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MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR MYLTEGA DT (DOLUTEGRAVIR SODIUM EQUIVALENT TO DOLUTEGRAVIR 10MG) DISPERSIBLE TABLETS

Version number 01, 03/01/2023

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1. Introduction

MYLTEGA DT is a generic medicine of Tivicay 5 mg dispersible tablets (of ViiV Healthcare UK Limited, United Kingdom). The proposed product is a tablet that contains, as the active ingredient, dolutegravir sodium (hereinafter referred to as Dolutegravir), antiviral for systemic use. 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. MYLTEGA DT is approved in Tanzania for use in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children of at least 4 weeks of age or older and weighing at least 3 kg.

1.1 Product details

Registration number	TAN 21 HM 0396
Brand name	MYLTEGA DT
Generic name, strength and form	10 mg Dolutegravir (as sodium) Dispersible Tablets
ATC classification	J05AJ03, Antivirals for systemic use, other antivirals
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Mylan Laboratories Limited Address: Plot No.564/A/22, Road No.92, Jubilee Hills, Hyderabad - 500096, Telangana, India.
Local Technical Representative	Synermed Pharmaceuticals (Tanzania) Limited Address: Plot No.: 31/32 Makaburini, Nyerere road, Dar- es- salaam, Tanzania.

1.2 Assessment procedure

The application for registration of MYLTEGA DT was submitted on 09/12/2020. The product underwent full assessment. Assessment was completed in 2(two) rounds of evaluation. MYLTEGA DT was registered on 09/10/2021.

1.3 Information for users

Visual description of the	Pink colored, film-coated, oval shape, biconvex tablet

<table>
<tr><td>finished product</td><td colspan="3">debossed with "D" to the left of the break line and "T" to the right of the break line on one side of the tablet and "M" to the left of the break line on the other side of the tablet</td></tr>
<tr><td>Primary packing material</td><td>Type of pack</td><td>Count</td><td>Primary Packaging Components</td></tr>
<tr><td></td><td>Blue HDPE bottle pack</td><td>30’s count</td><td>Container: Bottle HDPE 40 cc (40 ml) 33 mm Blue round opaque HDPE bottle.

Closure: Closure 33 mm Blue screw with SG 100 Liner (SP); 33 mm blue opaque polypropylene screw closure with wad containing aluminium induction sealing liner.</td></tr>
<tr><td></td><td>Blue HDPE bottle pack (with desiccant)</td><td>30’s count</td><td>Container: Bottle HDPE 60 cc (60 ml) 33 mm Blue round opaque HDPE bottle.

Closure: Closure 33 mm Blue screw with SG 100 Liner (SP); 33 mm blue opaque polypropylene screw closure with wad containing aluminium induction sealing liner.

Desiccant: Desiccant 1 g silica gel sachet (2 no.s) or Desiccant 2 g silica gel sachet (1 no.s)</td></tr>
<tr><td></td><td>Blue HDPE bottle pack</td><td>60’s count</td><td>Container: Bottle HDPE 40 cc (60 ml) 33 mm Blue round opaque HDPE bottle.

Closure: Closure 33 mm Blue screw with SG 100 Liner (SP); 33 mm blue opaque polypropylene screw closure with wad containing</td></tr>
</table>

			aluminium induction sealing liner.
	Blue HDPE bottle pack (with desiccant)	60's count	**Container:** Bottle HDPE 60 cc (60 ml) 33 mm Blue round opaque HDPE bottle. **Closure:** Closure 33 mm Blue screw with SG 100 Liner (SP); 33 mm blue opaque polypropylene screw closure with wad containing aluminium induction sealing liner. **Desiccant:** Desiccant 1 g silica gel sachet (2 no.s) or Desiccant 2 g silica gel sachet (1 no.s)
	Blue HDPE bottle pack	90's count	**Container:** Bottle HDPE 40 cc (60 ml) 33 mm Blue round opaque HDPE bottle. **Closure:** Closure 33 mm Blue screw with SG 100 Liner (SP); 33 mm blue opaque polypropylene screw closure with wad containing aluminium induction sealing liner**.**
	Blue HDPE bottle pack (with desiccant)	90's count	**Container:** Bottle HDPE 60 cc (60 ml) 33 mm Blue round opaque HDPE bottle. **Closure:** Closure 33 mm Blue screw with SG 100 Liner (SP); 33 mm blue opaque polypropylene screw closure with wad containing aluminium induction sealing liner**.** **Desiccant:** Desiccant 1 g silica gel sachet (2 no.s) or Desiccant 2 g silica gel

			sachet (1 no.s)
	Blue HDPE bottle pack (with desiccant)	180's count	**Container:** Bottle HDPE 75 cc 38 mm Blue round IND. **Closure:** Closure 38 mm Blue screw with SG 100 SP **Desiccant:** Desiccant 2 g silica gel sachet (1 no.s)
	Blue HDPE bottle pack (with desiccant)	270's count	**Container:** Bottle HDPE 120cc 38 mm Blue round IND. **Closure:** Closure 38 mm Blue screw with SG 100 SP **Desiccant:** Desiccant 2 g silica gel sachet (1 no.s)
	Simulated Bulk pack	400's count	Poly bag LDPE plain 150 mic 140x190 mm IND-DMF Poly bag triple laminated plain 170x220 mm Desiccant 1 g Silica gel sachet
Secondary packing materials	A printed carton box		
Shelf-life and storage condition	24 months, Do not store above 30°C. Store in the original container		
Route of administration	Oral		
Therapeutic indications	Indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection		

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 both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name: MYLTEGA DT

Composition: Dolutegravir sodium equivalent to dolutegravir 10 mg, mannitol

Pack size: 30's, 60's, 90's, 180's, 400's tablets

Manufacturing details: batch number, manufacturing date, expiry date

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

Manufacturer address: Mylan Laboratories Limited, Plot No. 11,12 & 13, Indore SEZ, Pharma Zone, Phase-II, Sector-III, Pithampur- 454775, Dist.- Dhar (MP) India.

Unique identifier: N/A

Special warnings/precautions or instructions for use: This medicine contains mannitol which may have a mild laxative effect

The details of the primary pack include:

Brand name and strength: MYLTEGA DT

Manufacturing details: batch number, manufacturing date, 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.

Comment [SU1]: Not required here, as we are giving separate comment on Mannitol

Comment [SU2]: Need to include 270's tablets

Comment [SU3]: Complete address of Manufacturer was mentioned in Label artwork

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

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

General properties

Dolutegravir sodium API is non-compendia.

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

Chemical names:

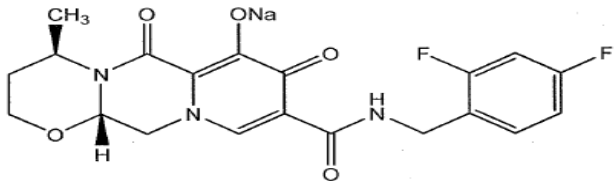
Sodium (4R,12aS)-N-[(2,4-Difluoro benzyl)carbamoyl] -4-methyl-6, 8-dioxo-3,4,6,8, 12,12a -hexahydro-2H-pyrido [l',2':4,5]pyrazino [2, 1-b] [1,3] oxazin-7-olate

Sodium (4R,12aS)-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-hexa hydro-7-hydroxy-4-methyl-6,8-dioxo-2H-pyrido[1',2':4,5] pyrazino[2,1-b][1,3] oxazine -9-carboxamide

Sodium (4R, 9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexa hydro-2H-1-oxa-4a,8a-diazaanthracene-7-carboxylic acid 2,4-difluorobenzylamide

Structure:



Dolutegravir Sodium

Critical physico-chemical properties are:

Dolutegravir is a white to light yellow non-hygroscopic crystalline substance; it is slightly soluble
in water, but practically not soluble over the physiological range. It presents 2 chiral centers and
pseudo-polymorphism. The most thermodynamically stable form is Form 1 (crystalline anhydrous). The manufacturer consistently produces the same polymorphic form.

Comment [SU4]: hygroscopic

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 specifications.

Manufacture

The API manufacturing site, Mylan Laboratories Limited (Unit-9), Plot No. 5, Road No.12, J.N. Pharma City, Tadi Village, Parawada Mandal, Visakhapatnam – 531021, Andhra Pradesh, India and Mylan Laboratories Limited (Unit-10), Plot No. 86, Ramky Pharma City (India) Ltd, SEZ, JN Pharma City, Parawada Mandal, Visakhapatnam – 531019 Andhra Pradesh, India was noted to comply with WHO GMP requirements as

evidenced by the GMP certificate issued by Drugs Control Administration of Andhra Padesh, 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 (visual), solubility, identification (IR, HPLC, and Sodium), assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), residual solvents (GC-HS), N-methyl Morpholine (GC-HS), water content (KF), solid state (XRPD), particle size distribution (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 Dolutegravir sodium API is 36 months when packed in antistatic white polyethylene bag (LDPE), securely twist-tied with a plastic rope, which is placed in HMLDPE bag. Both these bags are placed in triple laminated aluminum bag and heat sealed. Such poly bags are further packed in HDPE drums, closed with plastic lids having rubber gasket followed by locking ring and metal seal and stored at below 25°C, excursions permitted between 15°C and 30°C.

Quality of the Finished Pharmaceutical Product

Formulation

MYLTEGA DT is a pink colored, film-coated, oval shape, biconvex tablet debossed with "D" to the left of the break line and "T" to the right of the break line on one side of the tablet and "M" to the left of the break line on the other side of the tablets.

MYLTEGA DT contains Dolutegravir sodium and other ingredients listed here after: mannitol, microcrystalline cellulose, sodium starch glycolate, povidone, silicified microcrystalline cellulose, crospovidone, calcium sulfate, sucralose, strawberry cream flavor and sodium stearyl fumarate, hypromellose, macrogol/polyethylene glycol, titanium dioxide, red iron oxide, yellow iron oxide and black iron oxide. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8^{th} in terms of function and quantities. Ingredient, mannitol is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at 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 site to TMDA GMP standards was confirmed through site inspection on 22/09/2022.

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 (visual), identity of dolutegravir (HPLC (with PDA detector) and HPLC), assay (HPLC), uniformity of dosage (HPLC), dissolution (HPLC), water (KF), disintegration, fineness of dispersion, uniformity of mass (For subdivided tablets), microbial enumeration tests, and test for specified microorganisms. 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 30^0 ± 2°C & 75% ± 5% RH for 24 months and 40^0 ± 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 with silica gel sachet (desiccant) at Do not store above 30°C. Store in the original container.

Comment [SU5]: with desiccant and without desiccant for 30's, 60's & 90's bottle and with desiccant for 180's & 270's bottle

Safety and efficacy information

Safety and efficacy of MYLTEGA DT was established through bioequivalence trial.

BE trial report number DODT-1-19061 was submitted.

In case of BE:

Study title	Single dose fasting (Period-1 & 2) & fed (Period 3&4) oral bioequivalence study of Mylan's Dolutegravir dispersible tablets 10mg (1x10 mg) with GSK1349572, CQ, 5.0mg Manufactured by: GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, in Healthy adult male and female (not of childbearing potential) human volunteers
Study design	A randomized, balanced, two-treatment, four-period, two-sequence, Single dose fasting (Period 1 & 2) & fed (Period 3 & 4)
Study sites	Clinical, laboratory, pharmacokinetic, and statistical

	analysis facility: Aizant Drug Research Solutions Pvt. Ltd., Survey No.: 172 &173, Apparel Park Road, Dulapally Village, Quthbullapur Mandal, Hyderabad, India -500100. Analytical Laboratories: Mylan Laboratories Limited, Clinical Research Centre, Saradhi Chambers, Plot No. A-4, Beside Poulomi Hospital, Rukminipuri, Dr. A. S. Rao Nagar, Hyderabad 500062.	
Study dates	Dates of clinical phases: Fasting: 17 to 26 Jan 2020 Fed: 01 to 10 Feb 2020 Dates of subject sample analysis: 13 to 24 February 2020	
Primary objective	To investigate the bioequivalence of Mylan's Dolutegravir dispersible tablets 10 mg with GSK1349572, CQ, 5.0 mg, manufactured by: GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS, following a single oral dose of test product or reference product administration under fasting & fed conditions	
Secondary objective	To monitor the adverse events and to ensure the safety of the subjects	
Number of participants	Forty (40) subjects in period-1, Thirty-eight (38) subjects in period-2, Thirty-six (36) subjects in period-3 and Thirty six (38) subjects in period-4 were administered with the study drug and Thirty eight (38) subjects were completed the fasting study and Thirty six (36) subjects were completed the fed study in its entirety	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 10 mg Batch number: 2017720 Expiry date:07/2021	Strength: 5 mg Batch number: 182412533 Expiry date:11/2021
Analytical method	LC-MS/MS method was used for the determination of	

Comment [SU6]: Should be 36

	plasma concentration of analyte
Statistical method	Phoenix® WinNonlin® version 8.0 statistical software.

Efficacy results are summarized as follows:

For Dolutegravir (Fasting):

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC_{0-t} (ng. hr/mL)	19202.598	19431.254	98.82	96.23-101.49	36	6.9
AUC_{0-inf} (ng. hr/mL)	20661.496	21015.182	98.32	95.65-101.05	36	7.1
C_{max} (ng/mL)	1142.141	1154.215	98.95	95.74-102.27	36	8.5

Comment [SU7]: Should be 38

Comment [SU8]: Should be 38

Comment [SU9]: Should be 38

For Dolutegravir (Fed):

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC_{0-t} (ng. hr/mL)	18169.401	19084.274	95.2	91.67-98.88	34	9.5
AUC_{0-inf} (ng. hr/mL)	19970.920	20437.422	97.7	95.59-99.90	34	5.5
C_{max} (ng/mL)	798.197	786.100	101.5	98.82-104.33	34	6.8

Comment [SU10]: Should be 36

Comment [SU11]: Should be 36

Comment [SU12]: Should be 36

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, MYLTEGA DT is equivalent and interchangeable with GSK1349572, CQ, 5.0 mg, manufactured by GlaxoSmithKline Research & Development Limited 980 Great West Road, Brentford, Middlesex, TW8 9GS under acceptable in vivo experimental conditions.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe 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. MYLTEGA DT 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

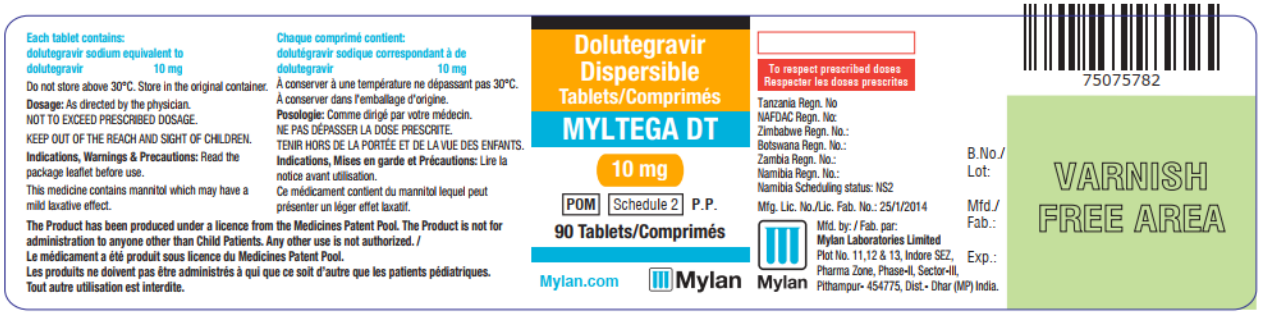
Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up label

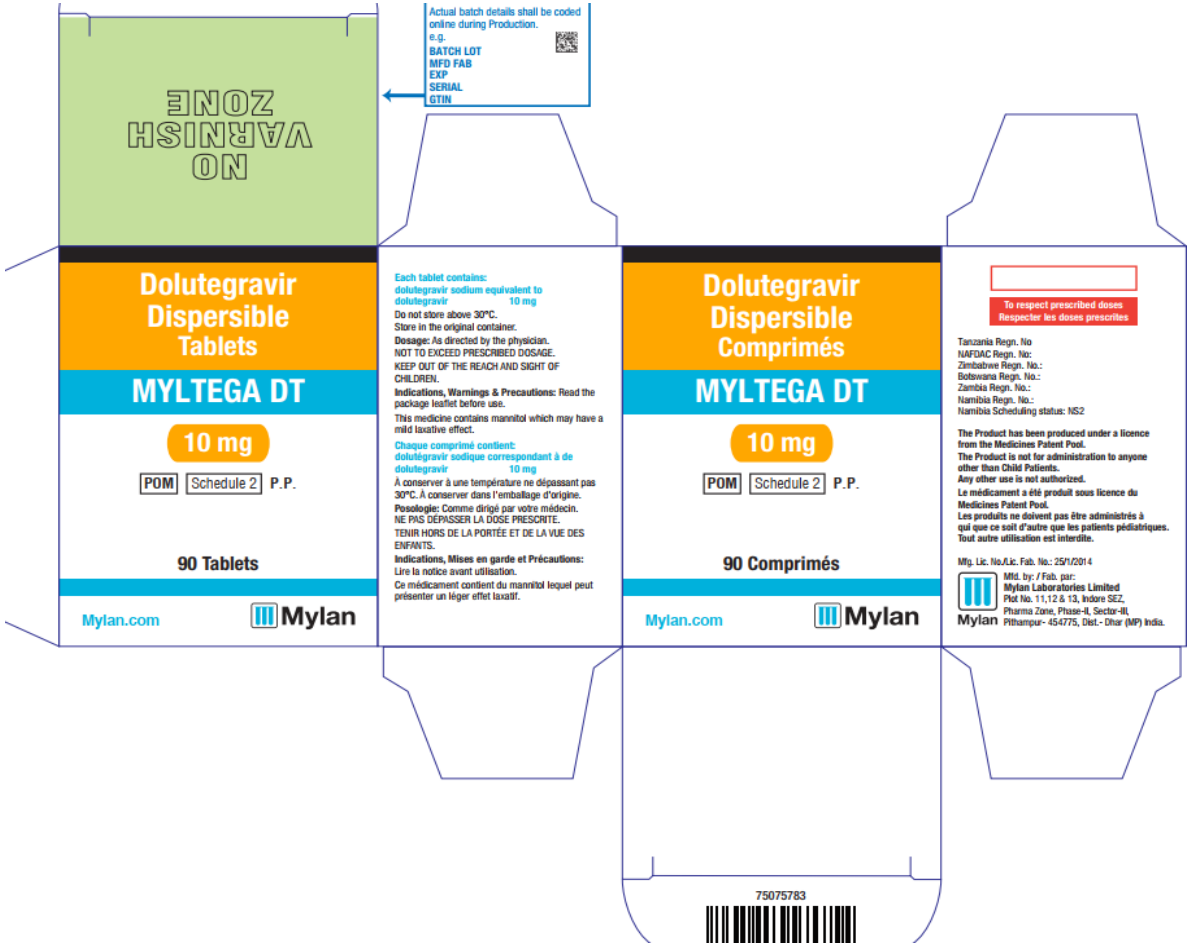
Primary label:

artwork - 100%

artwork - 150%



Secondary label



Effective date: 03/10/2022