fumarate or (R)-9-(2- phosphonomethoxypropyl)adenine Disoproxil fumarate

Structure:



Tenofovir disoproxil fumarate (TDF) is the salt of tenofovir disoproxil with fumaric acid. Tenofovir disoproxil is a diester pro-drug of the purine based nucleotide analogue, tenofovir. The pro-drug has increased oral bioavailability compared to tenofovir. TDF is a BCS Class 3 API, i.e. of high solubility and low permeability. TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p.
112-1140C) and a high melting form (m.p. 114-1180C). The high melting form, controlled by XRPD and melting point, is consistently produced. The test methods have been adequately validated

Manufacture

The API manufacturing site, Hetero Labs Limited, Survey.No.10 (Block- C and E), I.D.A., Gaddapotharam Village, Jinnaram Mandal, Medak District, Andhra Pradesh, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by WHO PQ. Tenofovir disoproxil fumarate API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per International Ph, in-house standards and ICHQ3A. The parameters monitored during quality control are: Description,
Solubility, Identification by IR and HPLC, XRD, Clarity of Solution, Water content by KF, Heavy Metals, Melting point by DSC, Related Compounds by HPLC, 9-Propenyladenine content by HPLC, enantiomeric, Impurity by HPLC, Assay by HPLC (on anhydrous and solvent free basis), Fumaric acid content by HPLC (on anhydrous and solvent free basis) and Residual solvents by GC. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Emtricitabine API is 60 months when packed in polythene bags in HDPE drum and stored at 2 - 8ºC.

Quality of the Finished Pharmaceutical Product

Formulation

Emtricitabine and Tenofovir Disoproxil Fumarate is a white to off-white, capsule shaped film coated tablets debossed with ‘RF14’ on one side and plain on the other side. Emtricitabine and Tenofovir Disoproxil Fumarate contains Emtricitabine, Tenofovir Disoproxil Fumarate and other ingredients listed here after Microcrystalline Cellulose, Anhydrous Lactose, Pregelatinised Starch, Magnesium Stearate, Microcrystalline Cellulose, Croscarmellose Sodium and Opadry II 31K58902 white. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th in terms of function and quantities. Ingredient, Anhydrous Lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Sun Pharmaceutical Industries, Village Ganguwala, Paonta Sahib District Sirmour Himachal Pradesh- 173025 India. The

compliance of the site to TMDA GMP standards was confirmed through site inspection on <date of GMP compliance>.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house and ICHQ3B requirements. The parameters monitored during quality control are: < description, identification, average weight, uniformity of dosage unit, water, dissolution, related substance, assay and microbial limit test. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three batches of the finished product stored at 30 °C ± 2 °C/75% RH ± 5% for 24 months and 40 °C ± 2 °C/75% RH ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in HDPE bottle at 30 °C.

Safety and efficacy information

Safety and efficacy of Emtricitabine 200 mg and Tenofovir Disoproxil Fumarate 300 mg was established through bioequivalence trial. BE trial report number 2033/11 was submitted.

In case of BE:

Study title	Single dose two-way crossover bioequivalence study of fixed dose combination tablets of Tenofovir Disoproxil Fumarate 300 mg and Emtricitabine 200 mg in healthy, adult, human subjects under fasting condition.
Study design	This study was an open label, balanced, randomized, two-sequence, two-treatment, two period, single dose, crossover, oral bioequivalence study in healthy, adult, human subjects under fasting condition.

Study site	<u>Clinical:</u> Clinical Pharmacology Unit, Ranbaxy Laboratories Limited, B-22, Sector 62, Fortis Hospital Complex, Noida- 201 301, Uttar Pradesh, India Clinical Pharmacology Unit, Ranbaxy Laboratories Limited, Hakeem Abdul Hameed Centenary Hospital (2nd Floor), Jamia Hamdard (Hamdard University), Hamdard Nagar, New Delhi 110 062, India. Clinical Laboratory **Ranbaxy Laboratories Limited, Plot No. GP5, Sector-18, HSIDC,** **Old Delhi- Gurgaon Road, Gurgaon-122015, Haryana, India** Statistical: Clinical Pharmacology & Pharmacokinetics Ranbaxy Laboratories Limited, Plot No. GP-5, Sector 18, HSIDC,	
Study dates	Period I: October 19, 2011 – October 24, 2011 Period II: November 01, 2011 – November 06, 2011	
Primary objective	To assess the bioequivalence of single-oral fixed dose combination tablets of Tenofovir Disoproxil Fumarate 300 mg and Emtricitabine 200 mg with fixed dose combination tablet TRUVADA® (containing Tenofovir Disoproxil Fumarate 300 mg and Emtricitabine 200 mg) in healthy, adult, human subjects under fasting condition.	
Secondary objective	To monitor the safety of the subjects.	
Number of participants	Twenty eight (28) subjects were enrolled into the study. Twenty seven (27) subjects completed both the periods of the study. One subject (subject number 25) dropped out from the study. Pharmacokinetic and statistical analyses were performed on data from 27 subjects who completed both the periods of the study.	
Monitored parameters	C_{max}, T_{max}, AUC_t, AUC_i, $AUC_{\_\%Extrap\_obs}$, K_{el} and t_{Half}	
Investigational medicinal	Test Product	Reference product

products	Strength: Emtricitabine and Tenofovir Disoproxil Fumarate tablets 200mg/300 mg by Shasun Pharmaceuticals Ltd Puducherry-605014 Batch number: 11DT002A Batch Size: 120,000 Tablets Expiry date: 07/2013	Strength: Truvada® tablets 200 mg/ 300 mg by Gilead Sciences, Inc. Foster City. CA 94404 Made in Ireland Batch number: 02008554 Expiry date: 07/2014
Analytical method	Liquid-liquid extraction and high performance liquid chromatography with tandem mass spectrometric detection,	
Statistical method	A mixed effects ANOVA model using Type III sum of squares	

Efficacy results are summarized as follows:

Emtricitabine

Pharmacokinetic Parameter	**Test formulation (T) arithmetic mean ± SD (*)**	**Reference (R) arithmetic mean ± SD (*)**	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional 90% CI (ANOVAlog)**
t_{max} (h)	1.23 ± 0.52	1.24 ± 0.35	-	-
C_{max} (ng/ml)	2732 ± 482 (2693)	2583 ± 367 (2557)	105.2	98.1 – 112.8
AUC_{0-t} (ng·h/ml)	12392 ± 1862 (12252)	12267 ± 1918 (12124)	101.1	96.1 – 106.3
AUC_{0-inf} (ng·h/ml)	12649 ± 1895 (12507)	12536 ± 1921 (12395)	100.9	96.1 – 106.0

Tenofovir disoproxil fumarate

Pharmacokinetic Parameter	**Test formulation (T) arithmetic mean ± SD (*)**	**Reference (R) arithmetic mean ± SD (*)**	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional 90% CI (ANOVAlog)**

t_{max} (h)	0.92 ± 0.52	0.90 ± 0.43	-	-
C_{max} (ng/ml)	376 ± 110 (360)	350 ± 102 (335)	107.1	98.0 – 117.1
AUC_{0-t} (ng·h/ml)	2262 ± 661 (2174)	2188 ± 734 (2079)	104.3	95.9 – 113.5
AUC_{0-inf} (ng·h/ml)	2492 ± 710 (2399)	2427 ± 759 (2317)	103.7	95.5 – 112.6

The acceptance limits of 80 – 125% are met by the AUC and Cmax values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, Emtricitabine 200 mg and Tenofovir Disoproxil Fumarate 300 mg is equivalent and interchangeable with Truvada® tablets 200 mg/300 mg by Gilead Sciences, Inc. Foster City. CA 94404 Made in Ireland under acceptable in vivo experimental conditions.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. Emtricitabine 200 mg and Tenofovir Disoproxil Fumarate 300 mg tablets is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

Version	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up label

SAP CODE : 5207578
PHARMA CODE : 07578

268 C
032 C
151 C
Black

Emtric. & Tenofovir Disop. Fumarate Tabs. 30's
Carton size : 52 x 58 x 92 mm
Market : FWA/ROA
SPIL/PKGDEV - J11/JUN/2019-V01
J21/AUG/2019-V02, J06/FEB/2020-V03
J07/FEB/2020-V04, J14/FEB/2020-V05
J28/JUL/2020-V06

OLD SAP CODE : 5200038

SAP CODE : 5207579

ITF CODE : 05207579

Emtric & Tenofovir Disop. Fumarate Tabs 30's

Label size : 98 x 45 mm

Market : FWA/ROA

SPIL/PKGDEV - J11/JUN/2019-V01

J06/FEB/2020-V02, J07/FEB/2020-V03

J014/FEB/2020-V04, J024/FEB/2020-V05

J27/FEB/2020-V06, J28/JUL/2020-V07

268 C	032 C	151 C	Black

OLD SAP CODE : 5200037