

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

DATE: March 14, 2019

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

SUBJECT: Deputy Director Memorandum for NDA 210649
Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate Tablets
400 mg/300 mg/300 mg

APPLICANT: Macleods Pharmaceuticals Limited (Macleods), India

TO: HFD-530/Division files

I. Background

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 Oct. 2006, FDA published a guidance entitled, "Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV." 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.

Macleods submitted this 505(b)(2) NDA for a fixed dose tablet containing three widely used antiretroviral drugs, lamivudine (3TC), tenofovir disoproxil fumarate (TDF) and efavirenz (EFV) initially for a potential tentative approval under the PEPFAR program on Sept. 14, 2017. At that time, there was remaining patent/exclusivity protection for certain reference listed drug (RLD) components of the fixed-dose combination (FDC) for the treatment of HIV indication. The application received two subsequent complete response (CR) actions on March 13, 2018 and Sept. 12, 2018, both due to inspectional issues. Macleods submitted a class 2 resubmission on Sept. 17, 2018, to address the CR. Because patent/exclusivity has expired for RLDs for the indication of HIV

treatment, this application is now eligible for final approval and marketing of the FDC in the United States.

II. Clinical Findings

This FDC is a complete HIV regimen in treatment naïve patients and allows for once daily dosing with a single tablet. 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 trial with this specific triple combination with a higher dose (600 mg) of EFV (see Trial 903 in the Clinical Studies section of the prescribing information). In addition, safety and efficacy of EFV 400 mg compared to EFV 600 mg was supported by one clinical trial called ENCORE1, a randomized, double-blind, placebo-controlled, clinical trial to compare the safety and efficacy of reduced dose EFV with standard dose EFV plus nucleos(t)ide analogues in antiretroviral-naïve HIV-infected individuals. Macleods obtained a right-of-reference for ENCORE1 and this trial is also described in the Clinical Studies section of the prescribing information for this product. The EFV 400mg product used in ENCORE1 was Mylan's product called EFAMAT. In brief, the regimen with the lower dose of EFV (400 mg) was noninferior to the regimen with standard dose EFV (600 mg). The lower bound of the confidence interval for the treatment difference (approximately -4%) was well within the specified margin (-10%). The slight numerical advantage for the lower dose was due to fewer discontinuations on the 400 mg dose arm.

The results from the relative bioavailability trial BEQ-1748-ELT(F)-2016 (See Clinical Pharmacology findings below), which used EFAMAT as one of the reference products, bridges the efficacy and safety information from ENCORE1 to the EFV/3TC/TDF 400 mg/300 mg/300 mg FDC tablet.

III. Chemistry, Manufacturing and Controls

Please refer to the Quality Assessment review prepared by the Office of Pharmaceutical Quality review team under Stephen Miller Ph.D., application team lead. Dr. Miller summarized changes included in the resubmission and recommends final approval from a product quality perspective.

IV. Clinical Pharmacology Findings

Please refer to the clinical pharmacology review prepared by Vikram Arya, Ph.D. and Kellie S. Reynolds, Pharm.D. The applicant conducted a relative bioavailability study, BEQ-1748-ELT(F)-2016. In that study, assessment of the relative bioavailability of EFV/3TC/TDF 400 mg/300 mg/300 mg tablets (test treatment) relative to EFV 400 mg (EFAMAT), 3TC 300 mg and TDF 300 mg (administered as individual innovator products; reference treatment) after single dose administration under fasting conditions. Because the prescribing information of SUSTIVA® (efavirenz) recommends that SUSTIVA® be administered under fasting conditions, a relative bioavailability trial under fed conditions is not needed. The results of the study showed that the geometric

mean ratio and 90% confidence intervals of C_{max} and AUC_{0-∞} (AUC₀₋₇₂ for EFV) for EFV, 3TC and Tenofovir after administration of the test and reference product were within the pre-specified 20% boundary for demonstrating similarity in systemic exposures.

The clinical and bioanalytical assessments were conducted at the Bioanalytical Department of Macleods Pharmaceuticals. The Office of Study Integrity and Surveillance (OSIS) recommended acceptance of data from the clinical and bioanalytical sites without an onsite inspection.

V. Labeling

Please refer to the labeling review prepared by Monica Zeballos, PharmD. The prescribing information and patient information provide similar information as the individual products and other similar FDCs and is deemed adequate to allow for safe and effective use of this FDC.

VI. Recommendation

Macleods' version of Efavirenz, Lamivudine, and Tenofovir disoproxil fumarate Tablets, 400 mg/300 mg/300 mg (no current tradename), should be approved as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg.

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