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APPLICATION NUMBER:

022142Orig1s000

CLINICAL REVIEW(S)

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: March 22, 2018

FROM: Jeffrey S. Murray M.D., M.P.H.
Division of Antiviral Products

SUBJECT: Deputy Director Memorandum for NDA 22-142
Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate Tablets
600 mg/300 mg/300 mg

APPLICANT: Mylan Laboratories Ltd. (Mylan)

TO: HFD-530/Division files

I. Background and Clinical Findings

The availability of a wide range of safe and effective antiretroviral drug products is hoped to facilitate a wider distribution of anti-HIV drugs to better meet the demands of the global HIV/AIDS pandemic. In May 2004, FDA published a draft guidance entitled “Fixed Dose Combinations (FDC) and Co-Packaged Drug Products for the Treatment of HIV.`` A final version of this guidance entitled, “Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV” was published on Oct. 2006. The guidance encourages sponsors to develop various drug product versions of previously approved antiretroviral drugs and encourages sponsors to submit drug applications for these products to FDA for review. Although many antiretroviral drug product versions of previously approved antiretroviral cannot be currently approved or marketed in the US because of patent and exclusivity restrictions, FDA can review these products for quality, safety and efficacy and potentially grant a tentative approval. The President’s Emergency Plan for AIDS Relief will consider procurement of products reviewed by FDA that have been granted approval or tentative approval. Such products may be distributed outside the US, depending on regulatory requirements in other countries.

Mylan (formerly Matrix Laboratories Limited) submitted this 505 (b)(2) NDA for a fixed dose tablet containing three widely used antiretroviral drugs, lamivudine, tenofovir and efavirenz for tentative approval under the PEPFAR program. The application was tentatively approved on Sept. 9, 2009. On September 22, 2017, Mylan submitted a class 2 resubmission requesting final approval and marketing in the United States.

The safety and efficacy of this triple FDC is supported by previously conducted adequate and controlled studies of the individually approved components and a previous clinical study with this specific triple combination. The safety of the drugs contained in these tablets has also been well characterized in the individual drug development programs of the individual innovator products and the extensive postmarketing experience of the innovator drugs. This FDC is a complete HIV regimen in treatment naïve patients, and allows for once daily dosing with a single tablet.

Please refer to the clinical pharmacology review prepared by Assad Noory, at the time of tentative approval, for details of the review of the bioequivalence study. In brief, Mylan's fixed dose tablets containing lamivudine 300 mg, tenofovir 300 mg, and efavirenz 600 mg were bioequivalent to the U.S. approved reference formulations of the individual products, Epivir® tablets (lamivudine) 150 mg GlaxoSmithKline, Research Triangle Park, NC 27709), Viread® tablets (tenofovir) 300 mg (Gilead Sciences), and Sustiva® tablets (efavirenz) 600 mg (manufactured by Bristol Myers Squib, USA) when the three single entity tablets were given together in a single dose to healthy volunteers under fasting conditions. The tablets are recommended to be taken on an empty stomach. An inspection of the clinical site for the bioequivalence study was acceptable. The analytical inspections were based on previous acceptable inspections.

Please refer to Dr. Rao V. Kambhampati's Chemistry, Manufacturing and Controls review, prepared at the time of the tentative approval in 2009 for details regarding the acceptability of the drug product. Also, refer to the Office of Pharmaceutical Quality memo prepared by team lead Stephen Miller, Ph.D. Dr. Miller summarized changes included in the resubmission and recommends final approval from a product quality perspective.

Please refer to the labeling review prepared by David Araojo, PharmD. The package insert and patient package insert provide similar information as the individual products and is deemed adequate to allow for safe and effective use of this FDC.

II. Recommendation

Mylan's Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate Tablets 600 mg/300 mg/300 mg, tradename SYMFI, should be approved for the treatment of HIV in adults and pediatric patients weighing at least 40 kg.

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/s/

JEFFREY S MURRAY
03/28/2018