CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204311Orig1s000

SUMMARY REVIEW

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTIVIRALS

DATE: December 22, 2023

FROM: Sarita Boyd, Pharm.D.
Associate Director for PEPFAR
Division of Antivirals (DAV)

SUBJECT: Decisional Memorandum for NDA 204311
Abacavir and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg
Applicant: Mylan Laboratories Limited, a Viatris Company, India (Mylan)

TO: Division Files

I. Introduction

The availability of a wide range of safe and effective antiretroviral drug products is hoped to facilitate a wider distribution of antiretroviral drugs to better meet the demands of the global HIV/AIDS epidemic. FDA encourages sponsors to develop various drug product versions of previously approved antiretroviral drugs and submit drug applications for these products to FDA for review. Although many antiretroviral drug product versions of previously approved antiretrovirals cannot be currently marketed in the U.S. because of patent and exclusivity restrictions, FDA can review these products for quality, safety, and efficacy and potentially grant a tentative approval. Once U.S. patent/exclusivity protection has expired, an application that was previously granted a tentatively approval may be resubmitted to FDA with a request for final approval. The President's Emergency Plan for AIDS Relief (PEPFAR) will consider procurement of products reviewed by FDA that have been granted approval or tentative approval. Such products may be distributed outside the U.S., depending on legal requirements in other countries.

II. Background and Regulatory History

On December 23, 2013, Mylan submitted a 505(b)(2) new drug application (NDA) for a fixed-dose combination (FDC) of abacavir and lamivudine formulated as tablets for oral suspension intended for use in the PEPFAR program in pediatric patients. Abacavir and lamivudine are two nucleoside reverse transcriptase inhibitors commonly used in pediatric patients that can be combined with at least one other antiretroviral agent to form a complete HIV treatment regimen. On October 23, 2014, FDA granted tentative approval of this product in combination with other antiretroviral agents for the treatment of HIV-1 infection. A tentative approval was granted because the reference listed drug (RLD) components of the FDC had remaining patent/ exclusivity protections for the treatment of HIV-1 indication.

On February 6, 2019, Mylan submitted a class 2 resubmission to request final approval and marketing in the U.S. following expiration of patent/exclusivity protection. The application received two subsequent complete response (CR) actions on August 6, 2019, and January 13, 2023, both due to unresolved inspectional issues. Mylan submitted the current class 2 resubmission on June 22, 2023.

III. Summary of Review Findings

Please refer to the integrated quality assessment by the Office of Pharmaceutical Quality (OPQ) review team, including the executive summary by the Application Technical Lead, Molly Lee, Ph.D. (dated December 11, 2023), which recommends approval of this application. The compliance status of the drug substance facility, previously OAI, is now NAI following a for-cause inspection in May 2023. The applicant previously provided adequate drug substance information. The applicant provided adequate drug product and biopharmaceutics information to ensure the identity, purity, and strength to support the proposed commercial drug product. The overall manufacturing process and controls were previously found adequate. All facilities are acceptable and approved for the proposed functions.

Please also refer the OPQ addendum prepared by David Claffey, Ph.D., (dated December 22, 2023) which explains the rationale for retaining the following language in the labeling for this product: "Store below 30°C (86°F)." In addition, the child-resistant packaging will be the only approved configuration for marketing in the U.S., even though the non-child-resistant packaging is otherwise acceptable for use in the PEPFAR program (previously tentatively approved). I concur with Dr. Claffey's conclusions.

In response to an Information Request during this review cycle, OPQ determined that the applicant provided sufficient data to support the conclusion that the risk for formation of potential (b) (4) In addition to the OPQ review, please also refer to the pharmacology/toxicology review dated December 13, 2023, by Zheng Li, Ph.D., which discusses (b) (4) and other impurities. Dr. Zheng concludes that (1) (b) (4) (b) (4) and (2) there are minimal concerns regarding safety of the drug product. Dr. Zheng agrees with approval of this application.

Please refer to the original biopharmaceutics review by Minerva Hughes, Ph.D. (dated September 11, 2014) and the Deputy Director memo from Jeff Murray, M.D. (dated October 23, 2014) for details pertaining to the two bioequivalence studies, fed and fasted, that compared abacavir and lamivudine tablets for oral suspension (60 mg/30 mg) to the RLDs, Ziagen (abacavir sulfate) oral solution (20 mg/mL) and Epivir (lamivudine) oral solution (10 mg/mL). The conclusion was that both studies met criteria for bioequivalence. In addition, the Office of Scientific Investigations found the data for the bioequivalence studies acceptable for review.

Please refer to the clinical pharmacology memo prepared by Yang Zhao, Ph.D., and Su-Young Choi, Pharm.D., Ph.D. (dated December 21, 2023), which explains the rationale for the recommended dosage for this product and summarize important labeling changes. I concur with the conclusions.

Please also refer to the addendum clinical/labeling memo by Monica Zeballos, Pharm.D., dated December 19, 2023, which summarizes the regulatory history, displays all recommended labeling changes, and recommends approval of this product.

IV. Recommendation

NDA 204311 for abacavir and lamivudine tablets for oral suspension, 60 mg/30 mg (no current tradename), should be approved in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients 3 months of age and older and weighing at least 5 kg.

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/

SARITA D BOYD
12/22/2023 02:19:54 PM

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: Oct. 21, 2014

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

SUBJECT: Deputy Director Memorandum for NDA 204311
Abacavir and Lamivudine Scored Tablets for Oral Suspension (60mg/30mg)

TO: Division files

I. Introduction

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. On Oct. 17, 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 antiretrovirals cannot be currently marketed in the US because of patent and exclusivity restrictions, FDA is able to 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 legal requirements in other countries.

II. Background

Mylan submitted this 505(b)(2) NDA for this scored fixed dose combination (FDC) tablet of abacavir and lamivudine intended for pediatric use. These tablets contain two commonly used nucleoside reverse transcriptase inhibitors that can be combined with a non-nucleoside reverse transcriptase inhibitor, integrase inhibitor, or a protease inhibitor to form a complete HIV treatment regimen. This scored tablet is a smaller dosage strength (60 mg of abacavir and 30 mg of lamivudine) version [redacted (b) (4)] The dose strengths of abacavir and lamivudine submitted in this application are intended for use in pediatric patients. Abacavir and Lamivudine Tablets can be suspended in water for pediatric patients unable to swallow tablets. FDA previously granted tentative approval of

NDA 202381 for Mylan's unscored FDC tablet containing Abacavir Sulfate and Lamivudine (60 mg/30 mg) intended for pediatric use.

III. Reviewers findings

Please refer to the labeling review prepared by Monica Zeballos PharmD for a description of dosing recommendations and other pertinent edits to the label. She recommends this product for tentative approval.

I concur with the CMC review prepared by Dr.Ragiv Agarwal, who recommends tentative approval of Abacavir Sulfate and Lamivudine Tablets for Oral Suspension. Dr. Agarwal states that the NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An 'Acceptable' site recommendation from the Office of Compliance has been made. The Product Quality Microbiology review also recommends tentative approval.

I concur with the Biopharmaceutics (ONDQA) review prepared by Dr. Minerva Hughes. Dr. Hughes recommends tentative approval of Abacavir and Lamivudine Scored Tablets for Oral Suspension. The Applicant conducted two bioequivalence studies, fed and fasted, comparing Abacavir Sulfate and Lamivudine Tablets for Oral Suspension (60 mg/ 30 mg) to the Reference Listed Drugs (RLD), ZIAGEN (Abacavir Sulfate) Oral Solution 20 mg/mL (NDA #020978) and EPIVIR (Lamivudine) Oral Solution, 10 mg/mL (NDA # 020596). Both studies met criteria for bioequivalence. The Office of Scientific Investigations found the data for the bioequivalence studies acceptable for review.

IV. Recommendations

Mylan's version of Abacavir and Lamivudine Scored Tablets for Oral Suspension (60mg/30 mg) intended for use in pediatric patients should receive tentative approval.

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Jeffrey S. Murray M.D., M.P.H.

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/s/

JEFFREY S MURRAY
10/23/2014