CLINICAL PHARMACOLOGY REVIEW

NDA	21,752
SDN	960
Receipt Date	May 13, 2015
Submission Type	Pediatric efficacy supplement (S-47)
Drug Name	Truvada (emtricitabine and tenofovir disoproxil fumarate)
Indication	Treatment of HIV-1
Dosing Regimen	Take one tablet (300 mg tenofovir disoproxil fumarate/200 mg emtricitabine)
	once daily orally with or without food
Primary Reviewer	Su-Young Choi, Pharm.D., Ph.D
Team Leader	Shirley Seo, Ph.D

1.1 Executive Summary

TRUVADA is a fixed dose combination tablet product containing 200 mg emtricitabine (FTC) and 300 mg tenofovir disoproxil fumarate (TDF or tenofovir DF) that is approved for the treatment of HIV-1 in adults and adolescent patients. The applicant submitted a pediatric efficacy supplement to support the use of three Truvada reduced-strength tablets in pediatric patients weighing at least 17 kg and (b) (4)

Table 1. Proposed dosing regimens for pediatric patients by the applicant

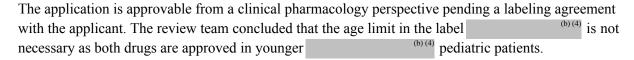
Body Weight (Kg)	Dosing of TRUVADA (FTC/TDF mg)
17 to < 22	One 100/150 mg tablet once daily
22 to < 28	One 133/200 mg tablet once daily
28 to < 35	One 167/250 mg tablet once daily

No clinical trial was conducted to support the approval. The individual components of TRUVADA, tenofovir disoproxil fumarate (VIREAD®) and emtricitabine (EMTRIVA®), have been approved for use in pediatric patients at least 2 years old (VIREAD®) or from birth (EMTRIVA®). The applicant is seeking approval based on 1) established safety, efficacy, and pharmacokinetics in pediatric patients for the individual components and 2) relative bioavailability between EMTRIVA, VIREAD, and TRUVADA full strength tablets. In addition, no trial was conducted to determine the pharmacokinetics of reduced strength tablets; the applicant stated that the reduced strength tablets are proportionally identical to the approved full strength tablets and requested a biowaiver.

The applicant also stated that this submission fulfills the following PMR.

PMR 2883-1: Deferred pediatric assessment under PREA for Truvada for the treatment of HIV-1 infection in pediatric subjects from ages 6 to less than 12 years, weighing at least 17 kg.

1.2 Recommendations



1.3 Summary of Important Findings

No new clinical data have been submitted to support the indication.

2. Question-Based Review

1. Are the tenofovir and emtricitabine exposures resulting from the administration of TRUVADA reduced strength tablets predicted to be comparable to those observed following the administration of the individual products in pediatric patients?

Tenofovir

Yes, the proposed dosing regimens of TRUVADA are identical to previously approved dosing regimens of VIREAD in pediatric patients.

Table 2. TDF doses and weight bands for VIREAD reduced strength tablets and TRUVADA reduced strength tablets

TDF doses in VIREAD reduced strength		TDF doses in TRUVADA reduced strength	
tablets		tablets	
TDF (mg)	Weight bands	TDF (mg)/FTC (mg)	Weight bands
150 mg	17 to < 22 kg	150 mg / 100 mg	17 to < 22 kg
200 mg	22 to < 28 kg	200 mg / 133 mg	22 to < 28 kg
250 mg	28 to < 35 kg	250 mg / 167 mg	28 to < 35 kg
300 mg	35 kg and above	300 mg / 200 mg	35 kg and above
(full strength)		(full strength)	

Emtricitabine (FTC)

Yes, predicted FTC exposures following the administration of TRUVADA reduced strength tablets are comparable to those observed following the administration of EMTRIVA solutions or capsules in pediatric patients.

It should be noted that EMTRIVA solutions and TRUVADA tablets are not bioequivalent, thus nominal mg/kg doses are not the same. In study FTC-110 (NDA 21,896 original NDA application), following the administration of EMTRIVA capsule, AUC_{inf} values were 24% higher compared to EMTRIVA oral solution. TRUVADA full strength tablets and EMTRIVA capsules are bioequivalent (Study GS-US-104-172, submitted in original NDA 21,752, TRUVADA). Therefore, a correction factor of 1.24 should be applied to compare doses for EMTRIVA oral solution to EMTRIVA capsule or TRUVADA tablets. When this correction factor is applied, 6 mg/kg of EMTRIVA oral solution is equivalent to 4.8 mg/kg of solid dosage forms (EMTRIVA capsule or TRUVADA tablets).

As shown in Table 3, FTC mg/kg doses in TRUVADA reduced strength tablets range from 4.6 mg/kg to 6.1 mg/kg. These are largely comparable with the approved dose of EMTRIVA solution, 4.8 mg/kg. Some pediatric patients may receive a slightly higher dose of EMTRIVA (up to 6.0 mg/kg) depending on their weight. This is acceptable based on the known favorable safety profile of EMTRIVA and the fact that patients will gain weight as they grow and their mg/kg doses will be gradually go down to 4.8 mg/kg. Observed and predicted FTC AUC values in pediatric and adult patients are summarized in Table 4.

Table 3. FTC doses and weight bands in pediatric patients for EMTRIVA oral solutions and TRUVADA reduced strength tablets

Approved FTC dose in	FTC doses in TRUVADA reduced strength tablet		
pediatric patients			
6 mg/kg with EMTRIVA	TDF (mg)/FTC (mg)	Weight bands	FTC mg/kg dose
solution (equivalent to 4.8	150 mg/ 100 mg	17 to < 22 kg	4.5 to 5.9 mg/kg
mg/kg TRUVADA	200 mg/ 133 mg	22 to < 28 kg	4.8 to 6.0 mg/kg
reduced strength tablet)	250 mg/ 167 mg	28 to < 35 kg	4.8 to 6.0 mg/kg
	300 mg/ 200 mg	35 kg and above	Adult dose
	(full strength, adult dose)		

Table 4. Observed and predicted FTC exposures in pediatric patients

Population	Formulation	FTC AUC _{tau} (µg·hr/mL)
		Geometric mean \pm SD
Adults	EMTRIVA Capsule	10.0 ± 3.1
13 to 17 years old (n=27)	EMTRIVA Capsule	12.6 ± 5.4
7 to 12 years old (n=17)	EMTRIVA Capsule and solution	12.6 ± 3.5
7 to 12 years old (n=7)	EMTRIVA solution	10.9 ± 4.0
25 months to 6 years old (n=19)	EMTRIVA solution	9.0 ± 3.0
3 months to 24 months (n=14)	EMTRIVA solution	8.7 ± 3.2
At 6.0 mg/kg (highest proposed FTC dose) At 4.5 mg/kg (lowest proposed FTC dose)	TRUVADA reduced strength tablet	Predicted* 13.9 ± 5.1 10.5 ± 4.0

Data source: EMTRIVA USPI, clinical pharmacology review for EMTRIVA solution approval, reviewer's guide for Truvada low-strength tablets (NDA 21,752 SDN 960)

3. Proposed Labeling Changes

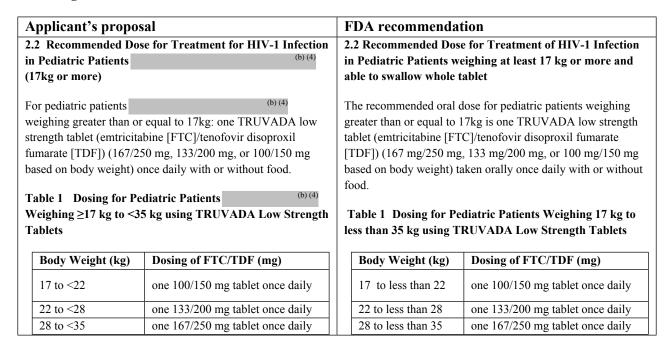
The following section highlights labeling recommendations by the Office of Clinical Pharmacology and Division of Antiviral Products. Labeling negotiation was ongoing at the time this review was finalized.

^{• *}Predicted based on observed AUC in pediatric populations for each weight band and applying the correction factor for the differences in relative bioavailability between Emtriva solution and Truvada tablets.

1. Indication

Applicant's proposal	FDA recommendation
TRUVADA®, a combination of EMTRIVA® and VIREAD®, is indicated in combination with other antiretroviral agents (b) (4)	TRUVADA®, a combination of EMTRIVA® and VIREAD®, is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease
for the treatment of HIV-1 infection in adults and pediatric patients (b) (4).	inhibitors) for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 17 kg.

2. Dosage and administration



8. Specific populations Pediatrics

Applicant's proposal	FDA recommendation
TRUVADA should only be administered	No pediatric clinical trial was conducted to evaluate the safety and efficacy of
to HIV-1 infected pediatric patients (b) (4)	TRUVADA. Data from previously conducted trials with the individual drug
with body weight greater	products, Emtriva and Viread, were relied upon to support dosing
than or equal to 17 kg. Because it is a	recommendations for TRUVADA. For additional information, please consult the
fixed-dose combination tablet, TRUVADA	prescribing information for Emtriva and Viread.
cannot be adjusted for patients (b) (4)	
weight.	TRUVADA should only be administered to HIV-1 infected pediatric patients with
	body weight greater than or equal to 17 kg and who are able to swallow whole
	tablet. Because it is a fixed-dose combination tablet, TRUVADA cannot be
	adjusted for patients of lower age and weight. TRUVADA has not been evaluated
	for use in pediatric patients weighing less than 17 kg.

12.3 Pharmacokinetics Pediatric Patients

