THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

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

Version number 1

03 January, 2022

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1. Introduction

Dolutegravir, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets is antiretroviral drug, indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 30 kg.

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, the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue.

Tenofovir disoproxil is converted in vivo to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate.

Lamivudine and tenofovir are phosphorylated by cellular enzymes to form lamivudine triphosphate and tenofovir diphosphate, respectively. Lamivudine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination. Both substances are active against HIV-1 and HIV-2, as well as against hepatitis B virus.

1.1 Product details

Registration number	TAN 21 HM 0408
Brand name	N/A
Generic name, strength, and form	Each film-coated tablet contains 50 mg dolutegravir (as sodium), 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate
ATC classification	Direct acting antivirals, Antivirals for treatment of HIV infections, combinations, ATC code: J05AR27
Distribution category	POM
Country of origin	Republic of Korea
Associated product	N/A
Marketing Authorization Holder	Celltrion, Inc. 23 Academy –ro, Yeonsu-gu, Incheon, 22014 Republic of Korea
Local Technical Representative	DAWA MEDICARE LIMITED Box 16215 Dar es salaam

1.2 Assessment procedure

The application for registration of Dolutegravir, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets was submitted in DD/MM/YY. The product underwent full assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 09 October 2021.

1.3 Information for users

Visual description of the finished product	White color capsule shaped film coated tablets with 'C7' debossed on one side and plain on other side
Primary packing material	HDPE bottle of 30's and 90's
Secondary packing materials	N/A
Shelf-life and storage condition	24 months, Do not store above 30°C. Dispense only in original container
Route of administration	Oral
Therapeutic indications	Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate 50 mg/ 300 mg/ 300 mg Tablets are indicated for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg. Consideration should be given to official treatment guidelines for HIV-1 infection, e.g., by WHO. For use of antiretroviral agents for post-exposure prophylaxis, the most recent official guidelines, e.g., those by WHO should be consulted.

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: Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate Tablets

Composition: Each film-coated tablet contains 50mg dolutegravir (as sodium), 300mg lamivudine and 300mg tenofovir disoproxil fumarate, contains lactose

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. Dispense only in original container

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: N/A

The details of the primary pack include:

Brand name and strength: Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate Tablets (50/300/300 mg)
Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Celltrion, Inc

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 the quality of the APIs was submitted in form of DMFs.

Dolutegravir Sodium

General Information
Dolutegravir sodium API is non-compendia.

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

Chemical names:

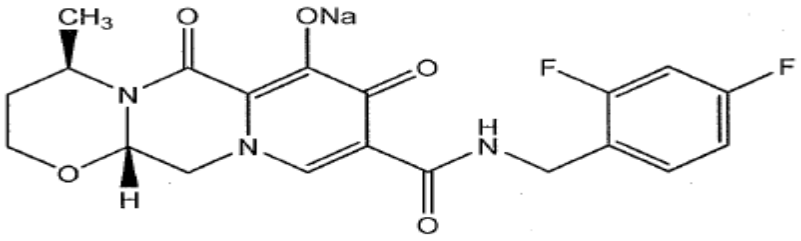
Sodium (4R,12aS)-N-[(2,4-Difluoro benzyl)carbamoyl] -4-methyl-6, 8-dioxo-3,4,6,8, 12,12a -hexahydro-2H-pyrido [l',2':4,5]pyrazino [2, 1-b] [1,3] oxazin-7-olate

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

Dolutegravir sodium API manufacturer is Shanghai Desano chemical Pharmaceuticals Co., Ltd, 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 the 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

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 and XRPD), sodium content, assay (HPLC), related substances (HPLC), diastereomer (HPLC), enantiomeric purity (HPLC), residual solvents (GC), water content (KF), 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 the original packing material and stored in a cool, dry and well-ventilated place out of direct sun light. Store in tightly closed containers. Do not store above 30ºC.

Lamivudine

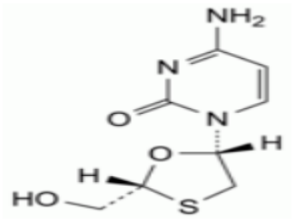
General Information

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

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 Shanghai Desano chemical Pharmaceuticals Co., Ltd, 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 the 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

Specifications

The API specifications were set as per USP standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, melting point, identification (IR and HPLC), assay (HPLC), limit of lamivudine enantiomer (HPLC), Other related compounds (HPLC), water determination (KF), light absorption, polymorphic identity (XRPD), residue on ignition, loss on drying, residual solvents (GC). 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 the original packing material and stored at below 30ºC.

Tenofovir disoproxil fumarate

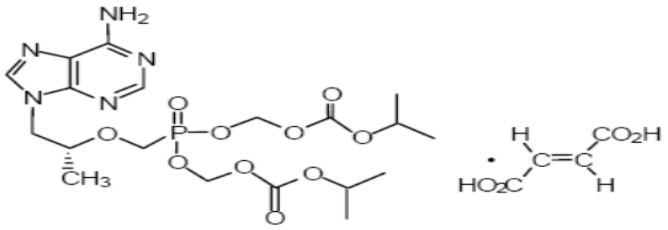
General Information

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 Shanghai Desano chemical Pharmaceuticals Co., Ltd, 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 the 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 USP/Ph. Eur. standards and ICHQ3A. The parameters monitored during quality control are: Description, Solubility, Identification (IR, HPLC, and XRPD), 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

Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate Tablets is a white color capsule shaped film coated tablets with 'C7' debossed on one side and plain on other side.

The product contains the Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate and other ingredients listed here after: croscarmellose sodium, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose (PH101, PH112), pigment yellow 42, povidone, pregelatinized starch, sodium starch glycolate, opadry II white 85F18422 (containing polyvinyl alcohol-part hydrolyzed, titanium dioxide,macrogol/PEG, and talc). 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. Ingredient, lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product manufacturers are Celltrion, Inc., 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do 28117, Republic of Korea. The compliance of the sites 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, Identification of the APIs (HPLC, TLC) and Colorants, Average weight, Water content (KF), Uniformity of dosage units (by content uniformity), Dissolution (HPLC detection), Related Substances (HPLC), Assay (HPLC) and Microbial limits. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 6(six) 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. Dispense only in original container'.

Safety and efficacy information

Safety and efficacy of Dolutegravir, Lamivudine and Tenofovir disoproxil fumarate Tablets was established through bioequivalence trial.

BE trial report number CT-G07 1.2 was submitted.

In case of BE:

Study title	A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of a fixed dosed combination film coated Test product containing Dolutegravir 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg tablets of Celltrion, Inc., Republic of Korea with Reference product (R= R1: TIVICAY® (Dolutegravir) 50 mg tablets manufactured by GlaxoSmithKline for ViiV Healthcare (ViiV) + R2: EPIVIR® (Lamivudine) 300 mg tablets manufactured by GlaxoSmithKline for ViiV Healthcare (ViiV) + R3: VIREAD® (Tenofovir disoproxil fumarate) 300 mg tablets manufactured by Gilead Sciences, Inc. (Gilead)) in normal healthy adult human subjects under fasting conditions
Study design	A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study in normal healthy adult human subjects under fasting conditions
Study sites	a) <u>Clinical Facility (Name and full mailing address)</u> M/s. Aizant Drug Research Solutions Private Limited, Clinical Pharmacology Unit-II, St. Theresa's Hospital, Clinical Pharmacology Department, 02nd Floor, Premises No.7-1-645/A, Sanathnagar, Hyderabad Telangana, India– 500018. b) <u>Clinical Laboratories (Name and full mailing address)</u> Diagnostics Department, Aizant Drug Research Solutions Private Limited, Survey No.: 172 &173, Apparel Park Road, Dulapally Village, Quthbullapur Mandal, Hyderabad, India-500100.

	c) <u>Analytical Laboratories (Name and full mailing address)</u> Bioanalytical Department, Clinical Development Division, Aizant Drug Research Solutions Pvt. Ltd., Survey No.: 172 &173, Apparel Park Road, Dulapally Village, Quthbullapur Mandal, Hyderabad, India -500100. d) <u>Company performing pharmacokinetic/statistical analysis (Name and full mailing address</u> Pharmacokinetics and Biostatistics Department, Clinical Development Division, Aizant Drug Research Solutions Private Limited, Survey No.: 172 &173, Apparel Park Road, Dulapally Village, Quthbullapur Mandal, Hyderabad, India-500100.	
Study dates	Period-1 09 Jan 2019 Period-2 20 Jan 2019	
Primary objective	To evaluate the oral bioequivalence study of a fixed dosed combination film coated Test product containing Dolutegravir 50 mg, Lamivudine 300 mg and Tenofovir Disoproxil Fumarate 300 mg tablets of Celltrion, Inc., Republic of Korea with Reference product (R= R1: TIVICAY® (Dolutegravir) 50 mg tablets manufactured by GlaxoSmithKline for ViiV Healthcare (ViiV) + R2: EPIVIR® (Lamivudine) 300 mg tablets manufactured by GlaxoSmithKline for ViiV Healthcare (ViiV) + R3: VIREAD® (Tenofovir disoproxil fumarate) 300 mg tablets manufactured by Gilead Sciences, Inc. (Gilead)) in normal healthy adult human subjects under fasting conditions	
Secondary objective	To monitor the adverse events and to ensure the safety of the subjects	
Number of participants	Sixty-two (62) subjects+02 additional subjects (standby-I & standby-II) were enrolled in this study and all subjects were healthy adults. A total of fifty-seven (57) subjects completed the clinical portion of the study in its entirety	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference products
	Strength: 50 mg/300 mg/300 mg Batch number: DLFTA1802B Expiry date: Oct 2020	TIVICAY® (Dolutegravir) tablets 50 mg Strength: 50 mg Batch number: (10)8ZP9194 Expiry date: Jan 2020 EPIVIR® (Lamivudine) tablets Strength: 300 mg

		Batch number: (10)8ZP8167 Expiry date: Sep 2020 VIREAD® (Tenofovir disoproxil fumarate) tablets Strength: 300 mg Batch number: 013187 Expiry date: Jul 2022
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analyte	
Statistical method	SAS® 9.2	

Efficacy results are summarized as follows:
Dolutegravir:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC_{0-t} (ng. hr/mL)	61586.797	53883.018	114.30	108.31-120.62	55	17.3
AUC_{0-inf} (ng.hr/mL)	64660.309	56665.443	114.11	108.25-120.28	55	16.9
C_{max} (ng/mL)	3395.488	2965.734	114.49	107.60-121.83	55	20.0

Lamivudine:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC_{0-t} (ng. hr/mL)	12383.415	12591.352	98.35	93.87-103.04	55	14.9
AUC_{0-inf} (ng.hr/mL)	12669.744	12857.772	98.54	94.18-103.10	55	14.5
C_{max} (ng/mL)	2108.930	2210.923	95.39	89.67-101.47	55	19.9

Tenofovir:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC_{0-t} (ng. hr/mL)	2818.221	2781.561	101.32	96.99-105.84	55	14.0
AUC_{0-inf} (ng.hr/mL)	3024.517	2985.023	101.32	97.06-105.77	55	13.8
C_{max} (ng/mL)	373.701	376.442	99.27	93.27-105.66	55	20.1

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, Dolutegravir 50 mg, Lamivudine 300 mg, and Tenofovir Disoproxil Fumarate 300 mg tablets of Celltrion, Inc., Republic of Korea is equivalent and interchangeable with TIVICAY® (Dolutegravir) 50 mg tablets manufactured by GlaxoSmithKline for ViiV Healthcare (ViiV), EPIVIR® (Lamivudine) 300 mg tablets manufactured by GlaxoSmithKline for ViiV Healthcare (ViiV), and VIREAD® (Tenofovir disoproxil fumarate) 300 mg tablets manufactured by Gilead Sciences, Inc. (Gilead)) under acceptable in vivo experimental conditions.

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>.

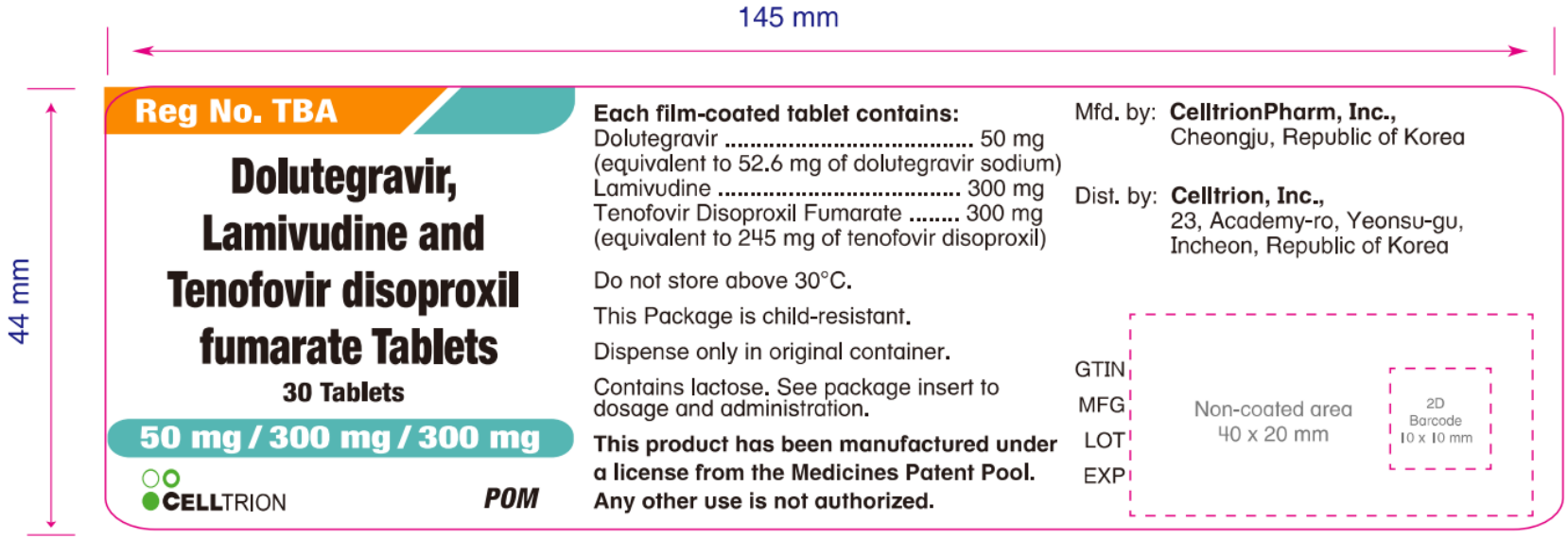
PART 5: CHANGE HISTORY

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

Annex I: Mock up labels;

Primary pack labels;

30T Container Labels



90T Container Label

Effective date: 03/10/2022