TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR TENOFOVIR ALAFENAMIDE (TENOFOVIR ALAFENAMIDE FUMARATE EQUIVALENT TO TENOFOVIR ALAFENAMIDE 25 MG) FILM COATEDTABLETS

Version number 1.0

11th April, 2022

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1. Introduction

Laurus Tenofovir Alafenamide is a generic medicine of Vemlidy® (Tenofovir Alafenamide) Tablets 25mg of Gilead sciences, Inc., Foster City, CA 94404. Laurus Tenofovir Alafenamide is an Antiviral medicine belonging to nucleoside and nucleotide reverse transcriptase inhibitors group. Laurus Tenofovir Alafenamide exerts is activity by the following mechanism:Tenofovir alafenamide is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide enters primary hepatocytes by passive diffusion and by the hepatic uptake transporters OATP1B1 and OATP1B3. Tenofovir alafenamide is primarily hydrolysed to form tenofovir by carboxylesterase 1 in primary hepatocytes. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HBV replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain termination. Laurus Tenofovir Alafenamide is approved in Tanzania for use in adults and adolescents (aged 12 years and older with body weight at least 35 kg).

1.1 Product details

Registration number	TAN 22 HM 0257
Brand name	Laurus Tenofovir Alafenamide
Generic name, strength and form	Tenofovir Alafenamide 25 mg Film Coated Tablets
ATC classification	ATC Code: J05AF13 Antiviral for systemic use, nucleoside and nucleotide reverse transcriptase inhibitors
Distribution category	POM
Country of origin	India
Associated product	NA
Marketing Authorization Holder	Laurus Labs Limited 2nd Floor, Serene Chambers, Road No.-7, Banjara Hills, Hyderabad, Telangana – 500034. India
Local Technical Representative	Planet Pharmaceutical Limited P.O. Box 38328, Plot no. 2360/75E, Kipawa Godown no 16 & 17, Vingunguti Area, Nyerere

1.2 Assessment procedure

The application for registration of Laurus Tenofovir Alafenamide was submitted on 10th February, 2021. The product underwent full assessment. Assessment was completed in 2 rounds of evaluation. Laurus Tenofovir Alafenamide was registered on 19th July 2022

1.3 Information for users

Visual description of the finished product	White to off white, round shaped, film coated tablets debossed with 'L3' on one side and plain on the other side
Primary packing material	HDPE bottles with propylene cap
Secondary packing materials	cardboard carton box

Shelf-life and storage condition	24 months, Store below 30^0C
Route of administration	Oral
Therapeutic indications	Tenofovir alafenamide tablets are indicated for the treatment of chronic hepatitis B in adults and adolescents (aged 12 years and older with body weight at least 35 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 the package insert contains full prescribing information as per SmPC

Container labels
The product label information is presented in English and French. Details in the secondary pack label include:
Brand name: Laurus Tenofovir Alafenamide
Composition: Tenofovir Alafenamide 25 mg
Pack size: 30 tablets per bottle
Manufacturing details: NA
Storage conditions: Do not store above 30ºC
Manufacturer address: Laurus Labs Limited (Unit II), Plot no. 19, 20 & 21, western sector, APSEZ, Atchutapuram Mandal, Visakhapatnam District, Andhra Pradesh – 531011, India.

Unique identifier: NA
Special warnings/precautions or instructions for use: The formulation contains Lactose

The details of the primary pack include:
Brand name and strength: Laurus Tenofovir Alafenamide 25 mg
Manufacturing details: The space for printing this details is reserved on the mock up label
Name of manufacturer: Laurus Labs Limited (Unit II),

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 Ingredient(s)

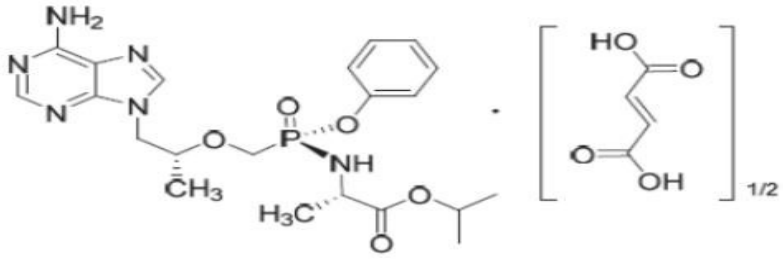
Information on quality of the API was submitted in form of Full details

General Information

Tenofovir Alafenamide API is compendia in International Pharmacopeia
Molecular formula: $C_{21}H_{29}O_5N_6P$

Chemical name: Propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9Hpurin-9-yl)propan-2-yl]-oxy}methyl) (phenoxy)phosphoryl]-L-alaninate, (2E)-but-2-enedioate (2:1)

Structure:



Physico-chemical properties of the API

Tenofovir alafenamide is a white to off-white, slightly hygroscopic powder. Tenofovir alafenamide fumarate is a BCS Class III compound, with pH-dependent aqueous solubility decreasing with increasing pH. It is soluble at low pH (pH 2.0) and slightly soluble at pH values up to 8.0. Tenofovir alafenamide is freely soluble in methanol, soluble in ethanol, sparingly soluble in isopropanol and slightly soluble in acetone.
Tenofovir alafenamide exhibits stereoisomerism due to the presence of three chiral centres. The chiral centre at the propyloxy- side chain is in the R-configuration. The absolute stereoconfiguration of the carbonylethylamino- substituent is derived from the amino acid L-alanine, which has the S- configuration at the alpha-carbon. The remaining stereocentre is located at the phosphorus atom and is in the S- configuration.
Polymorphism has been observed for tenofovir alafenamide. A single polymorphic form is consistently generated through the manufacturing process and this form has been adequately characterised by XRD and DSC analysis.

Manufacture

The API manufacturing site is Laurus Labs Limited, Plot No. 21, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam-531021, Andhra Pradesh, India. The manufacturing site complies with WHO prequalification GMP requirements on 17th October 2017. Tenofovir alafenamide 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, HPLC and DSC), Water content (KF), Fumaric acid content (potentiometry), related substances (by HPLC), Assay (by HPLC), Residual solvents (GC) and particle size distribution (by Malvern analysis). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of Tenofovir alafenamide API is 30 months when packed in Transparent Low Density Polyethylene (LDPE) and Triple Laminated Sunlight Barrier (TLSB) bags in HDPE drum and stored between 2-8°C

Quality of the Finished Pharmaceutical Product

Formulation
Laurus Tenofovir alafenamide is a White to off White, round shaped, film-coated tablets debossed with "L3" on one side and plain on the other side. Laurus Tenofovir alafenamide contains Tenofovir alafenamide and other ingredients listed here after: Microcrystalline cellulose, Lactose monohydrate, Croscarmellose Sodium, Magnesium Stearate, Purified water and Opadry II white 85F580019 (Polyvinyl Alcohol, Talc, Macrogol/PEG, Titanium dioxide)

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. Lactose monohydrate is of safety concern therefore appropriate warnings were included in the product label.

Manufacture
The finished product was manufactured at Laurus Labs Limited (Unit-2), Plot No:19, 20 & 21, Western Sector, APSEZ, Atchutapuram Mandal, Visakhapatnam-District-531011, Andhra Pradesh, India.The compliance of the site to TMDA GMP standards was confirmed through site inspection on 12th June 2018

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 (by HPLC an UV), water content (by KF), uniformity of dosage units (by HPLC), dissolution (by HPLC), assay (by HPLC), related substances (by HPLC), microbiological enumeration test and tests for specified microorganism.

Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system
Stability studies were conducted on three (3) batches of the finished product stored at 30 ± 2 °C, 75 ± 5 % RH for 24 months and 40 ± 2 °C, 75 ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in HDPE bottle at the following storage condition; "Do not store above 30°C"

Safety and efficacy information

Safety and efficacy of Laurus Tenofovir Alafenamide was established through bioequivalence trial. BE trial report number 20 -089 Version 01 of 17- Feb -2021 was submitted.

<table>
<tr><td>Study title</td><td>An open-label, balanced, randomized, two-treatment, two-sequence, four-period, crossover, fully replicate, single dose oral bioequivalence study of Tenofovir Alafenamide Tablets 25mg of Laurus Labs Limited, India with Vemlidy® (Tenofovir Alafenamide) Tablets 25mg of Gilead sciences, Inc., Foster City, CA 94404 in healthy, adult, human subjects under fasting conditions</td></tr>
<tr><td>Study design</td><td>An open-label, randomized, two-treatment, two-sequence, four-period, crossover, fully replicate, single dose oral bioequivalence study</td></tr>
<tr><td>Study site</td><td>Jeevan Scientific Technology Ltd,
Plot no: 1& 2, Sai Krupa Enclave, Near Lanco Hills , Golconda Post, Hyderabad 500 008, India</td></tr>
<tr><td>Study dates</td><td><table>
<tr><th>Activities</th><th>Dates</th></tr>
<tr><td>Period I (dosing)</td><td>19 February 2021 – 22nd Feb 2021</td></tr>
<tr><td>Period II (dosing)</td><td>28th Feb 2021 –04th Mar 2021</td></tr>
<tr><td>Period III (dosing)</td><td>11th March 2021- 14th March 2021</td></tr>
<tr><td>Period IV (Dosing)</td><td>21st March 2021-14th March 2021</td></tr>
<tr><td>Analysis (start date)</td><td>07th April 2021</td></tr>
<tr><td>Analysis (completion date)</td><td>21st May 2021</td></tr>
</table></td></tr>
<tr><td>Primary objective</td><td>To assess the in vivo response of the dosage form with respect to extent of and rate of absorption of Tenofovir Alafenamide Tablets 25mg of Laurus Labs Limited, India with Vemlidy® (Tenofovir Alafenamide) Tablets 25mg of Gilead sciences, Inc.</td></tr>
<tr><td>Secondary objective</td><td>To monitor the safety and tolerability of a single dose of Tenofovir Alafenamide Tablets administered in healthy human adults</td></tr>
<tr><td>Number of participants</td><td>Planned: 36 (+ 2 additional subjects)
Randomized: 36
Subjected completed period I: 36 (no drop out)
Subject completed period II: 33 (3 subject drop out of the study)
Subject completed period III: 35 (1 subject drop out of the study)
Subject completed period II: 33 (3 subject drop out of the study)
Subject completed period II: 36 (no drop out)
Number of subject completed all the four period: 32 subjects</td></tr>
<tr><td>Monitored parameters</td><td>Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2</td></tr>
</table>

Investigational medicinal products	Test Product	Reference product
	Strength: 25 mg Batch number: E1901612 Expiry date: March-2021	Strength: 25 mg Batch number: ZFTMA Expiry date: November, 2020
Analytical method	LC-MS/MS was used to estimate the level of Tenofovir Alafenamide in human plasma	
Statistical method	The statistical analysis was performed by Phoenix WinNonlin version 8.2 and SAS® Version 9.4	

Efficacy results are summarized as follows:

Table 1: Summary of bioequivalence parameters for Tenofovir Alafenamide Fumarate

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC_{0-t} (ng/mL)	151.4593	147.4605	102.71	95.14 - 110.89	34	26.41
AUC_{0-inf} (ng.hr/mL)	152.3663	148.2717	102.76	95.17 - 110.95	34	26.29
C_{max} (ng.hr/mL)	268.3390	263.0996	101.99	92.88 - 112.00	34	33.31

Table 2: Summary of bioequivalence parameters for metabolite (Tenofovir)

Parameter	Test	Reference	% Ratio of geometric means	DF	CV (%)
AUC_{0-t} (ng/mL)	224.8269	227.3273	98.90	34	22.11
AUC_{0-inf} (ng.hr/mL)	307.9612	309.5186	99.50	34	23.33
C_{max} (ng.hr/mL)	11.2912	11.5727	97.57	34	23.76

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, Tenofovir Alafenamide 25 mg film coated tablets of Laurus Labs Limited is equivalent and interchangeable with Vemlidy® (Tenofovir Alafenamide 25 mg) Tablets of Gilead sciences under acceptable in vivo experimental conditions.

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. Tenofovir Alafenamide 25 mg film coated tablets of Laurus Labs Limited 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

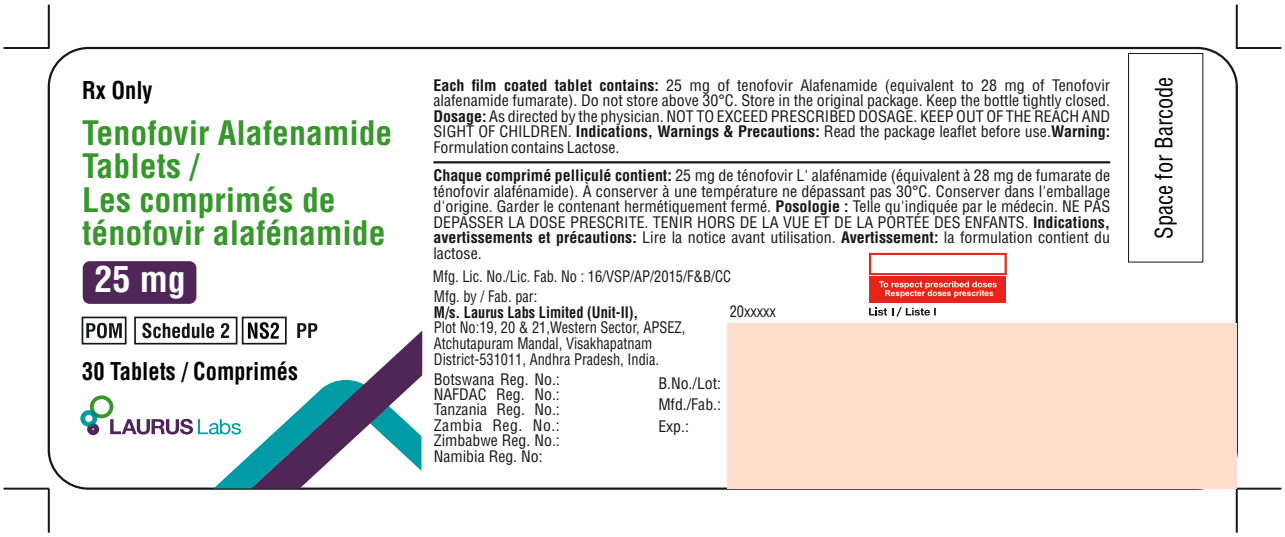
Re-registration applications

NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up label



105 x 40 mm