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**MINISTRY OF HEALTH**

**TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY**

# PUBLIC ASSESSMENT REPORT FOR TIVICAY (DOLUTEGRAVIR SODIUM EQUIVALENT TO DOLUTEGRAVIR 5 MG) DISPERSIBLE TABLETS

**Version number 01, 03/01/2023**

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## 1. Introduction

The drug product is an immediate release tablet for oral administration. Tivicay is presented as dispersible tablet containing 5 mg of dolutegravir (as dolutegravir sodium salt) as active substance, 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. Tivicay 5 mg 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 6 years of age or older and weighing at least 14 kg.

### 1.1.Product details

| | |
|---|---|
| Registration number | TAN 21 HM 0400 |
| Brand name | Tivicay 5 mg |
| Generic name, strength and form | 5 mg Dolutegravir (as sodium) Dispersible Tablets |
| ATC classification | J05AJ03, Antivirals for systemic use, other antivirals |
| Distribution category | POM |
| Country of origin | India |
| Associated product | Tivicay 50 mg, Tivicay 25 mg, and Tivicay 10 mg |
| Marketing Authorization Holder | GlaxoSmithKline Pharmaceutical Kenya Limited<br>P.O. Box 78392-00507, Likoni Road Industrial Area Nairobi Kenya |
| Local Technical Representative | JD Pharmacy Limited,<br>P.O. Box 1899,<br>Dar es Salaam |

### 1.2.Assessment procedure

The application for registration of Tivicay 5 mg was submitted on 05/08/2020. The product underwent full assessment. Assessment was completed in 2(two) rounds of evaluation. Tivicay 5 mg was registered on 09/10/2021.

### 1.3.Information for users

| | |
|---|---|
| Visual description of the finished product | Round (6 mm diameter), biconvex, white, film coated tablets, debossed “SV H 7S” on one face and “5” on the other face |
| Primary packing material | Opaque, white high density polyethylene (HDPE) bottles with polypropylene child resistant closures, with a polyethylene faced induction heat seal liner. A silica gel desiccant canister is also included in the bottle. |
| 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 in order to protect from moisture |
| Route of administration | Oral |
| Therapeutic indications | Indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults, adolescents and children of at least 6 years of age or older and weighing at least 14 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: Tivicay 5 mg

Composition: Dolutegravir sodium equivalent to dolutegravir 5 mg
Pack size: 60 tablets
Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Do not store above 30°C. Store in the original container in order to protect from moisture
Manufacturers addresses: Manufactured by: Glaxo Operations UK Ltd, Ware, SG12 0DJ, United Kingdom/Reino Unido/Royaume-Uni

Packed by: Glaxo Wellcome, S.A., Aranda de Duero, Spain/Espafia/Espagne

Unique identifier: N/A
Special warnings/precautions or instructions for use: Keep the bottle tightly dosed. Do not remove the desiccant

The details of the primary pack include:
Brand name and strength: Tivicay 5 mg
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Glaxo Operations UK Ltd and Glaxo Wellcome, S.A
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 Full details.

General properties
Dolutegravir sodium API is non-compendia.

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

Chemical names:

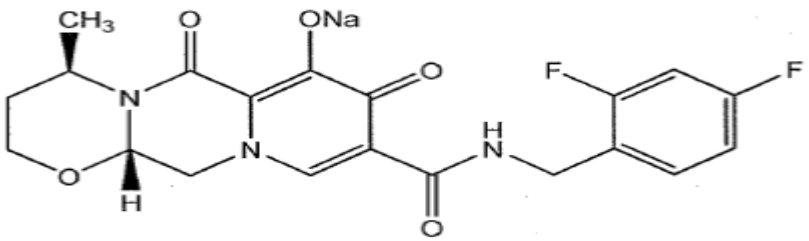
Sodium (4R,12aS)-N-[(2,4-Difluoro benzyl)carbamoyl] -4-methyl-6, 8-dioxo-3,4,6,8, 12,12a -hexahydro-2H-pyrido [l',2':4,5]pyrazino [2, 1-b] [1,3] oxazin-7-olate

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.

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,

| **Name and address (including block(s)/unit(s))** | **Responsibility** |
|---|---|
| Fujimoto Chemicals Co., Ltd. (Senboku plant)<br>1-24, Rinkai-cho<br>Izumiotsu, Osaka 595-0075, Japan | Manufacturing and Quality control testing of Dolutegravir free acid and |

| | |
|---|---|
| Fujimoto Chemicals Co., Ltd. (Kinraku plant)<br>1-2-38, Kinrakuji-cho<br>Amagasaki, Hyogo 660-0806, Japan | Quality control testing of Dolutegravir free acid |
| Shionogi Pharma Co., Ltd., 224-20, Hiraishiebisuno, Kawauchi-cho, Tokushima, Tokushima 771-0132, Japan | Manufacturing and Quality control testing of nonmicronised and micronised Dolutegravir sodium |
| Shionogi Pharma Co., Ltd., 1-3, Kuise Terajima 2-chome, Amagasaki, Hyogo 660-0813, Japan | Alternate quality control testing site for unmicronised Dolutegravir sodium |
| Glaxo Wellcome Manufacturing Pte Ltd<br>1 Pioneer Sector 1 | Manufacturing of nonmicronised Dolutegravir sodium |
| Catalent Micron Technologies Limited<br>Crossways Boulevard,<br>Crossways<br>Dartford, Kent<br>DA26QY<br>United Kingdom | Manufacturing of micronised Dolutegravir sodium |

All manufacturers were noted to comply with WHO GMP requirements. 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), sodium content, assay (HPLC), related substances (HPLC), diastereomer (HPLC), enantiomeric purity (HPLC), residual solvents (GC), 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 60 months when packed in double LDPE bags and sealed with plastic ties and stored up to 30 ºC and protected from light.

## Quality of the Finished Pharmaceutical Product

Formulation

Tivicay 5 mg is a round (6 mm diameter), biconvex, white, film coated tablets, debossed "SV H 7S" on one face and "5" on the other face.

Tivicay 5 mg contains Dolutegravir sodium and other ingredients listed here after: Mannitol, Microcrystalline Cellulose, Povidone K29/32, Sodium Starch Glycolate (Type A), Purified Water, Silicified Microcrystalline Cellulose, Crospovidone (Type B), Calcium sulfate dihydrate, Sucralose, Strawberry Cream Flavour Permaseal PHS-132963, Sodium Stearyl Fumarate, AquariusTM BP18237 White Film Coat or Opadry® OY-S-28876 White Film Coat (Hypromellose 2910, Titanium Dioxide, Polyethylene Glycol 400). 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.

Manufacture

The finished product was manufactured at Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations), Priory Street, Ware, Hertfordshire SG12 0DJ, UK, and Glaxo Wellcome, S.A., Avda. Extremadura, 3 09400 Aranda De Duero, Burgos, Spain. The compliance of the site to TMDA GMP standards was confirmed through site inspection on DD/MM/YY.

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 (UV and HPLC), assay (HPLC), uniformity of dosage (HPLC), dissolution (HPLC), water (KF), disintegration, 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 36 months and $40^0$ ± 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 silica gel sachet (desiccant) at Do not store above 30°C. Store in the original container in order to protect from moisture.

## Safety and efficacy information

Tivicay 5 mg (dolutegravir sodium equivalent to dolutegravir 5 mg) dispersible 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/002753/X/0058/G). In this context, re-assessment of this part is not considered as necessarily required.

## 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. Tivicay 5 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

Primary label:

Secondary label


PHARMA CODE N°. 1899
Tivicay 5 mg
dispersible tablets
tabletas dispersables
comprimés dispersibles
dolutegravir/dolutégravir
Each dispersible tablet contains 5 mg dolutegravir (as dolutegravir sodium).
Read the package leaflet before use.
Store up to 30°C. Store in the original package in order to protect from moisture.
Keep the bottle tightly closed. Do not remove the desiccant.
Keep out of the sight and reach of children.
Medicinal product subject to medical prescription.
Cada tableta dispersable contiene 5 mg de dolutegravir (como dolutegravir sódico).
Léase el prospecto del empaque antes de usarse.
No almacene a más de 30°C. Consérvese en el empaque original para protegerse de la humedad.
Mantenga la botella bien cerrada. No remueva el desecante.
Manténgase fuera de la vista y el alcance de los niños.
Medicamento sujeto a prescripción médica.
Chaque comprimé dispersible contient 5 mg de dolutégravir (sous forme de dolutégravir sodique).
Lire la notice avant utilisation.
RESPECTER LES DOSES PRESCRITES
Conserver jusqu'à 30°C. A conserver dans l'emballage d'origine, à l'abri de l'humidité.
Conserver le flacon soigneusement fermé. Ne pas retirer le déshydratant.
Tenir hors de la vue et de la portée des enfants.
Médicament soumis à prescription médicale.
Manufactured by/Fabricado por/Fabriqué par:
Glaxo Operations UK Ltd*
Ware
SG12 0DJ
United Kingdom/Reino Unido/Royaume-Uni.
Packed by/Empacado por/Conditionné par:
Glaxo Wellcome, S.A.*
Aranda de Duero
Spain/España/Espagne.
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Tivicay 5 mg
dispersible tablets
tabletas dispersables
comprimés dispersibles
dolutegravir/dolutégravir
For oral use
Para uso oral
Voie orale
This pack contains a dosing cup and dosing syringe.
Este empaque contiene una tapa dosificadora y jeringa dosificadora.
Ce conditionnement contient un gobelet doseur et une seringue doseuse.
60 dispersible tablets
60 tabletas dispersables
60 comprimés dispersibles
Lot/Lote:
Mfg/Fab:
Exp/Cad:
Tivicay 5 mg
dispersible tablets
tabletas dispersables
comprimés dispersibles
dolutegravir/dolutégravir
For oral use/Para uso oral
Voie orale
60 dispersible tablets
60 tabletas dispersables
60 comprimés dispersibles
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