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APPLICATION NUMBER:

022141Orig1s000

SUMMARY REVIEW

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: February 23, 2018

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

SUBJECT: Deputy Director Memorandum for NDA 22141
CIMDUO™ (Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 300mg/300mg)

APPLICANT: Mylan Laboratories LTD (Mylan)

TO: Division files

I. Background

Mylan submitted this 505(b)(2) new drug application (NDA) for CIMDUO™ Lamivudine (3TC) and Tenofovir Disoproxil Fumarate (TDF)Tablets, 300mg/300 mg, intended for adults 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 would make a complete regimen considered standard-of-care for a treatment naïve, HIV-1 infected patient.

This application was originally submitted on March 12, 2008 and received a Tentative Approval (TA) on Sept.12, 2008, under PEPFAR (President's Emergency Plan for AIDS Relief). The applicant resubmitted the application on Aug. 31, 2017, for marketing approval in the U.S. with expiration of relevant patents and exclusivity that previously precluded final approval in 2008.

II. Reviewers Findings

Please refer to the Office of Pharmaceutical Quality (OPQ) reviews for details on chemistry, manufacturing and controls (CMC). For this resubmission, refer to OPQ review #3 (resubmission 44) prepared with concurrence from the OPQ Application Team Lead, Stephen Miller, PhD. The OPQ reviewers recommend Mylan's Lamivudine and Tenofovir Disoproxil Fumarate Tablets for final approval. One issue of note, regarding manufacturing facilities, is excerpted below:

> *The* (b) (4) *) was withdrawn from NDA 22141 on Feb 8, 2018. This recommendation for final approval relies on the CMC and bioequivalence data submitted in this review cycle on the*

tablets manufactured at the Aurangabad facility, supported by the manufacturing experience documented in previous FDA reviews of this product. In the Feb 20, 2018 amendment Mylan confirms that future manufacture of both PEPFAR product and US product will only use the Aurangabad facility upon final approval of NDA 22141, (b) (4) *The Submission Overall Manufacturing Facility Status was "Approve" on Feb 26, 2018.*

Also refer to the Clinical Pharmacology review prepared by Islam Younis, Ph.D., who recommends approval. The initial TA was supported by Bioequivalence studies that were repeated for final marketing approval because of multiple changes/amendments in CMC since the 2008 TA. The applicant conducted two relative bioavailability studies under fasted (Study 234-17) and fed (Study 235-17) conditions to compare 3TC and TDF exposures following the administration of the 3TC/TDF FDC tablet and the individual TDF (VIREAD®) and 3TC (EPIVIR®) agents administered in combination. The exposures of 3TC and TDF were similar following the administration of Mylan's FDC relative to the individual agents. The Office of Study Integrity and Surveillance (OSIS) declined the request to inspect the clinical and analytical sites of the above mentioned studies because these sites were inspected recently and the inspection outcome was "No Action Needed". OSIS recommended accepting study data (Please see OSIS memorandum dated 11/03/2017).

Refer to the labeling memorandum, prepared by David Araojo Pharm.D., which summarizes updates to the label since initial TA and discusses the inclusion of pediatric age groups.

III. Recommendations

CIMDUO™, Mylan's Lamivudine and Tenofovir Disoproxil Fumarate FDC Tablets, 300mg/300mg, is recommended for final approval for adults and pediatric patients weighing at least 35 kg.

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/s/

JEFFREY S MURRAY
02/28/2018