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

The application is approvable from a clinical pharmacology perspective pending a labeling agreement with the applicant. The review team concluded that the age limit in the label (b) (4) is not necessary as both drugs are approved in younger (b) (4) pediatric patients.

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 tablets		TDF doses in TRUVADA reduced strength 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 (full strength)	35 kg and above	**300 mg**/ 200 mg (full strength)	35 kg and above

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

Table 4. Observed and predicted FTC exposures in pediatric patients

Population	**Formulation**	**FTC AUC_{tau} (µg·hr/mL) Geometric mean ± 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) 7 to 12 years old (n=7)	EMTRIVA Capsule and solution EMTRIVA solution	12.6 ± 3.5 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)
- *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.

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.

1. Indication

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

2. Dosage and administration

Applicant's proposal	FDA recommendation
2.2 Recommended Dose for Treatment for HIV-1 Infection in Pediatric Patients (b) (4) (17kg or more) For pediatric patients (b) (4) weighing greater than or equal to 17kg: one TRUVADA low strength tablet (emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF]) (167/250 mg, 133/200 mg, or 100/150 mg based on body weight) once daily with or without food. **Table 1 Dosing for Pediatric Patients (b) (4) Weighing ≥17 kg to <35 kg using TRUVADA Low Strength Tablets**	**2.2 Recommended Dose for Treatment of HIV-1 Infection in Pediatric Patients weighing at least 17 kg or more and able to swallow whole tablet** The recommended oral dose for pediatric patients weighing greater than or equal to 17kg is one TRUVADA low strength tablet (emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF]) (167 mg/250 mg, 133 mg/200 mg, or 100 mg/150 mg based on body weight) taken orally once daily with or without food. **Table 1 Dosing for Pediatric Patients Weighing 17 kg to less than 35 kg using TRUVADA Low Strength Tablets**

Body Weight (kg)	Dosing of 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

Body Weight (kg)	Dosing of FTC/TDF (mg)
17 to less than 22	one 100/150 mg tablet once daily
22 to less than 28	one 133/200 mg tablet once daily
28 to less than 35	one 167/250 mg tablet once daily

8. Specific populations

Pediatrics

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

Applicant's proposal	FDA recommendation
TRUVADA should not be administered to HIV-1 infected pediatric patients (b) (4) weighing less than 17 kg (b) (4) *Emtricitabine*: (b) (4) *Tenofovir Disoproxil Fumarate*: (b) (4)	The pharmacokinetic data for tenofovir and emtricitabine following administration of TRUVADA in pediatric subjects weighing 17 kg and above are not available. The dosing recommendations of TRUVADA in this population are based on the dosing recommendations of EMTRIVA and VIREAD in this population. Refer to the EMTRIVA and VIREAD USPI for pharmacokinetic information on the individual products in pediatric patients. TRUVADA should not be administered to HIV-1 infected pediatric patients weighing less than 17 kg (less than 37 lb).

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02/03/2016

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