THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

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

Version number 1.0
21 August 2023

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1. Introduction

The product is a fixed combination contains lamivudine, tenofovir disoproxil fumarate, and dolutegravir indicated for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1). 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, via its active metabolite 5'-triphosphates (TP) (an analogue for cytidine), inhibits reverse transcriptase of HIV-1 and HIV-2 through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine triphosphate shows significantly less affinity for host cell DNA polymerases.

Tenofovir disoproxil fumarate is a nucleotide reverse transcriptase inhibitor (NtRTI) and phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). Tenofovir disoproxil fumarate is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, tenofovir disoproxil fumarate is more efficient than tenofovir disoproxil fumarate in concentrating tenofovir in peripheral blood mononuclear cells (PBMCs) or HIV target cells including lymphocytes and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination.

The product is approved in Tanzania for use in adults and adolescents (aged 12 years and older with body weight at least 35 kg).

1.1 Product details

Registration number	TAN 23 H 0302
Brand name	N/A
Generic name, strength, and form	Each film coated tablet contains: Dolutegravir sodium equivalent to Dolutegravir 50 mg Lamivudine 300 mg Tenofovir disoproxil fumarate 300 equivalent to Tenofovir disoproxil 245 mg
ATC classification	J05AR27- Antivirals for treatment of HIV infections
Distribution category	POM
Country of origin	China
Associated product	N/A
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 P.O. Box 325, Dar es Salaam

1.2 Assessment procedure

The application for registration of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets was submitted on 29/08/2022. The product underwent abridged assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 01 June 2023.

1.3 Information for users

Visual description of the finished product	White to off white, film coated, capsule shaped, biconvex beveled edge tablet debossed with M on one side of the tablet and LD on the other side
Primary packing material	HDPE Bottle Pack: 30's count (With two silica gel sachets as desiccant) HDPE Bottle Pack: 90's count (With two silica gel sachets as desiccant)
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, Do not store above 30'C. Store and dispense in original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant
Route of administration	Oral
Therapeutic indications	Lamivudine, Tenofovir disoproxil fumarate and Dolutegravir Tablets 300 mg/25 mg/50 mg is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1

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

Brand name: Not applicable

Composition: Each film coated tablet contains: Dolutegravir sodium equivalent to Dolutegravir 50 mg, Lamivudine 300 mg, Tenofovir disoproxil fumarate 300 equivalent to Tenofovir disoproxil 245 mg

Pack size: 30’s and 90’s tablets

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Do not store above 30'C. Store and dispense in original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Do not store above 30'C. Store and dispense in original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant

The details of the primary pack include:

Brand name and strength: Not applicable

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Shanghai Desano Bio-Pharmaceutical Co., Ltd

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 Ingredients

Information on quality of the API was submitted in form of DMFs

<u>Dolutegravir Sodium</u>

General Information

Dolutegravir Sodium API is compendia in USP.

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

Chemical name:

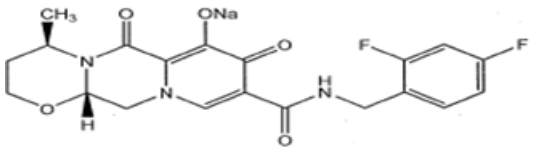
Sodium (4R,12aS)-N- [(2,4-Difluoro benzyl) carbamoyl]- 4-methyl-6, 8-dioxo- 3,4,6,8,12,12a-hexahydro-2H-pyrido [l',2': 4,5] pyrazino [2, 1 – b] [1,3] oxazin -7 -olate

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

Sodium (4R, 9aS)-5-hydroxy-4-rnethyl-6, 10-dioxo-3,4,6,9,9a,10-hexahydro-2H-] - oxa-4a,8a-diazaanthracene-7 -carboxylic acid 2,4 -difluoro benzylamide

Structure:



General properties

Dolutegravir Sodium is a white to pale yellow solid and exhibit polymorphism whereas the obtained spectra show Mylan consistently manufactures crystalline 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 specification.

Manufacture

Dolutegravir Sodium API manufacturer is Shanghai Desano Chemical Pharmaceutical Co., Ltd, K18, A16C, B15A, B16B, C18C, No.417, Binhai Road, Laogang Town, Pudong New Area, Shanghai 201302, China. The manufacturing complies with 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, Identification (by IR and PXRD), Water content, Sodium content, Related substances, Enantiomer, Diastereomer, Assay, Residual solvents, Particle size, and Microbiological quality. Compliance to these specifications were established via batch analysis data and stability studies.

<u>Stability and container closure system</u>

The re-test period of Dolutegravir Sodium API is 36 months when packed in Polyethylene bags with storage condition 'Do not store above 30°C, protect from moisture'.

Tenofovir disoproxil fumarate

General Information

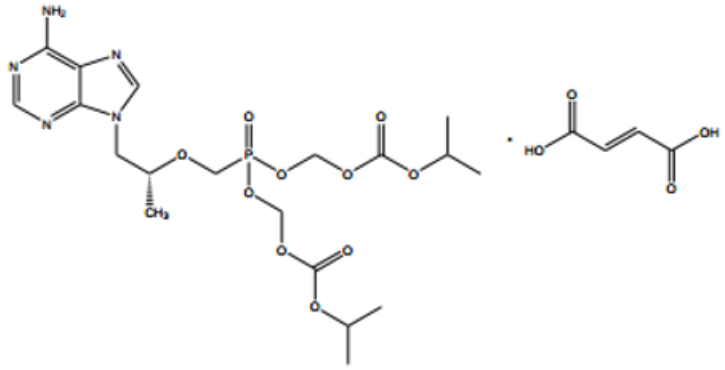
Tenofovir disoproxil fumarate API is compendia in Ph.Int.

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

Chemical name:

[[(1R)-2(6-Amino-9H-purin-9-yl)-1-methylethoxy] methyl] Phosphonate,bis (isopropyloxycarbonyloxymethyl ester), fumarate (1:1)

Structure:



General properties

Tenofovir disoproxil fumarate is a white to off-white crystalline powder soluble in methanol and dimethylformamide, slightly soluble in water.

Tenofovir disoproxil fumarate known to exhibit polymorphism. Polymorphism confirmed through PXRD and DSC concludes that Tenofovir Disoproxil Fumarate manufactured by Shanghai Desano is Form.

The submitted solubility data, in the physiological pH range at 37±1°C, show that Tenofovir disoproxil fumarate is a highly soluble molecule according to the Biopharmaceutics Classification System (BCS). Therefore, controlling polymorphism and particle size is considered not to be critical.

Manufacture

Tenofovir disoproxil fumarate API manufacturer is Shanghai Desano Chemical Pharmaceutical Co., Ltd, C18B, C18C, K13B, L17, B16A, C16A, C16B, No.417, Binhai Road, Laogang Town, Pudong New Area, Shanghai 201302, China. The manufacturing complies with 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: Description, Solubility, Identification (by IR, HPLC, and PXRD), Fumaric acid content, Clarity and colour of solution, Water content, Assay, Enantiomeric purity (S-isomer), Heavy metals, Related substances, Assay, Residual solvents, Particle size, and Microbiological quality. 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 48 months when packed in low density polythene bags with storage condition 'Store at 2-8°C in tight, light-resistant containers'.

Lamivudine

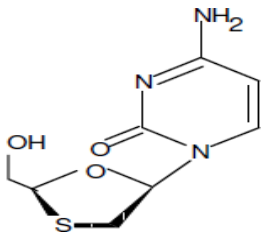
General Information

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

Molecular formula: $C_8H_{11}N_3O_5S$

Chemical name:

2R-cis)-4-amino-1-(2R-hydroxymethyl-[1,3] oxathiolan-5S-yl)- 1H-pyrimidin-2-one
Structure:



General properties

Lamivudine is a white to off-white solid and soluble in water. This active substance exhibits also stereoisomerism due to the presence of two chiral centres (1S,4R absolute configuration). Enantiomeric purity is controlled routinely by chiral HPLC and specific rotation. Lamivudine may exist as either of two pseudopolymorphs (Form I or Form II). The manufacturing process of Lamivudine is well controlled to manufacture only Form II.

Manufacture

Lamivudine API manufacturer is Shanghai Desano Chemical Pharmaceutical Co., Ltd., B14, B15, C18 (for process A), B15, L18 (for Process B), No.417, Binhai Road, Laogang Town, Pudong

New Area, Shanghai 201302, China. The manufacturing complies with GMP requirements as evidenced by the GMP certificate 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: Description, Identification by IR & HPLC, Light absorption, melting range, Water content, Limit of Lamivudine enantiomer, Other Related Compounds, Assay by HPLC, Residual solvents by GC, Residue on Ignition, Loss on drying, Light absorption, Bulk Density, Particle size and Microbiological quality. 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 60 months when packed in a clear, pharmaceutical grade low density polyethylene (LDPE) bag (inner bag) with storage condition ‘‘Do not store above 30°C, protect from moisture’.

Quality of the Finished Pharmaceutical Product

Formulation

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate tablets is a white colour capsule shaped tablets with ‘D15’ debossed on lower side and plain on upper side. Should be free from physical defects.

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate tablets contains the Dolutegravir sodium, Lamivudine, and Tenofovir disoproxil fumarate, and other ingredients listed here after: Mannitol, Microcrystalline Cellulose PH101, Microcrystalline Cellulose PH112, Lactose monohydrate, Povidone, Starch Pregelatinised, Croscarmellose sodium, Sodium Starch Glycolate Type A, Magnesium stearate, Pigment yellow 42, Opadry White 85F18422. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities.

Manufacture

The finished product manufacturer is Shanghai Desano Bio-Pharmaceutical Co., Ltd., 1479, Zhangheng Road, China (Shanghai) Pilot Free Trade Zone, Shanghai, 201203, China. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

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, Average Weight, Water content, Uniformity of dosage units (by Content

uniformity), Dissolution, Assay, Related Substance, Microbiological 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 (3) batches of the finished product stored 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 bottles with storage condition 'Do not store above 30'C. Store and dispense in original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant'.

Safety and efficacy information

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate tablets is already registered by USFDA (under PEPFAR Program) with NDA no.: NDA213556 granted on 15/03/2022. Information on clinical data has been fully evaluated during the registration of the product. 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. Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate tablets 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 labels;

Primary pack label;

Each film-coated tablet contains:
50 mg of dolutegravir (equivalent to 52.6 mg of dolutegravir sodium), 300 mg of lamivudine USP, and 300 mg of tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).

Usual Dosage: See prescribing information for dosage information.

Store below 30°C (86°F).

This bottle is child-resistant.
Store and dispense in original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant.

Keep out of the reach of children.

NDC 54741-115-02

Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets

50 mg/300 mg/300 mg

The product has been produced under a licence from the Medicines Patent Pool.

Any other use is not authorized.

Rx only **90 Tablets**

DESANO

Mfd. by: **Shanghai Desano Bio-Pharmaceutical Co., Ltd.**
1479 Zhangheng Road, China (Shanghai) Pilot Free Trade Zone, Shanghai 201203, China

Dist. by: **Shanghai Desano Bio-Pharmaceutical Co., Ltd.**
1479 Zhangheng Road, China (Shanghai) Pilot Free Trade Zone, Shanghai 201203, China

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2204

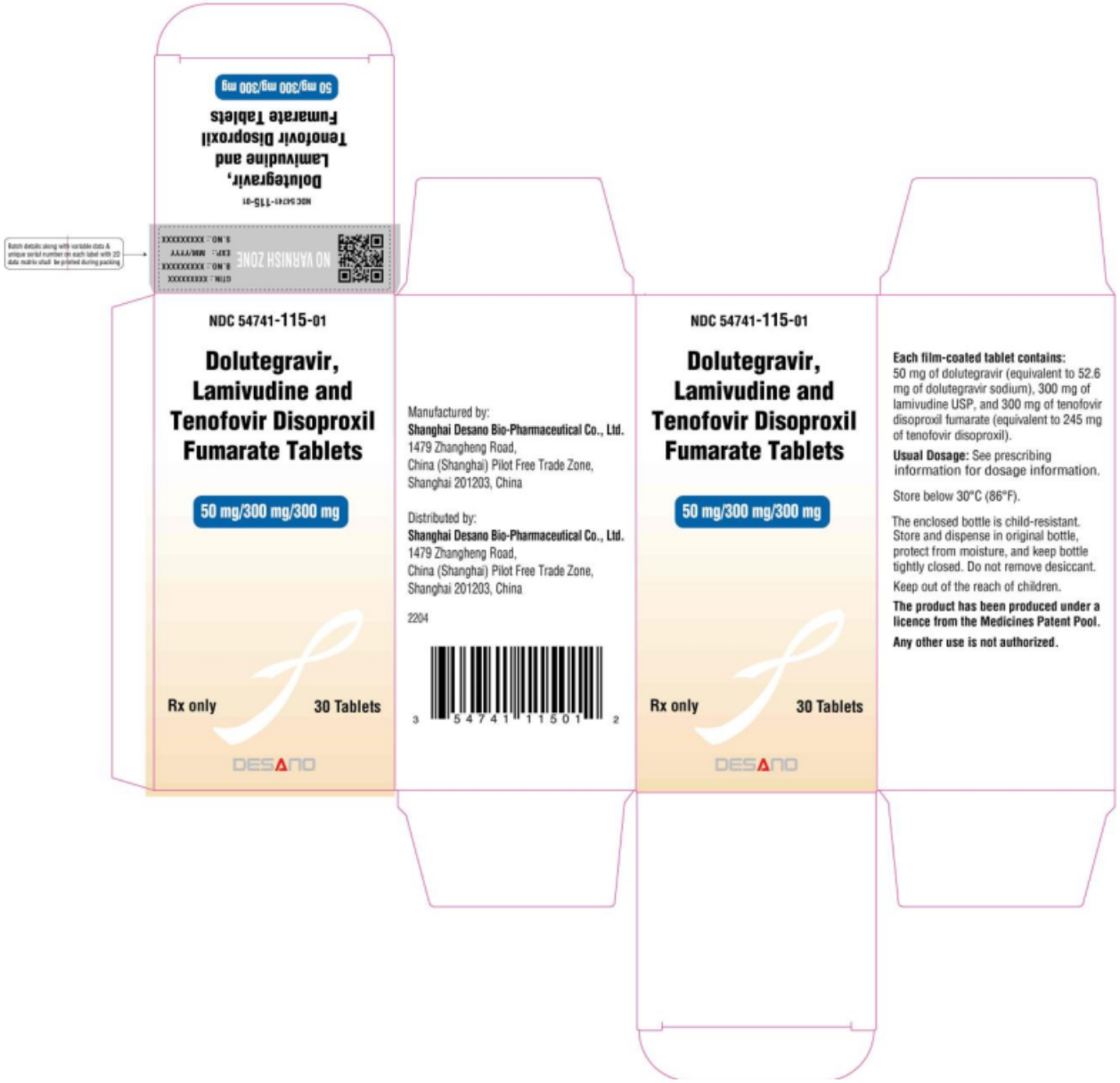
NO VARNISH ZONE

LOT:

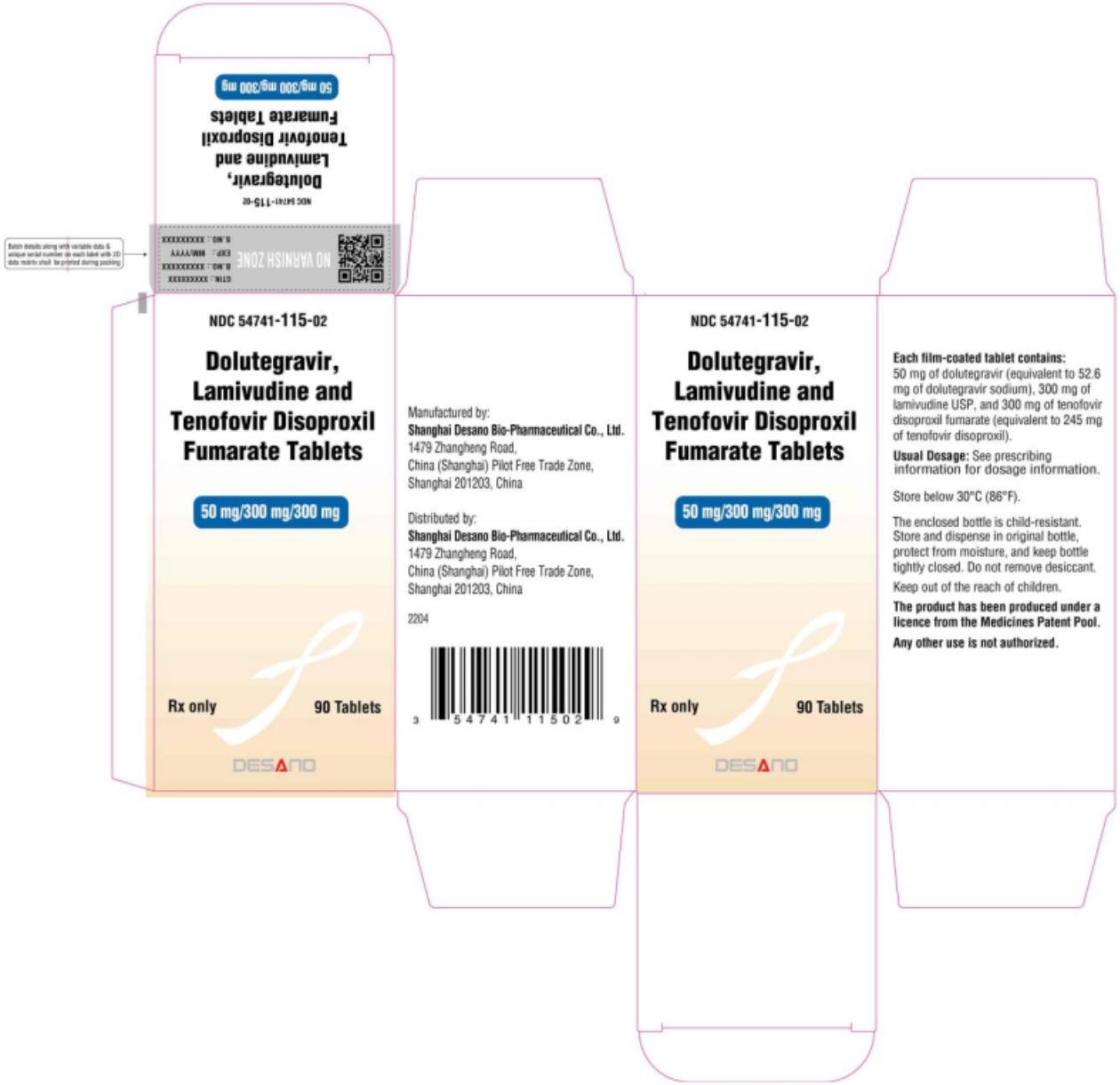
EXP:

Effective date: 03/10/2022

Secondary pack label;



Effective date: 03/10/2022



Effective date: 03/10/2022