

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211284Orig1s000

CLINICAL REVIEW(S)

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: Nov 15, 2018

FROM: Jeff Murray, M.D.
Division of Antiviral Products

SUBJECT: Deputy Director Memorandum for NDA 211284
Temyxis, Lamivudine and Tenofovir Disoproxil Fumarate Tablets,
300mg/300mg

APPLICANT: Celltrion Inc.

TO: Division files

I. Background

Celltrion submitted this 505(b)(2) new drug application (NDA) for Lamivudine (3TC) and Tenofovir Disoproxil Fumarate (TDF) Tablets, 300mg/300 mg, intended for adult and pediatric patients weighing at least 35 kg. The two drugs in this fixed dose combination (FDC) are widely used in antiretroviral regimens and with the addition of a third drug make a complete regimen considered standard-of-care for a treatment naïve, HIV-1 infected patient.

This application was originally submitted on Jan. 15, 2018. The filing, review, and approval of this product as a 505(b)(2) NDA (as opposed to an ANDA) was not impacted by the recent approvals of similar pharmaceutical equivalents (CIMDUO under NDA 22141 approved in February 2018 and Lamivudine and Tenofovir DF Tablets under NDA 22344 approved in May 2018) because NDA 211284 was submitted in January 2018, which was prior to the approval of both NDAs 22141 and 22344.

II. Reviewers Findings

Please refer to the Office of Pharmaceutical Quality (OPQ) reviews for details on chemistry, manufacturing and controls (CMC) with concurrence from the OPQ Application Team Lead, Stephen Miller, Ph.D. The OPQ reviewers recommend Celltrion's version of 3TC/TDF tablets, 300mg/300mg (Temyxis), for final approval.

Refer to the review prepared by Vikram Ayra Pharm. D., who concurs with the approval of Temyxis. The applicant conducted relative bioavailability studies in

both fed and fasted subjects comparing their fixed dose combination of lamivudine and tenofovir DF with reference products. The individual reference products were Epivir® (lamivudine 300 mg tablets) of GlaxoSmithKline, USA and Viread® (Tenofovir Disoproxil Fumarate 300 mg tablets) of Gilead Sciences, Inc. Trial CT-G02 1.2 was a single dose relative bioavailability trial conducted under fasting conditions and Trial CT-G02 1.1 was a single dose relative bioavailability trial conducted under fed conditions.

The results from both trials showed that geometric mean ratios and 90% confidence intervals of C_{max} and $AUC_{0-\infty}$ for 3TC and TFV (under fasting conditions) and 3TC and TFV (under fed conditions) after administration of the test and reference product lie within the pre-specified 20% boundary for demonstrating similarity in systemic exposures. The Office of Study Integrity and Surveillance (OSIS) recommended acceptance of data from the clinical and bioanalytical sites for both trials without an on-site inspection.

Refer to the labeling memorandum, prepared by Kyong Hyon RN, MA. The proposed PI and PPI were reviewed and should allow for the safe and effective use of this 2-drug FDC product. Celltrion has adequately responded to the Division's labeling revisions conveyed on October 17 and 31, 2018, via email correspondence; therefore, an approval action is warranted.

As stated in the labeling memorandum, as a new FDC, at the time of submission, this product was considered a new active ingredient; thus, it triggered Pediatric Research Equity Act (PREA). On May 2, 2018, the Pediatric Review Committee (PeRC) granted a partial waiver of studies for pediatric patients weighing less than 35 kg because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups.

III. Recommendations

I concur with the final approval of Temyxis, Celltrion's version of Lamivudine and Tenofovir Disoproxil Fumarate FDC Tablets, 300 mg/300 mg, for the treatment of HIV-1 in combination with other antiretroviral drugs in adult and pediatric patients weighing at least 35 kg.

Jeffrey S. Murray M.D., M.P.H.
Deputy Director, Division of Antiviral Products

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JEFFREY S MURRAY
11/15/2018

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Division of Antiviral Products
Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993

Clinical Labeling Review

Date	November 5, 2018
From	Kyong Hyon, RN, MA Safety Regulatory Project Manager Division of Antiviral Products (DAVP)
Through	Monica Zeballos, Pharm.D., Senior Program Consultant, DAVP
NDA #	NDA 211284 505 (b)(2)
Applicant	Celltrion Inc., South Korea
U.S. Agent	ELC Group s.r.o., POC: Jinny Han
Letter Date	January 15, 2018
Stamp Date	January 16, 2018
Goal Date	November 16, 2018
Established Name	Lamivudine and Tenofovir Disoproxil Fumarate
Proprietary Name	TEMIXYS
Dosage Form/Strength	Tablets, 300 mg/300 mg
Materials Reviewed and Labeling Consultant Reviews	<ol style="list-style-type: none">1. Electronic submission (SDN14) dated and received October 9, 20182. Current U.S. labeling for the reference products: a) NDA 20564/S-038 EPIVIR (lamivudine) tablets, 300 mg approved on April 27, 2018 and b) NDA 21356/S-056 VIREAD (tenofovir disoproxil fumarate) tablets, 300 mg approved July 30, 20183. OSE/DMEPA^a Review of the PI & Container Labeling dated August 1, 20184. OMP/OPDP^b Review of the PI and Container Labeling dated October 11, 20185. Combined OMP/OPDP^b and OMP/DMPP^c Review of the PPI dated October 12, 20186. OPQ^d Labeling Recommendations for the PI/PPI & Container Labeling dated September 7, 2018
Recommended	Approval

^aOffice of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis

^bOffice of Medical Policy/Office of Prescription Drug Promotion (formerly DDMAC)

^cOffice of Medical Policy/Division of Medical Policy Programs (Patient Labeling Team)

^dOffice of Product Quality

I. Background

On January 15, 2018, Celltrion, Inc. (Celltrion) submitted an original 505(b)(2) New Drug Application (NDA) to gain approval and marketing in the United States for a fixed-dose combination tablet of lamivudine and tenofovir disoproxil fumarate (TDF), 300 mg/300 mg. The listed drugs (reference products) this application is relying upon are EPIVIR® (lamivudine) Tablets 300 mg, which was approved under NDA 20564 and VIREAD® (tenofovir disoproxil fumarate) Tablets 300 mg, which was approved under NDA 21356.

Celltrion's original proposed indication for use in combination with other antiretroviral agents for the treatment of HIV-1 infection "in adult and pediatric patients weighing at least 35 kg" was first revised by DAVP to "in adults and pediatric patients older than 12 years of age or weighing at least 35 kg." However, DAVP subsequently determined not to include the age limit of 12 years old. As a new combination, this product is considered a new active ingredient; thus, it triggered Pediatric Research Equity Act (PREA). On May 2, 2018, the Pediatric Review Committee (PerC) granted a partial waiver of studies for pediatric patients weighing less than 35 kg because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups.

The filing, review, and approval of NDA 211284 are not impacted by the approval of similar pharmaceutical equivalents (CIMDUO under NDA 22141 approved in February 2018 and Lamivudine and Tenofovir DF Tablets under NDA 22344 approved in May 2018) because a complete NDA 211284 was submitted in January 2018, which is prior to the approval of both NDAs 22141 and 22344.

II. Labeling Review

On October 5 and 9, 2018, Celltrion submitted labeling amendments to include October 1, 2018 FDA's container labeling recommendations and to update the Prescribing Information (PI) and Patient Package Insert (PPI) to reflect the most recent labeling updates of EPIVIR (last approved on April 27, 2018) and VIREAD (last approved on July 30, 2018).

All sections of the PI and PPI for this 2-drug fixed-dose combination (FDC) product were reviewed, updated, and compared to the latest approved U.S. labeling for EPIVIR and VIREAD. Labeling recommendations for the PI and PPI from consulting offices (OPQ, OSE/DMEPA, OMP/OPDP, OMP/DMPP) are included in the annotated PI and the content and format of the PPI was completely reformatted to be consistent with VIREAD and EPIVIR's PPI and current practices. A clean copy of the PPI and an annotated PI (conveyed to Celltrion on October 17, and 31, 2018) are attached at the end of this memo. Labeling recommendations for the container labels were addressed separately.

Additionally, DMEPA has reviewed the proposed proprietary name, TEMIXYS, and concluded that the name is conditionally acceptable. Please refer to the OSE/DMEPA's Proprietary Name Review dated April 16, 2018.

The content and format of the proposed PI have been updated and revised. Notable revisions include:

1. Revised the proposed INDICATION AND USAGE section as follows:

TEMIXYS is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adult and pediatric patients weighing at least 35 kg.

2. Addition to DOSAGE AND ADMINISTRATION:

2.1 Testing Prior to Initiation and During Treatment with TEMIXYS

Prior to initiation treatment with TEMIXYS, test patients for hepatitis B virus infection [see *Warnings and Precautions* (5.2)].

It is recommended that serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein be assessed before initiating TEMIXYS and during therapy in all patients as clinically appropriate [see *Warnings and Precautions* (5.5)].

3. Revised the proposed DOSAGE AND ADMINISTRATION

2.2 Recommended Dose for Adult and Pediatric Patients Weighing at Least 35 kg

TEMIXYS is a two-drug fixed-dose combination product containing 300 mg of lamivudine (3TC) and 300 mg of tenofovir disoproxil fumarate (TDF). The recommended dosage of TEMIXYS in HIV-1-infected adult and pediatric patients weighing at least 35 kg is one tablet taken orally once daily with or without food.

2.3 Not Recommended in Renal Impairment

Because TEMIXYS is a fixed-dose combination formulation and cannot be dose adjusted, it is not recommended for patients with impaired renal function (creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis [see *Use in Specific Population* (8.6)].

4. Important information for the individual components (EPIVIR and VIREAD) relevant to the use of this combination product was added/revised to the WARNINGS AND PRECAUTIONS (5), DRUG INTERACTIONS (7), USE IN SPECIFIC POPULATIONS (8), CLINICAL PHARMACOLOGY (12), HOW SUPPLIED/STORAGE AND HANDLING (16), and PATIENT COUNSELING INFORMATION (17) sections as follows:

- Section 5: Added updated information regarding Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV for lamivudine and TDF and Bone Effects for TDF
- Section 7: Added information about Drug Inhibiting Organic Cation Transporters and Sorbitol for lamivudine in 7.3 and 7.4. Updated table 3 in 7.2 to present data and clinical recommendations to conform to best labeling practices
- Subsections 8.1 and 8.2: Information related to lamivudine was updated to conform with the Pregnancy and Lactation Labeling Rule
- Subsection 8.4: Added pediatric use language
- Subsection 8.6: Renal Impairment information revised to be consistent with Subsection 2.3, Not Recommended in Renal Impairment
- Subsection 12.3: Added summarized pharmacokinetics information in adults for both lamivudine and TDF and added specific populations information for renal impairment for both lamivudine and TDF
- Section 16: Per OPQ's recommendations, removed the information regarding (b) (4)

- Section 17: Added information on New Onset or Worsening Renal Impairment, Drug Interactions, Pregnancy Registry, Missed Dosage, and Storage

III. Recommended Regulatory Action

The proposed PI and PPI were reviewed and should allow for the safe and effective use of this 2-drug FDC product. Celltrion has adequately responded to the Division's labeling revisions conveyed on October 17 and 31, 2018, via email correspondence; therefore, an approval action is warranted.

Kyong Hyon, RN, MA.
Safety Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

72 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KYONG M HYON
11/08/2018

MONICA I ZEBALLOS
11/08/2018