CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204311Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY MEMO

NDA/SDN	204311/39
Submission date	06/22/2023
Submission type	Resubmission
Drug	Abacavir and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg (ABC/3TC TOS)
Applicant	Mylan Pharmaceuticals Inc.
Indication	In combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in pediatric patients aged 3 months and older and weighing at least 5 kg
OCP Division	DIDP
OND Division	DAV
Review Team	Yang Zhao, Su-Young Choi

Regulatory History

The Applicant, Mylan Pharmaceuticals Inc., previously submitted a 505 (b)(2) application under the President's Emergency Plan for AIDS Relief (PEPFAR) program for Abacavir Sulfate and Lamivudine Tablets for Oral Suspension (ABC/3TC TOS) 60 mg/30 mg on 12/23/2013. The original application received tentative approval on 10/23/2014. Currently, it is eligible for final approval.

The reference products (Listed Drugs) are ZIAGEN® (Abacavir Sulfate) Oral Solution 20 mg/mL (NDA 020978), and EPIVIR® (Lamivudine) Oral Solution 10 mg/mL (NDA 020596), manufactured by ViiV Healthcare, Research Triangle Park, USA. The original application included pharmacokinetic data from fasted (study BA12101519-01) and fed (study BA12101520-01) relative bioavailability (BA) studies using the forementioned reference products. These studies were reviewed and deemed acceptable to establish a bridge between the Applicant's product and reference products (refer to the biopharmaceutics reviews by Dr. Hughes dated 9/11/2014 and 10/14/2014).

This memo summarizes the review of the proposed labeling changes for ABC/3TC TOS US Prescribing Information (USPI).

Summary of Proposed Labeling Revisions and Recommendations:

Revisions related to clinical pharmacology were incorporated into Sections 2, 7, 8, and 12; given the establishment of a bridge through the demonstration of comparable exposures of lamivudine and abacavir between the Applicant's product and the reference products, corresponding clinical pharmacology information from Sections 2, 7, 8, and 12 of ZIAGEN and EPIVIR USPIs has been integrated into the USPI of the Applicant's product. Additionally, a paragraph detailing the results of the rBA study, the pivotal data supporting the bridge, have been included in Section 12.3.

Reference ID: 5298766

The information deviates from the USPIs of ZIAGEN and EPIVIR, and the rationale for supporting such deviation is described below.

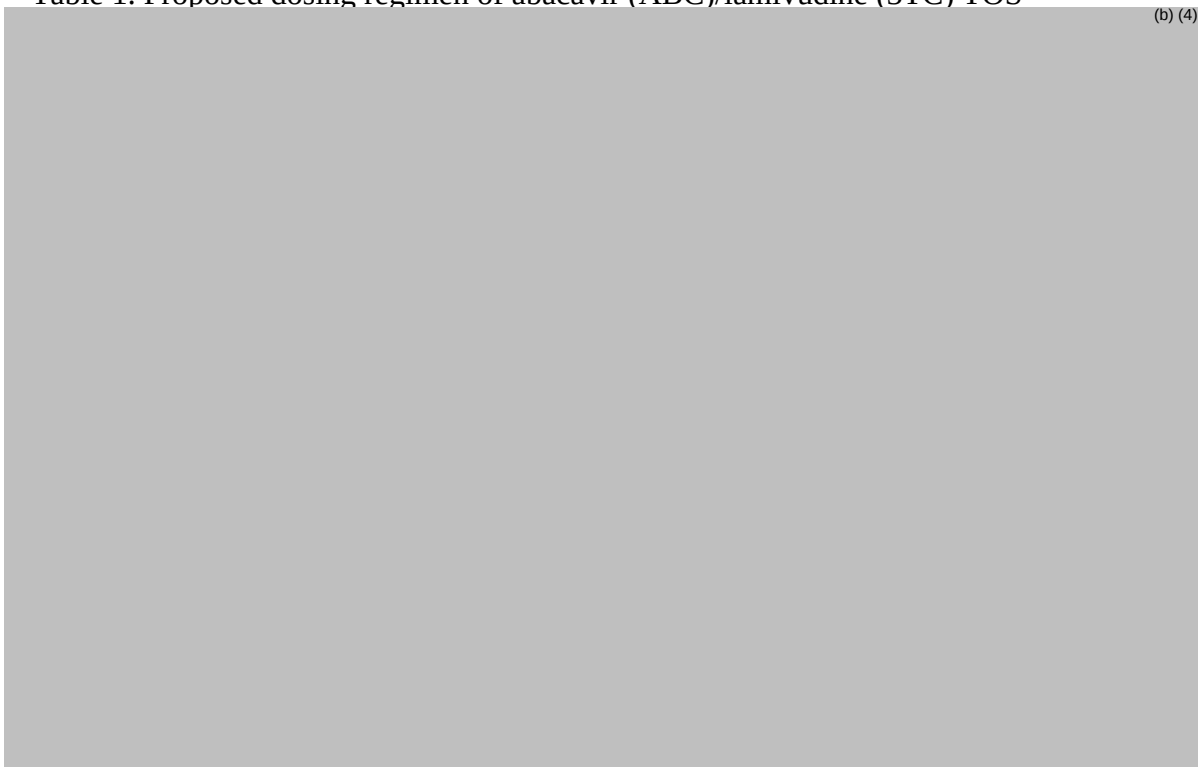
Dosing regimen

As summarized in Table 1, the proposed dosing regimen closely mirrors the currently approved dosing regimen of ZIAGEN oral solution, 16 mg/kg/day. The maximum deviation from the approved regimen and the proposed one is less than 20%. The difference isn't deemed clinically significant, considering the established exposure-response relationship of abacavir and supported by safety, PK, and efficacy data from various pediatric trials employing diverse formulations and dosing regimens of abacavir.

For lamivudine, the proposed dosing regimen closely mirrors the previously approved dosing regimen of EPIVIR oral solution, 8 mg/kg/day. While the current EPIVIR dosing is at 10 mg/kg/day, the primary purpose of the dosage increase (from 8 mg/kg/day to 10 mg/kg/day) was to manage a drug-excipient interaction between lamivudine and sorbitol in ZIAGEN solution. Further details are available in the EPIVIR USPI and Choi S, *et al.* Clin Pharmacol Ther. 2018;104(5):785-787 (PMID: 30084119). Since this product (ABC/3TC TOS) won't be co-administered with ZIAGEN, adopting the dosing regimen based on the previously approved regimen of EPIVIR is acceptable. Also, as this is a fixed dose combination product, a dose increase of lamivudine without a dose increase of abacavir is not feasible.

Table 1. Proposed dosing regimen of abacavir (ABC)/lamivudine (3TC) TOS

(b) (4)



Renal impairment

The proposed labeling related to renal impairment, not recommending in patients with creatinine clearance less than 30 mL per minute (instead of creatinine clearance less than 50 mL per minute as specified in EPIVIR USPI), is supported by published literature (Karam M et al. To dose-adjust or not to dose-adjust: lamivudine dose in kidney impairment. AIDS. 2021;35(8):1201-1208. Available at: https://pubmed.ncbi.nlm.nih.gov/34076616). Along with available extensive safety data from various trials and post-marketing experience with lamivudine, the review team agrees to this change. This also aligns with the approved dosing regimen in fixed-dose combination products containing lamivudine, such as TRIUMEQ (b) (4)

Food effects

Our recommended language regarding food effects in Section 12.3, *"Food is unlikely to have a clinically meaningful effect on systemic exposures of abacavir and lamivudine following the administration of abacavir and lamivudine tablets for oral suspension"*, is based on the fact that the Applicant did not conduct a standalone food effect study. Instead, the two rBA studies were conducted under fasted and fed (high fat) conditions. The results support the use of ABC/3TC TOS in alignment with the dosing instruction of the reference products with respect to food (i.e., administration without regard to food).

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/s/

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