THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ENVUTEG (LAMIVUDINE, TENOFOVIR ALAFENAMIDE, AND DOLUTEGRAVIR 300 MG/25 MG/50 MG) TABLETS

Version number 1.0
21 August 2023

TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Hombolo 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

The product is a fixed combination contains lamivudine, tenofovir alafenamide, and dolutegravir indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 40 kg) infected with human immunodeficiency virus type 1 (HIV-1). Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Lamivudine, via its active metabolite 5'-triphosphates (TP) (an analogue for cytidine), inhibits reverse transcriptase of HIV-1 and HIV-2 through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine triphosphate shows significantly less affinity for host cell DNA polymerases.

Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir alafenamide is more efficient than tenofovir disoproxil fumarate in concentrating tenofovir in peripheral blood mononuclear cells (PBMCs) or HIV target cells including lymphocytes and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination.

ENVUTEG tablets is approved in Tanzania for use in adults and adolescents (aged 12 years and older with body weight at least 40 kg).

1.1 Product details

Registration number	TAN 23 H 0283
Brand name	ENVUTEG
Generic name, strength, and form	Each film coated tablet contains: Dolutegravir sodium equivalent to Dolutegravir 50 mg Lamivudine 300 mg Tenofovir Alafenamide Fumarate equivalent to Tenofovir Alafenamide 25 mg
ATC classification	
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
Local Technical Representative	Synermed Pharmaceuticals (Tanzania) Limited, Plot No. 31/32 Makaburini, Nyerere Road, Dar es Salaam

1.2 Assessment procedure

The application for registration of ENVUTEG was submitted on 09/09/2021. The product underwent abridged assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 01 June 2023.

1.3 Information for users

Visual description of the finished product	White to off white, film coated, capsule shaped, biconvex beveled edge tablet debossed with M on one side of the tablet and LD on the other side
Primary packing material	HDPE Bottle Pack: 30's count (With 2g Molecular Sieve) Container: Bottle HDPE 60CC 33mm Blue round (12G) TP Closure: Closure 33mm Blue screw with SG100 SP. Desiccant: 2g Molecular Sieve Canister - SC 2g9 Molecular Sieve Sachet. HDPE Bottle Pack: 30's count (With 4g Molecular Sieve) Container: Bottle HDPE 75CC 38mm Blue round (HWT) TP Closure: Closure 38mm Blue screw with SG100 SP. Desiccant: 2g Molecular Sieve Canister - SC (2 Nos) 2g Molecular Sieve Sachet (2 Nos) HDPE Bottle Pack: 90's count Container: Bottle HDPE 150CC 38mm Blue round (HWT) TP Closure: Closure 38mm Blue screw with SG100 SP. Desiccant: 3g Molecular Sieve Canister - SC (2 Nos) HDPE Bottle Pack: 18O's count Container: Bottle HDPE 400CC 53mm Blue round (HWT) TP
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, Do not store above 30'C, store in original container.
Route of administration	Oral
Therapeutic indications	Lamivudine, Tenofovir Alafenamide and Dolutegravir Tablets 300 mg/25 mg/50 mg is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least

	40 kg) infected with human immunodeficiency virus type 1 (HIV-1

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: ENVUTEG

Composition: Each film coated tablet contains: Dolutegravir sodium equivalent to Dolutegravir 50 mg, Lamivudine 300 mg, Tenofovir Alafenamide Fumarate equivalent to Tenofovir Alafenamide 25 mg

Pack size: 30’s, 60’s, 90’s, 180’s tablets

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

Storage conditions: Do not store above 30'C, store in original container

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Formulation contains Lactose; Read the package leaflet before use

The details of the primary pack include:

Brand name and strength: ENVUTEG

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Mylan Laboratories 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 quality of the API was submitted in form of DMFs

Dolutegravir Sodium

General Information

Dolutegravir Sodium API is compendia in USP.

Molecular formula: $C_{20}H_{18}F_2N_3NaO_5$

Chemical name:

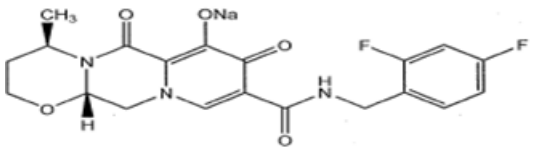
Sodium (4R,12aS)-N- [(2,4-Difluoro benzyl) carbamoyl]- 4-methyl-6, 8-dioxo- 3,4,6,8,12,12a-hexahydro-2H-pyrido [l',2': 4,5] pyrazino [2, 1 – b] [1,3] oxazin -7 -olate

Sodium (4R, I 2aS)-9- [(2,4-Difluoro benzyl) carbamoyl] -4-methyl-6, 8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido [l',2': 4,5] pyrazino[2,1-b] [1,3] oxazin -7 -olate

Sodium (4R, 12aS)-N-[(2,4-Di-fluorophenyl) methyl] - 3,4,6,8,12,12a-hexahydro-7-hydroxy- 4-methyl-6, 8-dioxo-2H-pyrido [1',2' :4,5] pyrazino [2, l-b] [1,3] oxazine -9- carboxamide

Sodium (4R, 9aS)-5-hydroxy-4-rnethyl-6, 10-dioxo-3,4,6,9,9a,10-hexahydro-2H-] - oxa-4a,8a-diazaanthracene-7 -carboxylic acid 2,4 -difluoro benzylamide

Structure:



General properties

Dolutegravir Sodium is a white to pale yellow solid and exhibit polymorphism whereas the obtained spectra show Mylan consistently manufactures crystalline form.

Dolutegravir is classified as either BCS class II or IV molecule, therefore control of polymorphism and particle size is considered critical. The control of particle size distribution was demonstrated in the API specification.

Manufacture

Dolutegravir Sodium API manufacturer is Mylan Laboratories Limited (Unit-9) Plot No. 5, Road No. 12, J.N. Pharma City, Tadi Village, Parawada Mandal, Visakhapatnam – 531021, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP

certificate issued by Food & Drugs Control Administration of Andhra Pradesh, India. Dolutegravir Sodium 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, PXRD and Test for Sodium), Water content by KF, Heavy metals, Related substances by HPLC, Chiral purity for Enantiomer, Isomer-1 and Isomer-2, Assay by HPLC, Residual solvents by GC and Limit of N-Methyl Morpholine and Particle size are the In-house methods. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Dolutegravir Sodium API is 24 months when packed in antistatic white polyethylene bag (LDPE), securely twist-tied with a plastic rope with storage condition 'Store in well closed containers at 25°C, excursions permitted to 15°C and 30°C'.

Tenofovir Alafenamide Fumarate

General Information

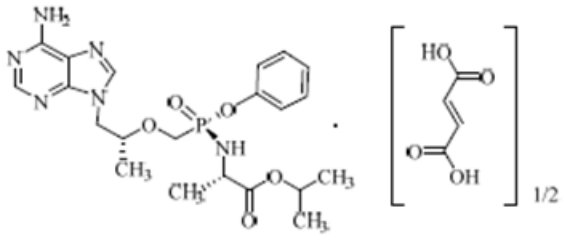
Tenofovir Alafenamide Fumarate API is non-compendia.

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-phosphinyl] methoxy] propyl} adenine hemi fumarate

Structure:



General properties

Tenofovir Alafenamide Fumarate is white to off-white powder or Light tan powder soluble in methanol, very slightly soluble in water and practically insoluble in Ethyl acetate.

Tenofovir Alfenamide Fumarate known to exhibit polymorphism. Polymorphism confirmed through PXRD and DSC concludes that Tenofovir Alafenamide Fumarate manufactured by Mylan is consistent and stable crystalline form.

The submitted solubility data, in the physiological pH range at 37±1°C, show that Tenofovir Alafenamide Fumarate is a highly soluble molecule according to the Biopharmaceutics Classification System (BCS). Therefore, controlling polymorphism and particle size is considered not to be critical.

Manufacture

Tenofovir Alfenamide 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 Food & Drugs Control Administration of Andhra Pradesh, India. Tenofovir Alfenamide 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, HPLC, and PXRD), Water content by KF, Heavy metals, Related substances by HPLC, Chiral purity for Enantiomer, Diastereomer-2 and Diastereomer-3, Assay by HPLC, Residual solvents by GC and Particle size are the In-house methods. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Tenofovir Alfenamide Fumarate API is 24 months when packed in HMLDPE bag, heated sealed under vaccuminised nitrogen with storage condition ‘Store in tight, light-resistant containers at below 25°C’.

Lamivudine from Mylan Laboratories Limited

General Information

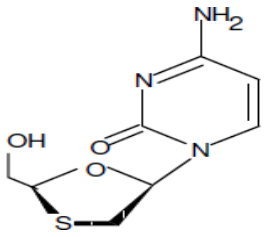
Lamivudine API is compendia in Ph.Int., USP, Ph.Eur., and BP.

Molecular formula: $C_8H_{11}N_3O_5S$

Chemical name:

2R-cis)-4-amino-1-(2R-hydroxymethyl-[1,3] oxathiolan-5S-yl)- 1H-pyrimidin-2-one

Structure:



General properties

Lamivudine is a white to off-white solid and soluble in water. This active substance exhibits also stereoisomerism due to the presence of two chiral centres (1S,4R absolute configuration). Enantiomeric purity is controlled routinely by chiral HPLC and specific rotation. Lamivudine may exist as either of two pseudopolymorphs (Form I or Form II). The manufacturing process of Lamivudine is well controlled to manufacture only Form II.

Manufacture

Lamivudine API manufacturer is Mylan Laboratories Limited (Unit-1), Survey No. 10/42, Gaddapotharam, Kazipally Industrial Area, Medak District -502319, Telangana, India; Mylan laboratories Limited (Unit-2), Survey No. 10/42, Gaddapotharam, Kazipally Industrial Area, Medak District -502319, Telangana, India; Mylan Laboratories Limited (Unit-8), G. Chodavaram, Poosapatirega Mandal, Vizianagaram District- 535204, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates submitted. 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

The API specifications were set as per USP standards and ICHQ3A. The parameters monitored during quality control are: Description, Solubility, Identification by IR & HPLC, Light absorption, melting range, Water content, Limit of Lamivudine enantiomer, Chromatographic purity by HPLC, Assay by HPLC, Residual solvents by GC, Residue on Ignition, Heavy metals, Specific optical rotation, Bulk density & Tapped density and Particle size are the USP/In-house methods. Compliance to these specifications were established via batch analysis data and stability studies.

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

The re-test period of Lamivudine API is 60 months when packed in transparent low-density polyethylene (LDPE) bag, securely folded and twist-tied with a self-sealing plastic rope with storage condition ‘Do not store above 30°C’.

Lamivudine from Hetero Labs Limited

General Information

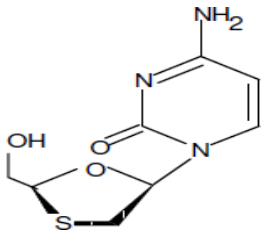
Lamivudine API is compendia in Ph.Int., USP, Ph.Eur., and BP.

Molecular formula: $C_8H_{11}N_3O_5S$

Chemical name:

2R-cis)-4-amino-1-(2R-hydroxymethyl-[1,3] oxathiolan-5S-yl)- 1H-pyrimidin-2-one

Structure:



General properties

Lamivudine is a white to off-white solid and soluble in water. This active substance exhibits also stereoisomerism due to the presence of two chiral centres (1S,4R absolute configuration). Enantiomeric purity is controlled routinely by chiral HPLC and specific rotation. Lamivudine may exist as either of two pseudopolymorphs (Form I or Form II). The manufacturing process of Lamivudine is well controlled to manufacture only Form II.

Manufacture

Lamivudine API manufacturer is Hetero Labs Limited, Unit-IX, Plot No.2, Hetero Infrastructure SEZ Ltd., N. Narasapuram (Village), Nakkapalli (Mandal), Visakhapatnam District- 531081, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates submitted. 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

The API specifications were set as per <USP/BP/JP/International Ph/in-house> standards and ICHQ3A. The parameters monitored during quality control are: <list the specification tests>. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The <shelf-life/re-test> period of <molecule> API is <number> months when packed in <container closure system> and stored at <storage conditions>.

Lamivudine from Shanghai Desano Chemical Pharmaceutical Co., Ltd

General Information

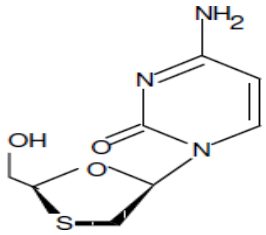
Lamivudine API is compendia in Ph.Int., USP, Ph.Eur., and BP.

Molecular formula: $C_8H_{11}N_3O_5S$

Chemical name:

2R-cis)-4-amino-1-(2R-hydroxymethyl-[1,3] oxathiolan-5S-yl)- 1H-pyrimidin-2-one

Structure:



General properties

Lamivudine is a white to off-white solid and soluble in water. This active substance exhibits also stereoisomerism due to the presence of two chiral centres (1S,4R absolute configuration). Enantiomeric purity is controlled routinely by chiral HPLC and specific rotation. Lamivudine may exist as either of two pseudopolymorphs (Form I or Form II). The manufacturing process of Lamivudine is well controlled to manufacture only Form II.

Manufacture

Lamivudine API manufacturer is Shanghai Desano Chemical Pharmaceutical Co., Ltd., No. 417 Binhai road, Laogang Town, Pudong New Area, Shaghai 201302, China. The manufacturing complies with GMP requirements as evidenced by the GMP certificate submitted. 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

The API specifications were set as per <USP/BP/JP/International Ph/in-house> standards and ICHQ3A. The parameters monitored during quality control are: <list the specification tests>. 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 transparent low-density polyethylene (LDPE) bag, securely folded and twist-tied with a self-sealing plastic rope with storage condition ‘Do not store above 30°C’.

Effective date: 03/10/2022

Quality of the Finished Pharmaceutical Product

Formulation

ENVUTEG tablets is a white to off white, film coated, capsule shaped, biconvex, beveled edge tablet debossed with M on one side of the tablet and LD on the other side.

ENVUTEG tablets contains the Dolutegravir sodium, Lamivudine, and Tenofovir Alafenamide Fumarate, and other ingredients listed here after: Mannitol, Microcrystalline cellulose, Povidone, Sodium Starch Glycolate, Lactose monohydrate, Croscarmellose sodium & Magnesium stearate 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. Ingredient, Lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product manufacturer is 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 DD/MM/YYYY.

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 APIs by HPLC and HPLC (with PDA Detector), Dissolution by HPLC) Uniformity of dosage units by content uniformity), Assay by HPLC, Related Substances by HPLC, Water (By KF), Microbiological test. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on four (4) 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 HDPE bottles with storage condition ‘Do not store above 30°C, store in original container’.

Safety and efficacy information

Safety and efficacy of ENVUTEG was established through bioequivalence trial.

BE trial report number LTAD-180112 was submitted.

Study title	Single-Dose Fasting Bioequivalence Study of Lamivudine, Tenofovir Alafenamide and Dolutegravir Tablets (300 mg/25

	mg/50 mg; Mylan) versus EPIVIR® Tablets (300 mg; ViiV), DESCOVY® Tablets (200 mg/25 mg; Gilead) and TIVICAY® Tablets (50 mg; ViiV) in Healthy Adult Volunteers
Study design	This was a randomized, four-period, two-treatment, replicate design, crossover, single dose bioequivalence study of Mylan's lamivudine tenofovir alafenamide and dolutegravir tablets, 300 mg/25 mg/50 mg to ViiV's EPIVIR® Tablets, 300 mg, Gilead's DESCOVY® Tablets, 200 mg/25 mg and ViiV's TIVICAY® Tablets, 50 mg following administration of a single, oral 300 mg/25 mg/50 mg (1 x 300 mg/25 mg/50 mg) dose of lamivudine, tenofovir alafenamide and dolutegravir tablets or single doses of 300 mg (1 x 300 mg), 200 mg/25 mg (1 x 200 mg/25 mg) and 50 mg (1 x 50 mg) of EPIVIR® Tablets, DESCOVY® Tablets and TIVICAY® Tablets, respectively, administered under fasting conditions
Study sites	Clinical Facility (Name and full mailing address) BioPharma Services Inc. 4000 Weston Road Toronto, Ontario, Canada, M9L 3A2 Clinical Laboratories (Name and full mailing address) Dynacare Medical Laboratories 115 Midair Court Brampton, Ontario, Canada, L6T 5M3 Analytical Laboratories (Name and full mailing address) Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Road Morgantown, WV 26505, USA Company performing pharmacokinetic/statistical analysis (Name and full mailing address) Mylan Pharmaceuticals Inc. PK/DM Department 3711 Collins Ferry Road Morgantown, WV 26505, USA

Study dates	<u>Start and stop dates for each phase of the clinical study:</u> Period 1: 09-Apr-2018 – 14-Apr-2018 Period 2: 23-Apr-2018 – 28-Apr-2018 Period 3: 07-May-2018 – 12-May-2018 Period 4: 21-May-2018 – 26-May-2018 <u>Dates of product administration:</u> Period 1: 10-Apr-2018 Period 2: 24-Apr-2018 Period 3: 08-May-2018 Period 4: 22-May-2018
Primary objective	The objective of this study was to investigate the bioequivalence of Mylan's lamivudine, tenofovir alafenamide and dolutegravir tablets, 300 mg/25 mg/50 mg to ViiV's EPIVIR® Tablets, 300 mg, Gilead's DESCOVY® Tablets, 200 mg/25 mg and ViiV's TIVICAY® Tablets, 50 mg following administration of a single, oral 300 mg/25 mg/50 mg (1 x 300 mg/25 mg/50 mg) dose of Mylan's lamivudine, tenofovir alafenamide and dolutegravir tablets or single doses of 300 mg (1 x 300 mg), 200 mg/25 mg (1 x 200 mg/25 mg) and 50 mg (1 x 50 mg) of EPIVIR® Tablets, DESCOVY® Tablets and TIVICAY® Tablets, respectively, in forty-eight (48) healthy volunteers under fasting conditions.
Secondary objective	To monitor safety of these two products
Number of participants	Number of subjects enrolled in the study: Forty-eight (48) subjects were enrolled in the study. Withdrawals/dropouts: Subject 18 was discontinued due to an adverse event (vomiting) during Period 1. Subjects 28 and 37 withdrew consent due to adverse events (cough and headache, fever, cough, respectively) prior to Period 2 dosing. Subject 26 withdrew consent due to personal reasons prior to Period 3 dosing. Subject 43 did not report to clinic for Period 3 check-in. Subject 22 withdrew consent due to adverse events (bruising and pain left venipuncture site, bruising right venipuncture site) during Period 3.

	Subject 23 withdrew consent due to new safety information provided prior to Period 4 dosing.	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference products
	Strength: 300 mg/25 mg/50 mg) dose of lamivudine, tenofovir alafenamide and dolutegravir tablets Batch number: 201369 Expiry date: 06/2019	EPIVIR® Tablets Strength: 300 mg Lot No.: 6ZP7456 Expiry date: 09/2018 DESCOVY® Tablets Strength: 200 mg/25 mg Lot No.: 5882716A Expiry date: 05/2019 TIVICAY® Tablets Strength: 50 mg Lot No.: 7ZP6442 Expiry date: 10/2019
Analytical method	Tandem mass spectrometry (LC-MS/MS)	
Statistical method	PROC Mixed Models Procedure (PROC MIXED) of SAS Software (SAS Institute, Cary, NC).	

Efficacy results are summarized as follows:

Lamivudine

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng*hr/mL)	12381	12598	98.28%	95.22% – 101.44%	39	11.04
AUC0-inf (ng*hr/mL)	12649	12958	97.62%	94.65% – 100.69%	39	10.80
Cmax (ng/mL)	2434	2482	98.06%	93.29% – 103.07%	39	13.77

Tenofovir Alafenamide

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)

AUC0-t (ng*hr/mL)	126.6	136.5	92.75%	87.46% – 98.36%	119	23.29
AUC0-inf (ng*hr/mL)	129.8	138.9	93.48%	88.08% – 99.20%	113	23.29
Cmax (ng/mL)	177.8	200.6	88.63%	80.39% – 97.73%	86	35.47

Dolutegravir

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng*hr/mL)	58788	61294	95.91%	90.98% – 101.11%	72	22.75
AUC0-inf (ng*hr/mL)	60566	63281	95.71%	90.87% – 100.81%	71	22.35
Cmax (ng/mL)	3065	3295	93.03%	87.41% – 99.00%	39	21.34

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 and Dolutegravir Tablets (300 mg/25 mg/50 mg; Mylan) is equivalent and interchangeable with EPIVIR® Tablets (300 mg; ViiV), DESCOVY® Tablets (200 mg/25 mg; Gilead) and TIVICAY® Tablets (50 mg; ViiV) 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. ENVUTEG 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

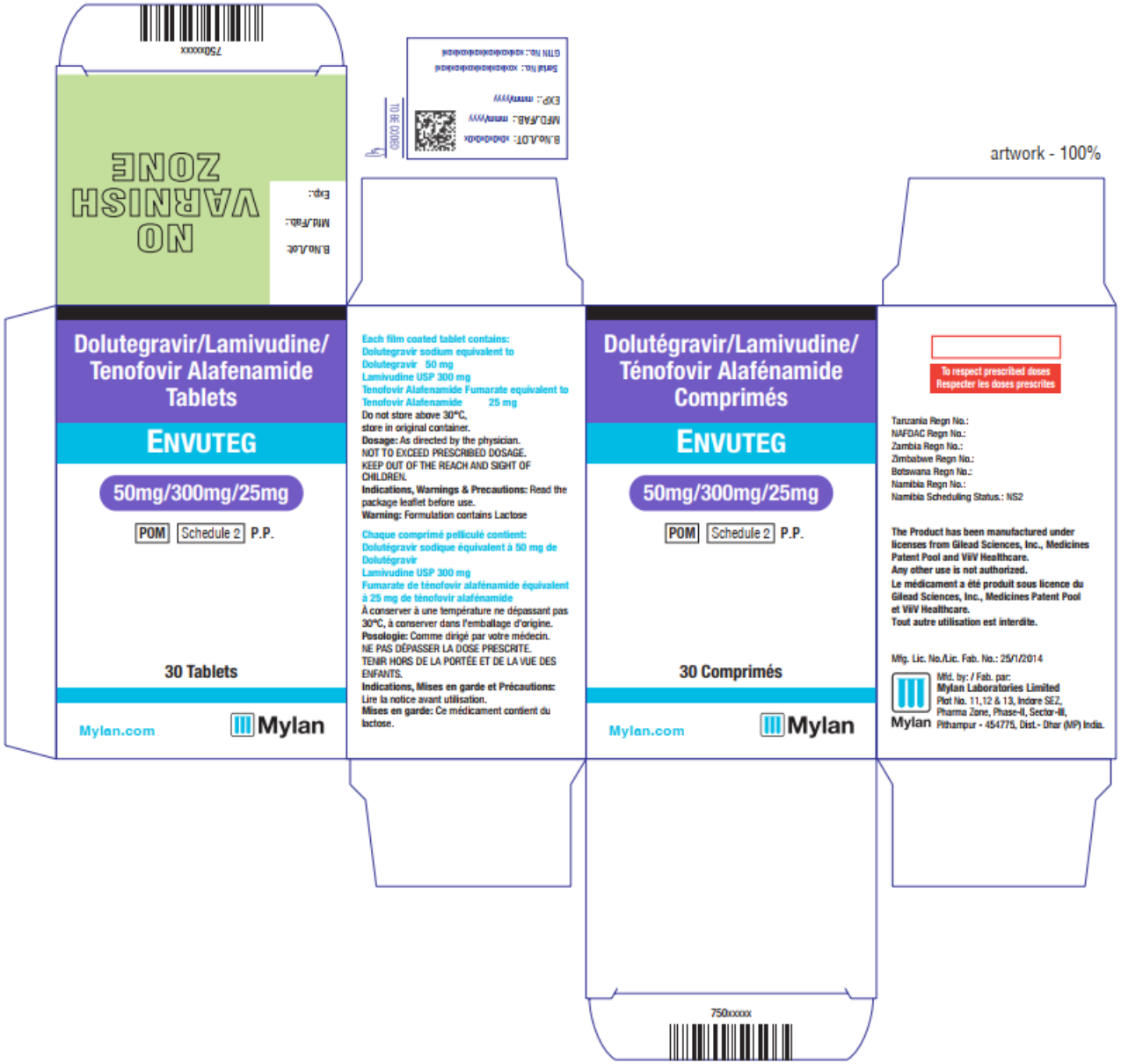
Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;

Effective date: 03/10/2022

Secondary pack label;



Effective date: 03/10/2022