THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR DOLUTEGRAVIR (AS SODIUM) 50 MG FILM COATED TABLETS

Version number 01

03/01/2023

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1. Introduction

Dolutegravir is integrase inhibitor which has been studied in a full range of HIV treatment populations; in those without prior HIV therapy, in patients with prior failing therapies and resistance to drug classes other than integrase inhibitors, and in patients who also had failed therapy with an integrase inhibitor with consequent integrase inhibitor class resistance. medicine belonging to antivirals for systemic use, other antivirals, ATC code: J05AJ03.

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.

Dolutegravir Tablets 50 mg is approved in Tanzania for the treatment of human immunodeficiency virus (HIV) infection in patients weighing at least 20 kg.

1.1 Product details

Registration number	TAN 22 HM 0309
Brand name	Dolutegravir
Generic name, strength and form	Dolutegravir
ATC classification	J05AJ03
Distribution category	POM
Country of origin	People's Republic of China
Associated product	Not applicable
Marketing Authorization Holder	Shanghai Desano Bio-Pharmaceutical Co., Ltd., 1479 Zhangheng Road, China (Shanghai) Pilot Free Trade Zone, Shanghai 201203, China
Local Technical Representative	RK Pharmaceuticals (TZ) Limited, Plot No. 9, Block no. 28, Uhuru/Swahili St. Kariakoo, P.O. Box 325, Dar Es Salaam, Tanzania

1.2 Assessment procedure

The application for registration of Dolutegravir was submitted on 01/06/2022. The product underwent abridged assessment. Assessment was completed in one round of evaluation. Dolutegravir was registered on 04/08/2022.

1.3 Information for users

Visual description of the finished product	Pink, round, film-coated, biconvex tablets, debossed with “D08” on one side and plain on the other side
Primary packing material	HDPE bottle. 30 tablets per bottle
Secondary packing materials	Carton box alongside with a package insert
Shelf-life and storage condition	36 months Do not store above 30°C. Store in the original container
Route of administration	Oral
Therapeutic indications	Dolutegravir Tablets 50 mg is indicated, in combination with other antiretroviral medicines, for the treatment of human immunodeficiency virus (HIV) infection in patients weighing at least 20 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 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: Dolutegravir

Composition: Dolutegravir sodium equivalent to dolutegravir 50 mg, mannitol

Pack size: 30’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: Shanghai Desano Bio-Pharmaceutical Co., Ltd. Block No. 2, 1479 Zhangheng Road, China (Shanghai) Pilot, Free Trade Zone, Shanghai 201203, P.R. China.

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: Dolutegravir
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Shanghai Desano Bio-Pharmaceutical Co., Ltd. Block No. 2, 1479 Zhangheng Road, China (Shanghai) Pilot, Free Trade Zone, Shanghai 201203, P.R. China.

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 Ingredient(s)

Information on quality of the API was submitted in form of WHO Prequalification proof.

General properties
Dolutegravir sodium API is non-compendia.

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

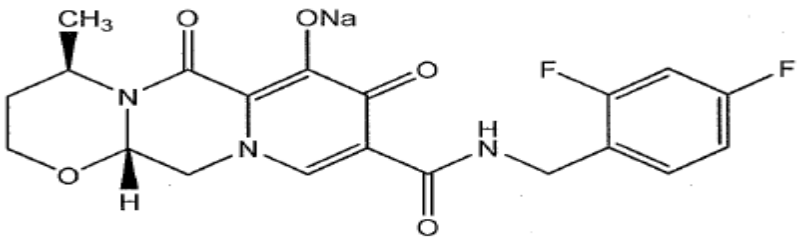
Chemical names:
Sodium (4R,12aS)-N-[(2,4-Difluoro benzyl)carbamoyl] -4-methyl-6, 8-dioxo-3,4,6,8, 12,12a -hexahydro-2H-pyrido [l',2':4,5]pyrazino [2, 1-b] [1,3] oxazin-7-olate

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. Dolutegravir sodium exists in four polymorphic forms. Form-I, Form-II and Form-III and Form-III were reported in the literature. These forms were distinguished by X-ray powder diffraction (XRPD) technique. The polymorphic form of Dolutegravir sodium manufactured by Shanghai DESANO has been demonstrated by X-ray powder diffraction patterns and DSC to be Form-I.

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, Shanghai Desano Chemical Pharmaceutical Co., Ltd, Block No., K18, A16C, B15A, No. 417 Binhai Road, Laogang Town, Pudong New area, Shanghai 201302 China was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by_____. 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), identification (IR), assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), residual solvents (GC-HS), heavy metals, Sodium content, 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 two Polyethylene bags, which are sealed with plastic slide fastener; Polyethylene bags containing material is then placed in aluminum foil bag and closed by heat-seal and stored in well closed container do not store above 30°C.

Quality of the Finished Pharmaceutical Product

Formulation

Dolutegravir 50 mg film coated tablet is a Pink, round, film-coated, biconvex tablets, debossed with “D08” on one side and plain on the other side.

Dolutegravir 50 mg film coated tablet contains Dolutegravir sodium and other ingredients listed here after: Mannitol, Microcrystalline Cellulose, Polyvinyl Pyrrolidone, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Opadry II Pink 85F640040 and Purified water. 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. Ingredient, Mannitol is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Shanghai Desano Bio-Pharmaceutical Co., Ltd. Block No. 2, 1479 Zhangheng Road, China (Shanghai) Pilot, Free Trade Zone, Shanghai 201203, P.R. China. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 13-14th June, 2018. The GMP certificate issued by TMDA is already expired, therefore the facility is waiting for GMP re-inspection.

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, UV), assay (HPLC), uniformity of dosage, Enantiomer, Diastereomer and dissolution (HPLC) and 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 ± 2°C & 75% ± 5% RH for 36 months and 40 ± 2°C & 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in HDPE bottle with 33 mm Saf-Cap at Do not store above 30°C. Store in the original container.

Safety and efficacy information

The product was assessed using an abridged review process; therefore, the data under this section was considered sufficient as submitted hence was not evaluated.

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. Dolutegravir 50 mg film coated tablet 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