TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR DELSTRIGO™ 100 MG/300MG/300MG (DORAVIRINE 100 MG, LAMIVUDINE 300 MG AND TENOFOVIR DISOPROXIL FUMARATE 300 MG) FILM COATED TABLETS

Version number 1.0

31 March, 2022

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1. Introduction

Delstrigo is a fixed-dose combination product of the individual components that make up of doravirine, lamivudine and tenofovir disoproxil fumarate is an antiretroviral medicine that has activity against HIV-1. The active pharmaceutical ingredients (APIs) of Delstrigo are non-nucleoside reverse transcriptase inhibitor doravirine and the nucleoside reverse transcriptase inhibitors Lamivudine and Tenofovir disoproxil fumarate. Delstrigo is approved in Tanzania for use in adult patients.

1.1 Product details

Registration number	TAN 22 0271
Brand name	Delstrigo
Generic name, strength, and form	Each film coated tablet contains: Doravirine 100 mg Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg equivalent to Tenofovir Disoproxil 245 mg.
ATC classification	ATC Code: J05AR24-Antivirals for systemic use
Distribution category	POM
Country of origin	Netherlands
Associated product	N/A
Marketing Authorization Holder	MSD (Pty) Ltd 117 16th Road, Halfway House, 1685, Midrand South Africa Email: lydia.nkutha@merck.com
Local Technical Representative	JD Pharmacy Limited Nyerere Road, 10 Vingunguti, Dar es Salaam Tanzania info@jdpharmacy.co.tz

1.2 Assessment procedure

The application for registration of Delstrigo was submitted on 20 December 2021. The product underwent abridged and joint EAC assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 19th July, 2022.

1.3 Information for users

Visual description of the finished product	Yellow, oval-shaped, tablet debossed with the corporate logo and 776 on one side and plain on the other side
Primary packing material	HDPE bottle containing 6g of silica gel with polypropylene (PP) closure
Secondary packing materials	Carton box
Shelf-life and storage condition	24 months, Store at or below 30 °C. Keep the bottle tightly closed in order to protect from moisture
Route of administration	Oral
Therapeutic indications	Indicated for the treatment of adults infected with HIV 1 without past or present evidence of

	resistance to the NNRTI class, lamivudine, or tenofovir

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 N/A
The product label information is presented in English. Details in the secondary pack label include:
Brand name: Delstrigo

Composition: Each film coated tablet contains: Doravirine 100 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg equivalent to Tenofovir Disoproxil 245 mg.

Pack size: 30 Tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store at or below 30 °C. Keep the bottle tightly closed in order to protect from moisture

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Contains lactose. Read the package leaflet before use

The details of the primary pack include:
Brand name and strength: Delstrigo 100 mg/300 mg/245 mg

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: MSD

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 Ingredients

Information on the quality of the APIs was submitted in form of DMF and CEP.

Doravirine

General Information

Doravirine API is non-compendia.

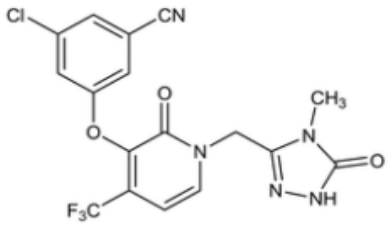
The active substance doravirine is a New Active Substance (NAS) and full information on the quality has been included in the form of DMF.

Molecular formula: $C_{17}H_{11}ClF_3N_5O_3$

Chemical name:

3-Chloro-5-({1-[(4-methyl-5-oxo-4,5-dihydro-1H -1,2,4- triazol-3-yl)methyl]-2-oxo-4-(trifluoromethyl)-1,2-dihydropyridin-3-yl}oxy)benzonitrile

Structure:



General properties

Doravirine is a white to off-white, non-hygroscopic, crystalline powder which is practically insoluble in water. Doravirine has a non - chiral molecular structure. Polymorphism has been observed for doravirine.

Doravirine is considered a Biopharmaceutical Classification System (BCS) class II compound (i.e., low solubility and high permeability at a human dose of 100 mg).

Manufacture

Doravirine API manufacturer is MSD International GmbH, Kilsheelan, Clonmel, Co. Tipperary, Ireland (IRL). The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Health Products Regulatory Authority of Ireland (HPRA). Doravirine 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, Identification (IR), Water content (KF), Related substances (By HPLC), Assay (HPLC), and Residual solvents (GC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The retest period of Doravirine API is 36 months when packed in double, low-density polyethylene (LDPE) liners in an outer containment of a fiberboard drum or high-density polyethylene (HDPE) drum, when stored at temperature not exceeding 25°C.

Lamivudine

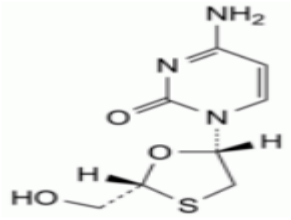
General Information

Lamivudine API is compendia in USP, BP, and International Pharmacopeia. As there is a monograph of lamivudine in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application.

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 Laurus Labs Limited, Plot No. 21, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam-531 021, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the EU. 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 Ph.Eur. standards and ICHQ3A. The parameters monitored during quality control are: Description, Solubility, Melting point, Identification (IR and HPLC), Chiral purity, Light absorption, Sulphated ash, Water content, Limit of lamivudine enantiomer, Loss on drying, Residue on ignition, Related substances (HPLC), Assay (HPLC), and Residual solvents (GC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The retest period of Lamivudine API is 48 months when packed in transparent low density polyethylene bag with strip seal followed by secondary pack with black low density polyethylene bag with strip seal and finally kept in high density polyethylene (HDPE) container with storage condition 'Store in a well closed container, protected from light and at a temperature not exceeding 30°C'.

Tenofovir disoproxil fumarate

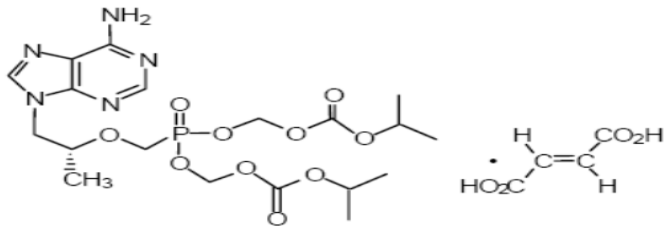
General Information

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

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 Laurus Labs Limited, Plot No. 21, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam-531 021, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the USFDA. 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 USP/Ph. Eur. standards and ICHQ3A. The parameters monitored during quality control are: Description, Solubility, Identification (IR and HPLC), Water content, Melting range, Residue of ignition, Fumaric acid content, Related substances (HPLC), Enantiomeric purity ((S)-isomer), Assay (HPLC), and Residual solvents (GC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Tenofovir disoproxil fumarate API is 48 months when packed in transparent low density polyethylene bag (LDPE) with strip seal, followed by another transparent low density polyethylene bag with strip seal. Secondary pack is Triple Laminated Sunlight Barrier bag (TLSB) with heat sealed and finally kept in High Density polyethylene (HDPE) drum with storage condition ‘Store in a well closed container at 2-8°C, protected from light’.

Quality of the Finished Pharmaceutical Product

Formulation

Delstrigo is a yellow, oval-shaped, tablet debossed with the corporate logo and 776 on one side and plain on the other side

Delstrigo contains the Doravirine, Lamivudine, and Tenofovir Disoproxil Fumarate and other ingredients listed here after: Croscarmellose sodium (E468), Hypromellose acetate succinate, Magnesium stearate (E470b), Microcrystalline cellulose (E460), Silica, colloidal anhydrous (E551), Sodium stearyl fumarate, Carnauba wax (E903), Hypromellose (E464), Iron oxide yellow (E172), Lactose monohydrate, Titanium dioxide (E171), Triacetin (E1518)). 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 provided in the table below. The compliance of the site to TMDA GMP standards was confirmed through desk-review.

Name and address **(include block(s)/unit(s))**	**Responsibility**
Hovione FarmaCiencia S.A., Sete Casas,2674-506 Loures, Portugal	Doravirine Spray Dried Intermediate: Manufacture/Analytical Testing
F.I.S. – Fabbrica Italiana Sintetici S.p.A., Viale Milano, 26 36075 Montecchio Maggiore (Vicenza), Italy	Doravirine Spray Dried Intermediate: Manufacture/Analytical Testing
MSD International GmbH Kilsheelan, Clonmel, Co. Tipperary, Ireland	Roller Compaction, Blending/Lubrication of Doravirine Granules and Lamivudine/Tenofovir Disoproxil Fumarate Granules; Compression, and Film Coating Analytical Release Testing
Merck Sharp & Dohme B.V.,Waarderweg 39 Haarlem, 2031 BN, Netherlands	Primary and Secondary Packaging Batch Release

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 (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (HPLC), dissolution (HPLC) and microbial quality (Ph. Eur). 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 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 bottle containing 6g of silica gel with polypropylene (PP) closure with storage condition ‘Store at or below 30 °C. Keep the bottle tightly closed in order to protect from moisture’.

Safety and efficacy information

Delstrigo (Doravirine 100 mg, Lamivudine 300 mg and Tenofovir disoproxil fumarate 300 mg (equivalent to 245 mg of Tenofovir Disoproxil) film-coated tablet is new product which is already registered by EMA. Information on clinical data has been fully evaluated during the clinical studies

of the product (Refer: EMA PAR No. EMEA/H/C/004746/0000). 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. Delstrigo 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

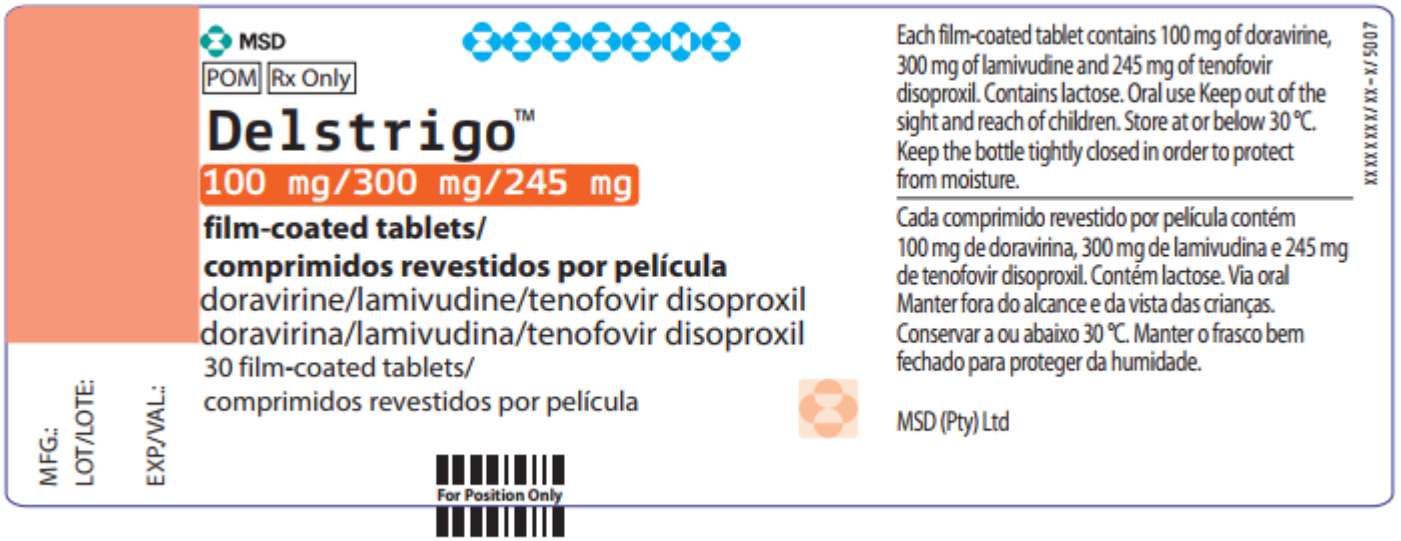
Re-registration applications

NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up labels;
Primary pack label;



Secondary pack label;