OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	NDA 21652 S-19
Submission Date	11/20/14
PDUFA Goal Date	9/20/2015
Name	Epzicom ®
Clinical Pharmacology Reviewer	Su-Young Choi, Pharm.D., Ph.D
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D
OCP Division	Division of Clinical Pharmacology IV
OND Division	Division of Antiviral Products (DAVP)
Applicant	GSK
Formulation/Strength	A fixed dose combination tablet containing lamivudine (300 mg) and abacavir (600mg)
Indication	Treatment of HIV-1
Dosage and Administration	The recommended oral dose of Epzicom is one tablet daily in combination with other antiretroviral agents.

Executive Summary

Epzicom® is a fixed-dose combination (FDC) tablet containing 600 mg abacavir (ABC) and 300 mg lamivudine (3TC), two nucleoside reverse transcriptase inhibitors (NRTIs) approved for the treatment of HIV-1 infection in combination with other antiretroviral agents. The original approval of Epzicom® was based on a relative bioavailability study demonstrating comparable exposures between Epzicom® and single entity products (Ziagen® and Epivir®). It is currently approved in adults only and the product is not recommended for use in patients younger than 18 years of age. At the time of approval, the following PREA PMR was issued.

PMR 612-1

Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages 3 month to 17 years.

The purpose of this supplemental NDA is to extend once-daily administration of Epzicom® to pediatric patients weighing ≥ 25 kg and fulfill the PREA PMR. In addition, the applicant requested a waiver conducting studies in pediatric subjects weighing less than 25 kg, stating that weight/age-appropriate fixed-dose combination (FDC) formulations would not represent a meaningful benefit over existing therapies for this population of pediatric patients in the US and would not likely be used by a substantial number of US patients.

The proposed pediatric dosing regimen is supported by one pivotal clinical trial, ARROW **(A**nti**R**etroviral **R**esearch f**O**r **W**atoto; Study COL105677). ARROW was a 5-year randomized, multicenter trial which evaluated multiple aspects of clinical management of HIV-1 infection in pediatric patients. HIV-1

infected, treatment-naïve subjects aged 3 months to 17 years were enrolled and treated with a first line regimen containing ABC and 3TC, dosed twice daily according to WHO recommendations. Subjects on anti-retroviral therapy for at least 36 weeks were eligible for participating in Randomization 3, a fully powered comparison of once-daily versus twice-daily dosing of ABC and 3TC for the evaluation of efficacy and safety outcomes. The primary efficacy endpoint of ARROW Randomization 3 was viral load at 48 weeks after randomization to once-daily or twice-daily dosing of ABC and 3TC. Once daily dosing of 3TC and ABC has been demonstrated to be non-inferior to twice-daily dosing. The review team concluded that the study results support the use of the once-daily regimen of 3TC and ABC in pediatric patients aged 3 months and above. For pediatric patients weighing 25 kg and above, the adult doses of ABC and 3TC (600 mg and 300 mg, respectively) were approved.

As single entity products were approved for once daily use in pediatric patients, the applicant submitted this efficacy supplement to support once daily dosing regimen of Epzicom® in pediatric subjects weighing 25 kg and above. In the ARROW Randomization 3, 101 subjects received at least one dose of Epzicom® during the clinical trial.

Recommendations
The Office of Clinical Pharmacology has reviewed the submission and the applicant's proposed labeling. The review team agrees that the ARROW study results support once daily administration of Epzicom ® in pediatric patients weighing 25 kg and above.

Post-Marketing Requirements (PMR)
None

Summary of Important Clinical Pharmacology Findings
The ARROW study was previously reviewed to support the once-daily regimen of single entity products in pediatric patients. No additional study was submitted to support the pediatric dosing regimen of Epzicom ®. Refer to clinical pharmacology review submitted on 02/13/2015 under NDA 20977 S-027, 20978 S-031, 20564 S-033 and 20596 S-032.

Labeling Recommendations
The applicant's proposed language and the clinical pharmacology reviewer's recommendation is shown below. Labeling recommendations were under discussion at the time of this review and therefore the applicant and FDA have not come to an agreement on the language.

12.3 Pharmacokinetics

Pediatric patients

Applicant's proposal	Reviewer's recommendation
(b) (4)	*Pediatric Patients: Abacavir and Lamivudine:* The pharmacokinetic profiles of abacavir and lamivudine following administration of

(b) (4)	EPZICOM in pediatric subjects weighing 25 kg and above is limited. The dosing recommendations in this population are based on the safety and efficacy established in a controlled trial conducted with the combination of EPIVIR and ZIAGEN. Refer to the EPIVIR and ZIAGEN USPI for pharmacokinetic information on the individual products in pediatric patients. [*see Dosage and Administration (2.2), Adverse Reactions (6.1), and Clinical Studies (14.2)]*.

Reviewer comments

While the applicant's proposal is based on the single entity products' USPI (Epivir and Ziagen), some parts of this paragraph are not relevant to Epzicom®. The proposed labeling language (b) (4)

dosing regimens.

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/s/

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08/13/2015

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08/14/2015