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MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR DOLUTEGRAVIR SODIUM/ LAMIVUDINE AND TENOFOVIR DISOPROXIL FUMARATE (DOLUTEGRAVIR SODIUM 50 MG, LAMIVUDINE 300 MG, TENOFOVIR DISOPROXIL FUMARATE 300 MG) FILM COATED TABLETS

Version number 1.0
3rd January, 2023

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1. Introduction

Dolutegravir Sodium, Lamivudine/Tenofovir Disoproxil Fumarate is a generic medicine of Tivicay film-coated tablets, Viread 245 mg film-coated tablets and Epivir 300 mg film-coated tablets. Dolutegravir Sodium, Lamivudine/Tenofovir Disoproxil Fumarate is an Antiviral medicine belonging to J05AF07 (nucleoside and nucleotide reverse transcriptase inhibitors), J05AF0 (nucleoside analogue) and J05AJ03 (other antivirals) group.
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 is a nucleoside analogue which has activity against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). It is metabolised intracellularly to the active moiety, lamivudine 5'-triphosphate. Its main mode of action is as a chain terminator of viral reverse transcription. The triphosphate has selective inhibitory activity against HIV-1 and HIV-2 replication in vitro, it is also active against zidovudine-resistant clinical isolates of HIV. No antagonistic effects in vitro were seen with lamivudine and other anti retrovirals (tested agents: abacavir, didanosine, nevirapine and zidovudine

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.

Dolutegravir Sodium, Lamivudine/Tenofovir Disoproxil Fumarate is approved in Tanzania for use in adults, children, elderly.

1.1. Product details

Registration number	TAN 21 HM 0220
Brand name	Dolutegravir Sodium, Lamivudine, Tenofovir Disoproxil Fumarate
Generic name, strength and form	Dolutegravir Sodium 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg

ATC classification	Antivirals for treatment of HIV infections, combinations, (J05AR)
Distribution category	POM
Country of origin	Uganda
Associated product	Tenofovir Disoproxil Fumarate 300mg Tablets.
Marketing Authorization Holder	Cipla Quality Chemical Industries Limited. Address: Plot 1-7,1"1 Ring Road, Luzira Industrial Park, P.O Box 34871, Kampala-Uganda Uganda
Local Technical Representative	SALAMA PHARMACEUTICALS UMITED. Address: P 0 BOX 65235, 13/19 UHURU/NYAMWEZI STREET, KARIAKOO DAR ES SALAAM Telephone: +255 22 2183787/2185110/2183290 E-Mail: hms@SalamaPharma.co.tz

1.2. Assessment procedure

The application for registration of Dolutegravir Sodium, Lamivudine, Tenofovir Disoproxil Fumarate was submitted on 29th October, 2018. The product underwent joint EAC assessment. Assessment was completed in two rounds of evaluation. Dolutegravir Sodium, Lamivudine, Tenofovir Disoproxil was registered on 03rd June, 2021

1.3. Information for users

Visual description of the finished product	Blue coloured, capsule shaped biconvex film coated tablet, debossed with 'C' on one side and plain on other side
Primary packing material	85 cc white HDPE bottle with 38 mm Non-CRC cap for 30’s and “200 cc white HDPE bottle with 45mm screw cap containing 90 tablets
Secondary packing materials	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	Treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents 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: Dolutegravir Sodium, Lamivudine, Tenofovir Disoproxil Fumarate

Composition: Dolutegravir Sodium 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg, Microcrystalline cellulose, Mannittol, Sodium Starch Glycolate, Magnesium Stearate, Povidone, Cross Carmellose Sodium

Pack size: 30's, 90's

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

Storage conditions: Do not store above 30°C

Manufacturer address: Cipla QCIL, Plot 1-7 1ST Ring Road, Luzira Industrial Park P 0 Box 34871, Kampala, Uganda

Unique identifier: GTIN

Special warnings/precautions or instructions for use: Discard 90 days after opening

The details of the primary pack include:

Brand name and strength: Dolutegravir Sodium 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg

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

Name of manufacturer: Cipla QCIL

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 WHO Prequalification proof.

General properties

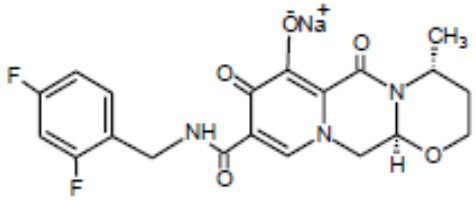
Dolutegravir Sodium

Dolutegravir Sodium API is compendia in International Pharmacopeia

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

Chemical name: Sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dio 3,4,6,8, 12,12a-hexahydro-2H-pyrido[1 ',2':4,5]pyrazino[2, 1-b] [1,3]oxazin-7 -olate

Structure:



Dolutegravir Sodium is Off-white to pale yellow coloured powder, Dolutegravir sodium is critically insoluble (of BCS low solubility across the physiological pH range),
hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications. The API exhibits (pseudo)polymorphism and it has been demonstrated by X-ray powder diffraction (XRPD) and infrared spectroscopy (IR) that the manufacturing process consistently yields one polymorphic form, called Form I. The acceptance criteria for PSD we set on information of the API lot used in the FPP biobatch

Manufacture

was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by WHO. 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 (IR, HPLC and Sodium content), assay (HPLC), related substances (HPLC), Isomeric purity (HPLC), residual solvents (GC), water content (KF), particle size distribution (laser diffraction), polymorphic identity (XRPD), Benzene content (GC, ≤5 ppm), Rhodium Content (ICP-MS, ≤10 ppm). 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 Double clear HMHD (high molecular high density) polyethylene bags and hermetically sealed, placed in a fibre drum and stored below 30°C, protect from moisture.

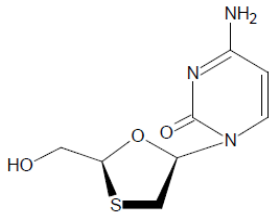
Lamivudine

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

Molecular formula: $C_8H_{11}N_3O_3S$

Chemical name: 2',3'-dideoxy-3'-thiacytidine 4-Amino-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one

Structure:



Lamivudine

Lamivudine is a white to off white solid, Lamivudine is soluble in water (of BCS highly solubility across the physiological pH range),
hence particle size distribution (PSD) is considered not critical parameters and form part of the FPP manufacturer's API specifications. The API exhibits This substance also exhibits polymorphism. The consistency of the crystalline form (form II) produced has been adequately demonstrated. Form II to be thermodynamically most stable while other forms such I and III DSC show that these are metastable and undergo heat mediated transformation to FormI_H and Form III_H, respectively.

Manufacture

Hetero Labs Limited, Unit-IX, Plot No.2, HETERO INFRASTRUCTURE LTD.-SEZ, N. Narasapuram (Village), Nakkapally (Mandal), Visakhapatnam District, Andhra Pradesh, INDIA, Manufacturing Block : " H2 & H7" (LAN) was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by 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

The API specifications were set as per USP standards and ICHQ3A. The parameters monitored during quality control are: The API specifications are pharmacopoeial based and include tests for 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, melting range, tapped density, residual solvents (GC), toluene sulfonates (LC-MS; each ≤ 5 ppm) and methane sulfonates (GC-MS; each ≤ 5 ppm)

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 24 months when packed in polyethylene bags and placed in a HDPE drum and stored below 30°C, protect from moisture.

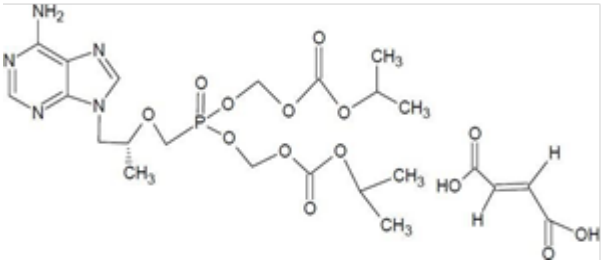
Tenofovir Disoproxil Fumarate

Tenofovir Disoproxil Fumarate API is compendia in non-compendia.

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

Chemical name: 9-[(R)-2- [[bis[[(isopropoxycarbonyl)oxy] methoxy]phosphinyl]methoxy] propyl]adenine Fumarate

Structure:



Tenofovir Disoproxil Fumarate is a white to off-white crystalline powder soluble in water: methanol (1:1), Practically insoluble in Diethyl ether, Sparingly soluble in Ethanol, Sparingly soluble in Acetone, Freely soluble in Methanol. Tenofovir Disoproxil Fumarateis classified as a drug substance with high solubility and low permeability,BCS Class 3. TDF is known to exhibit polymorphism and exists in two forms. Tenofovir Disoproxil Fumarate manufactured by Cipla exhibits consistent crystalline form as evaluated by XRPD and DSC. The XRPD of our production batches of Tenofovir Disoproxil Fumarate are concordant with each other and with the working standard of Tenofovir Disoproxil Fumarate. The DSC scans of our production batches of Tenofovir Disoproxil Fumarate are concordant with each other and with the working standard of Tenofovir Disoproxil Fumarate. As part of release specification, the polymorphism of production batches of Tenofovir Disoproxil Fumarate is checked by XRPD and DSC

Manufacture

Cipla Ltd. – Kurkumbh
Cipla Limited
Manufacturing Division, Plot No. D-22, Manufacturing
Block: Bulk Drug-I, III
and IV MIDC Industrial Area, Kurkumbh Village Taluka– Daund, District - Pune
(Maharashtra) INDIA

was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by 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: The API specifications are pharmacopoeial based and include tests for description, solubility, identification (By IR $ HPLC), clarity of solution, water content, heavy metals, Polymorphic identity (Differential

scanning colorimetry $ XRPD,) mutagenic 9-Propenyladenine is controlled at NMT 5.0 ppm (HPLC), related substance (HPLC method A, GC method B), enantiomeric purity (NMT 1.0%; chiral HPLC), assay (HPLC), fumaric acid content (HPLC), residual solvents (GC) and particle size(Laser Diffraction). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test 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 and stored at 2-8 ºC.

Quality of the Finished Pharmaceutical Product

Formulation

Dolutegravir Sodium 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg is a Blue coloured, capsule shaped biconvex film coated tablet, debossed with 'C' on one side and plain on other side and white HDPE container with white HDPE Non- Child Resistant Cap. Dolutegravir Sodium 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg contains Dolutegravir Sodium, Lamivudine and Tenofovir Disoproxil Fumarate and other ingredients listed here after Mannitol, Microcrystalline Cellulose, Sodium Starch Glycolate, Povidone, Purified Water, Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose, Hydroxy Propyl Methyl Cellulose, Isopropyl Alcohol USP, Film Coating (Opadry AMB II 88A505017 Blue). 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.

Manufacture

The finished product was manufactured at CiplaQCIL Plot 1-7 1ST Ring road, Luzira Industrial, Park, P.O Box 34871, Kampala, Uganda. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 24th and 26th April, 2019.

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, water content (KF), uniformity of dosage unit, dissolution (HPLC), related substance (HPLC), assay (HPLC), residual solvents (GC) 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 ± 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 85 CC white HDPE container with 38 mm white HDPE Non-CR cap and 2x2 g silica bag stored at 30°C

Safety and efficacy information

Safety and efficacy of Dolutegravir Sodium 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg was established through bioequivalence trial

The bioequivalence study was done to demonstrate the safety and efficacy of drug product with the individual reference product Tivicay® (dolutegravir) 50 mg tablets (ViiV Healthcare), Epivir® (lamivudine) 300 mg tablets (ViiV Healthcare) and Viread® (tenofovir disoproxil fumarate) 300 mg tablets (Gilead Sciences, Inc. USA). The reliance mode was applied and the clinical study data were considered acceptable demonstrating the similarity of the safety profile between the test product and individual reference products.

BE trial report number 2118 was submitted.
In case of BE:

Study title	A single-dose, randomized, open-label, two-way crossover bioequivalence study of [HA702 trade name] (Cipla Ltd., India) and Tivicay® (dolutegravir) 50 mg tablets (ViiV Healthcare), Epivir® (lamivudine) 300 mg tablets (ViiV Healthcare) and Viread® (tenofovir disoproxil fumarate) 300 mg tablets (Gilead Sciences, Inc. USA) in healthy male and female volunteers under fasting conditions
Study design	single centre, open label, randomized, crossover study in healthy subjects under fasting condition
Study site	
Study dates	
Primary objective	The objective of the study was to compare the bioavailability of the dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) manufactured by Cipla Ltd., India (test drug) with the reference formulations Tivicay® (ViiV Healthcare), Epivir® (ViiV Healthcare) and Viread® (Gilead Sciences, Inc.) and to assess bioequivalence

Secondary objective	To monitor the safety of the subjects	
Number of participants	60	
Monitored parameters	AUC, Cmax, Tmax	
Investigational medicinal products	Test Product	Reference product
	Strength: (dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch number: GG70245	Tivicay® (dolutegravir 50 mg) Batch no. 5ZP3006 Epivir® (lamivudine 300 mg) Batch no. 5ZP1465 Viread® (tenofovir disoproxil fumarate 300 mg) Batch no. 005384
Analytical method	LC-MS/MS	

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, dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) is equivalent and interchangeable with Tivicay® (ViiV Healthcare), Epivir® (ViiV Healthcare) and Viread® (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. Dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) 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