THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR LAMIVUDINE/TENOFOVIR DISOPROXIL FUMARATE 300MG/300MG FILM COATED TABLETS

Version number 1.0
21 August, 2023

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1. Introduction

Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets is antiretroviral drug, indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and patients from 10 years of age and weighing at least 30 kg. The active pharmaceutical ingredient (API) of Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets are the nucleoside reverse transcriptase inhibitors lamivudine and the nucleotide reverse transcriptase inhibitor tenofovir disoproxil fumarate

Lamivudine and tenofovir are phosphorylated by cellular enzymes to form lamivudine triphosphate and tenofovir diphosphate, respectively. Lamivudine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

1.1 Product details

Registration number	TAN 23 HM 0274
Brand name	N/A
Generic name, strength, and form	Each film-coated tablet contains lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg equivalent to tenofovir disoproxil 245 mg or 136 mg of tenofovir
ATC classification	J05AR12 – Anti-retroviral
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Cipla Quality Chemical Industries Limited Address: Plot No. 1-7, 1st Ring Road, Luzira Industrial Park, P. O. Box 34871, Kampala Uganda.
Local Technical Representative	Salama Pharmaceuticals Limited 19 Uhuru / Nyamwezi Street, Kariakoo - Dar es Salaam

1.2 Assessment procedure

The application for registration of Lamivudine/Tenofovir Disoproxil Fumarate 300mg/300mg Tablets was submitted in 31/08/2022. The product underwent abridged assessment. Assessment was completed in 1 (one) rounds of evaluation and the product was registered on 01/06/2023.

1.3 Information for users

Visual description of the finished product	White to off white coloured, capsule shaped, biconvex, film coated tablets with ‘‘LT’’ debossed on one side and plain on other side
Primary packing material	HDPE bottle
Secondary packing materials	N/A
Shelf-life and storage condition	24 months, Do not store above 30°C.

Route of administration	Oral
Therapeutic indications	Lamivudine/Tenofovir Disoproxil Fumarate 300 mg/300 mg Tablets is indicated in combination with other antiretroviral products for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and patients from 10 years of age and weighing at least 30 kg. Lamivudine/Tenofovir Disoproxil Fumarate 300 mg/300 mg Tablets may be used in combination with other measures for pre-exposure exposure prophylaxis (PrEP) in adults and patients weighing at least 35 kg at substantial risk of HIV infection. Lamivudine/Tenofovir Disoproxil Fumarate 300 mg/300 mg Tablets may be used for post exposure prophylaxis (PEP) in adults and patients weighing at least 30 kg with an exposure that has potential for HIV transmission.

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, 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: Lamivudine and Tenofovir disoproxil fumarate Tablets

Composition: Each film-coated tablet contains lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg equivalent to tenofovir disoproxil 245 mg or 136 mg of tenofovir

Pack size: 30's tablets

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Do not store above 30°C.

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: N/A

The details of the primary pack include:

Brand name and strength: Lamivudine and Tenofovir disoproxil fumarate Tablets (300/300 mg)

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Cipla Quality Chemical 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.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredients

Information on the quality of the APIs was submitted in form of WHO Prequalification proof.

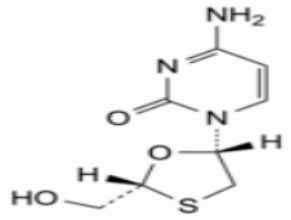
Lamivudine

General Information
Lamivudine API is compendia in Ph.Int., USP, Ph.Eur., and BP.

Molecular formula: $C_8H_{11}N_3O_3S$

Chemical name:
4-Amino-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1H)-one

Structure:



General properties

Lamivudine is a white or almost white powder. It is soluble in water, sparingly soluble in methanol, slightly soluble in ethanol. Three relevant crystalline forms of lamivudine had been identified (Form I, Form II and Form III). Form II, anhydrous, is the most stable form, was used to manufacture the finished product. The kinetic solubility of lamivudine Form II in water is 98 mg/mL at 25°C and is considered a BCS class III compound.

Lamivudine exhibits stereoisomerism due to the presence of two chiral centres. Enantiomeric purity is controlled routinely by chiral HPLC.

Manufacture

Lamivudine API manufacturer is Hetero Labs Limited (Unit III) 120,128,150 (Part),150/1,151/2 & 158/1, , N. Narasapuram (Vill), Nallamattipalem(V), Nakkapally (Mandal), Visakhapatnam (Dist) - 531081, Andhra Pradesh, INDIA. Manufacturing Block: “E”, Anhui Biochem United Pharmaceutical Co., Ltd Zone B, Industrial Park Taihe (236604), Anhui, CHINA, Honour Lab Limited (Unit - I), Survey No.: 200,202,203E,204&206A, Bonthapelly (Village), Gummadidaia (Mandal), Sangareddy (Dist.), Telangana 502313, INDIA, Manufacturing Block: “F, D, G & I” Hetero Labs Limited, Unit-I, Survey No. 10, I.D.A., Gaddapotharam Village, Jinnaram Mandal, Sangareddy District – 502319, Telangana, INDIA. Manufacturing Block: “H” (LVD) Hetero Labs Limited Unit-IX, Plot No.2, Hetero Infrastructure SEZ Ltd., N. Narasapuram (Village), Nakkapalli (Mandal), Vishakapatnam District-531081, Andhra Pradesh, INDIA. Manufacturing Block: “H2, H7 & D” (LAN). The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the WHO. Lamivudine 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

Specifications

The API specifications were set as per USP standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, melting point, identification (IR and HPLC), assay (HPLC), limit of lamivudine enantiomer (HPLC), Other related compounds (HPLC), water determination (KF), light absorption, polymorphic identity (XRPD), residue on ignition, loss on drying, residual solvents (GC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Lamivudine API is 60 months when packed in food grade double polythene bags and stored at below 30ºC.

Tenofovir disoproxil fumarate

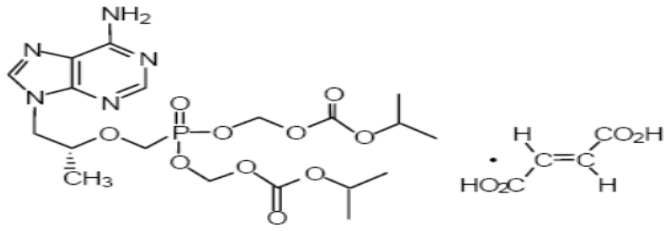
General Information

Tenofovir disoproxil fumarate API is compendia in International Pharmacopeia and information on the quality has been included in the form of WHO Prequalification proof.

Molecular formula: $C_{19}H_{30}N_5O_{10}P$, $C_4H_4O_4$

Chemical name:
[[(1R)-2(6-Amino-9H-purin-9-yl)-1-methylethoxy] methyl] phosphonate, bis (isopropyloxycarbonyloxymethyl ester), fumarate (1:1)

Structure:



General properties

The active substance is a white to almost-white, crystalline powder. Tenofovir disoproxil fumarate is slightly soluble in water, soluble in methanol, very slightly soluble in dichloromethane.

Polymorphism has been observed for Tenofovir disoproxil fumarate. The manufacturing process for the drug substance, Tenofovir disoproxil fumarate followed by the proposed manufacturer, consistently produces “Form I”. Nonetheless, Tenofovir disoproxil fumarate is a BCS high soluble drug so neither polymorphism nor particle size distribution can affect the quality or performance of the finished product.

Manufacture

Tenofovir disoproxil fumarate API manufacturer is Cipla – Kurkumbh, Cipla Limited, Manufacturing Division, Plot No. D-22, MIDC Industrial Area, Kurkumbh Village, Taluka-Daund, District - Pune (Maharashtra), INDIA, Cipla – Kurkumbh, Cipla Limited, Manufacturing Division, Plot No. D-27, MIDC Industrial Area, Kurkumbh Village, Taluka – Daund, District - Pune (Maharashtra), INDIA, Cipla Limited, Cipla House, Peninsula Business Park, Ganpatrao Kadam, Marg, Lower Parel, Mumbai – 400 013, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the WHO. 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 in-house standards and ICHQ3A. The parameters monitored during quality control are: Description, solubility, identification by IR and HPLC, water content, clarity and colour of solution, Fumaric acid content, heavy metals, content of 9-propenyladenine, assay, polymorphic identity, residual solvents by GC, particle size, related substances and test for Benzene and Residual solvents (GC). Compliance to these specifications were established via batch analysis data and stability studies.

<u>Stability and container closure system</u>

The retest period of Tenofovir disoproxil fumarate API is 24 months when packed in double clear HMHD (high molecular high density) polyethylene bags placed in triple laminated high barrier bag and hermetically sealed, in a fibre drum with storage condition ‘Store in a well closed container at 2-8°C, protected from light’.

Quality of the Finished Pharmaceutical Product

Formulation

Lamivudine and Tenofovir disoproxil fumarate Tablet is a white to off white coloured, capsule shaped, biconvex, film coated tablet with “LT” debossed on one side and plain on other side

The product contains the Lamivudine and Tenofovir disoproxil fumarate and other ingredients listed here after: Core tablet: microcrystalline cellulose, croscarmellose sodium, partially pregelatinised starch, magnesium stearate. Film coat: hypromellose polyvinyl alcohol, titanium dioxide, talc, macrogol/peg, and lecithin (soya). The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities.

Manufacture

The finished product manufacturers are Cipla Quality Chemical Industries Limited (Cipla QCIL) , Plot 1-7 1ST Ring road, Luzira Industrial Park, P. O. Box 34871, Kampala, Uganda. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YY.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: description, identification of the APIs (HPLC, TLC) and the colorant, average weight, water content (KF), uniformity of dosage units (by weight variation), dissolution (HPLC detection), degradation products (HPLC), assay (HPLC), residual solvents and microbiological examination of non-sterile products. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3(three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 24 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in 50 CC white HDPE container containing 30 tablets and 3 silica gel bags of 1 gm each with 38 mm Non-CRC cap having induction seal with storage condition ‘Do not store above 30°C’.

Safety and efficacy information

Cipla’s Lamivudine and Tenofovir disoproxil fumarate Tablet is already registered by WHO. Information on clinical data has been fully evaluated during the registration of the product (Refer: WHO pre-qualification reference Number HA666). In this context, re-assessment of this part is not considered as necessarily required.

4. Benefit-Risk Assessment and Conclusion

On basis of the 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. Lamivudine/Tenofovir disoproxil fumarate 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>.

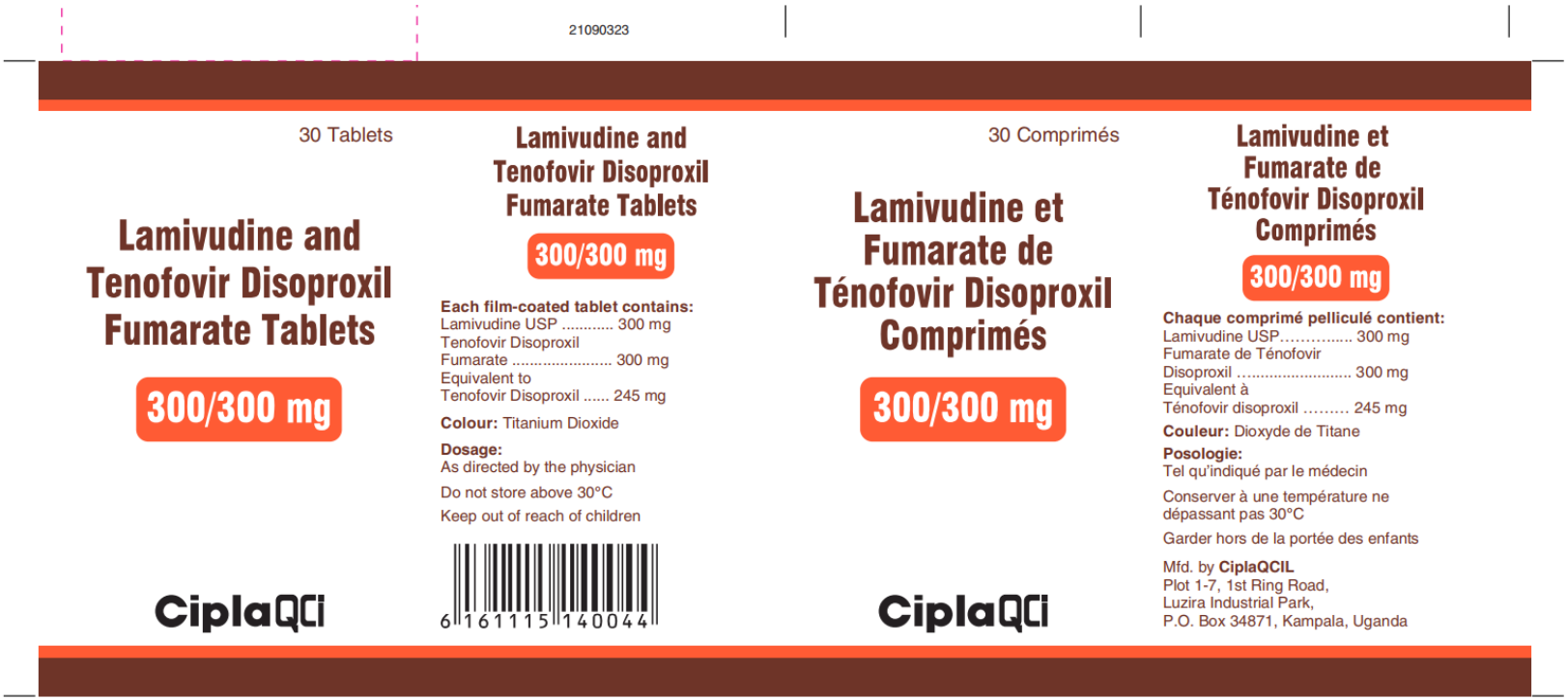
PART 5: CHANGE HISTORY

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

Annex I: Mock up labels;

Primary pack label;

Secondary pack label:



Effective date: 03/10/2022