THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR HEPBEST (25 MG TENOFOVIR ALEFENAMIDE (AS FUMARATE)) FILM COATED TABLETS

Version number 1
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1. Introduction

HepBest is a generic medicine of Vemlidy 25 mg film coated tablets, Gilead Sciences Inc. HepBest is antihepatitis B medicine belong to nucleoside and nucleotide reverse transcriptase inhibitors group. HepBest contains Tenofovir alafenamide, a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). 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 hepatitis B virus (HBV) replication through incorporation into viral DNA by the HBV reverse transcriptase, which results in DNA chain termination. HepBest 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 21 HM 0452
Brand name	HepBest
Generic name, strength, and form	Each film-coated tablet contains Tenofovir Alafenamide Fumarate equivalent to Tenofovir Alafenamide 25 mg
ATC classification	ATC Code- J05AF13, Antiviral for systemic use, Nucleoside and Nucleotide Reverse Transcriptase Inhibitor
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Mylan Laboratories Limited Plot No.564/A/22, Road No.92, Jubilee Hills Hyderabad - 500096, Telangana, India. E-mail: kulbhushan.Ganotra@mylan.in
Local Technical Representative	Pyramid Pharma Limited 1st floor, TTCL Building, Garden Road/New Bagamoyo Road, Kijitonyama, P.O. Box 16215, Dar es Salaam, Tanzania E-Mail: aokor@pyramidpharma.com

1.2 Assessment procedure

The application for registration of HepBest was submitted on 11December 2017. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 26 November 2021.

1.3 Information for users

Visual description of the finished product	A white to off-white, film-coated, round, biconvex tablet debossed with M on one side of the tablet and TFI on the other side
Primary packing material	HDPE bottle

Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, do not store above 30ºC. Store in the original container
Route of administration	Oral
Therapeutic indications	Tenofovir Alafenamide tablets 25 mg is 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. Details in the secondary pack label include:
Brand name: HepBest

Composition: Each film-coated tablet contains Tenofovir Alafenamide Fumarate equivalent to Tenofovir Alafenamide 25 mg

Pack size: 30 film-coated tablets

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

Storage conditions: Do not store above 30ºC. Store in the original container

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Not to exceed prescribed dosage. Read the leaflet before use, formulation contains lactose.

The details of the primary pack include:

Brand name and strength: HepBest

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Mylan

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 API was submitted in form of DMF.

General Information

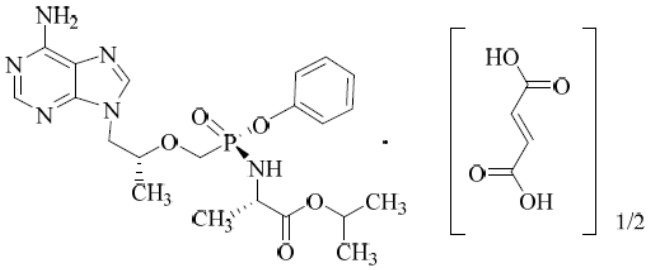
Tenofovir Alafenamide Fumarate API is non-compendia.

Molecular formula: $C_{21}H_{29}N_6O_5P$. ½ $C_4H_4O_4$

Chemical name:

9-{(R)-2-[[(S)-{[(S)-1-(isopropoxycarbonyl)ethyl] amino} phenoxy-phosphonyl] methoxy] propyl} adenine hemi fumarate

Structure:



General properties

The active substance is a white to off-white or tan, slightly hygroscopic powder. Tenofovir alafenamide fumarate is a BCS Class III compound, with pH-dependent aqueous solubility decreasing with increasing basicity. It is soluble at low pH (pH 2.0), sparingly soluble at pH 3.8, and slightly soluble at pH values up to 8.0. Tenofovir alafenamide fumarate is freely soluble in methanol, soluble in ethanol, sparingly soluble in isopropanol and slightly soluble in acetone. The substance shows polymorphism and stereoisomerism. The manufacturer consistently produces the correct isomer and the same polymorphic form.

Manufacture

Tenofovir alafenamide fumarate API manufacturer is Mylan Laboratories Limited (Unit-10), Plot No. 86, Ramky Pharma City (India) Ltd, SEZ, JN Pharma City, Parawada Mandal, Visakhapatnam District – 531019, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration, Andhra Pradesh. Tenofovir alafenamide 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, identity (IR, HPLC and PXRD), loss on drying, residue on ignition, heavy metals, chiral purity (HPLC), residual solvent (GC), assay (HPLC), related impurities (HPLC), and water content (KF). 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 fumarate API is 6 months when packed in HMLDPE bag, heat sealed under vacuumised nitrogen with storage condition ‘Store in tight, light-resistant containers at below 25°C’.

Quality of the Finished Pharmaceutical Product

Formulation

HepBest is a white to off-white, film-coated, round, biconvex tablet debossed with M on one side of the tablet and TFI on the other side.

HepBest contains the Tenofovir alafenamide fumarate and other ingredients listed here after: Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Magnesium Stearate, Polyvinyl Alcohol, Polyethylene Glycol, Titanium Dioxide, and Talc. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8^{th} Edition in terms of function and quantities.

Manufacture

The finished product manufacturers are Mylan Laboratories Limited, Plot No.11, 12 & 13, Indore Special Economic Zone, Pharma Zone, Phase-II, Sector-III, Pithampur-454775 Dist. Dhar, Madhya Pradesh, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on 23 September 2019.

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 API (UV and HPLC), identification of colourant, assay, dissolution, uniformity of dosage units, related impurities, water content, and microbial purity. 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 per each pack size identified in the application (30's, 90's, and 180's pack size) 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 HDPE bottles with storage condition 'Do not store above 30ºC. Store in the original container'.

Safety and efficacy information

Safety and efficacy of HepBest was established through a bioequivalence trial.

BE trial report number 1216 was submitted.

Study title	An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Tenofovir Alafenamide tablets 25mg of Mylan Laboratories Limited, India with VEMLIDY® (Tenofovir Alafenamide) 25mg tablets of Gilead Sciences, Inc. Foster City, CA 94404 in normal healthy adult human subjects under fasting conditions
Study design	Open label, fed state, single dose, two treatment, two-sequence, and two-way crossover study with a washout interval of thirteen (13) days between dosing
Study site	Clinical, Pharmacokinetic and Statistical facility: Aizant Drug Research Solutions Pvt. Ltd, Survey No.: 172 &173, Apparel Park Road, Dulapally Village, Quthbullapur Mandal, Hyderabad, India-500100. Bio analytical facility: Mylan Laboratories Limited, Clinical Research Centre, Saradhi Chambers, Plot No. 4-A, Beside Poulomi Hospital, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad. India – 500062.
Study dates	17 Jun 2017- 03 Aug 2017
Primary objective	To evaluate the oral bioequivalence of Tenofovir Alafenamide tablets 25mg of Mylan Laboratories Limited, India with VEMLIDY® (Tenofovir Alafenamide) 25mg tablets of Gilead Sciences, Inc. Foster City, CA 94404 in normal healthy adult human subjects under fasting conditions
Secondary objective	To monitor the adverse events and to ensure the safety of the subjects
Number of participants	Planned – 72 subjects + A maximum of 02 additional subjects in each group if possible. Enrolled: Group-I: 42 subjects (subject numbers 01 to 42) + 01 additional subject (Stand by-I) Group-II: 30 subjects (subject numbers: 43 to 72) + 02 additional subjects (Stand by-III & Stand by-IV)

	Dosed: Group-I: Period-1: 42 subjects, Period-2: 41 subjects, Group-II: Period-1: 30 subjects, Period-2: 29 subjects, Withdrawn - 02 subjects (subject numbers 36 & 51), Completed- 70 subjects, Bio-sample analyzed - 70 subjects Pharmacokinetic and statistical data analyzed – 70 subjects	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 25 mg Batch number: 2012170 Expiry date: 07/2018	Strength: 25 mg Batch number: 008477 Expiry date: 06/2018
Analytical method	LC-MS/MS method was used for the determination of plasma concentrations of analyte	
Statistical method	SAS® procedure PROC Mixed Software 9.2 version (SAS Institute Inc., USA)	

Efficacy results are summarized as follows:

For Tenofovir alafenamide

Parameter	Test	Reference	90 % Confidence interval	DF	CV (%)
AUC0-t (hr.ng/mL)	220.714	222.928	91.45-107.18	68	28.7
AUC0-inf (ng.hr/mL)	228.581	230.271	91.78-107.36	68	27.9
Cmax (ng/mL)	382.683	394.312	88.43-106.52	68	33.9

For Tenofovir

Parameter	Test	Reference	90 % Confidence interval	DF	CV (%)
AUC0-t (hr.ng/mL)	191.667	185.164	97.75-109.61	68	21.4
AUC0-inf (ng.hr/mL)	264.390	251.216	99.38-111.46	68	20.5
Cmax (ng/mL)	7.919	7.636	87.76-99.17	68	20.6

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, Tenofovir Alafenamide tablets 25mg of Mylan Laboratories Limited, India is equivalent and

interchangeable with VEMLIDY® (Tenofovir Alafenamide) 25mg tablets of Gilead Sciences Inc. 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. HepBest 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