M E M O R A N D U M **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.

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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