CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21752 (960)
Priority or Standard	Standard
Submit Date(s)	May 13, 2015
Received Date(s)	May 13, 2015
PDUFA Goal Date	February 5, 2016
Division / Office	Division of Anti-Viral Products/ Office of Antimicrobial Products
Reviewer Name(s)	Andres, Alarcon M.D.
Review Completion Date	January 28, 2016
Established Name	Emtricitabine/tenofovir disoproxil fumarate tablets
Trade Name	Truvada
Therapeutic Class	Nucleoside reverse transcriptase inhibitor, Nucleotide reverse transcriptase inhibitor
Applicant	Gilead
Formulation(s)	Fixed-dose combination regimen containing emtricitabine/tenofovir disoproxil fumarate
Dosing Regimen	One tablet taken once daily with food
Indication(s)	Treatment of HIV-1 Infection
Intended Population(s)	HIV-1 infected treatment naïve patient (b) (4) [redacted]

1 Recommendation/Risk-Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends the approval of this supplemental NDA, submitted on May 13, 2015 for Truvada low-strength tablets for the treatment of HIV infection in combination with other ARVs in pediatric patients weighing at least 17 kg and able to swallow tablets.

Tenofovir (Viread, TDF) and emtricitabine (Emtriva, FTC) are approved for treatment of HIV infection in pediatric patients. Truvada (TVD), a low-strength FDC product containing tenofovir and emtricitabine will allow for alternative dosing form.

The sponsor did not conduct a pediatric trial to evaluate the pharmacokinetics (PK), safety, tolerability, and efficacy of the proposed Truvada low-strength tablets, and no new safety or efficacy data were submitted. The predicted exposures for the weight-band low strength TVD dosing were calculated by the sponsor using existing PK data. Because safety, PK and efficacy are already available on the individual drug products in pediatric and adult patients, the review team was able to rely on previous findings from the original and supplemental NDAs to support the recommendations. As bioequivalency was established between full strength tablets, the Sponsor requested a biowaiver with the justification that in vitro dissolution tests are sufficient in lieu of healthy volunteer PK studies. After review of the in vitro dissolution data was completed, biowaiver was granted (refer to section 4.1 of the current review for further details).

While the proposed doses for the tenofovir part of the FDC are identical to the approved doses, the emtricitabine dosing recommendation with this low-strength FDC tablets ranges from 4.6 to 6.1 mg/kg, resulting in exposures that are generally comparable to those observed in adults (and pediatric patients). Of note, the approved mg/kg dosing recommendation for emtricitabine is 6mg/kg as Emtriva solutions (which is equivalent to 4.8 mg/kg as Truvada tablets)

The Sponsor proposes the following dosing recommendation:

Table 1: Proposed Truvada Weight Based Dosing for Low Strength Tablets

Body Weight	Tablets Once Daily
17 to <22	150 mg
22 to <28	200 mg
28 to <35	250 mg
[redacted]	(b) (4)

Source: Gilead, sNDA 021752 (Reviewer's Guide for Truvada Low-Strength Tablets), Submission: 05/05/2015

Based on the information reviewed, the review team agrees with the proposed recommendations for pediatric patients weighing at least 17 kg and able to swallow tablets. The new low-strength Truvada® tablets will be available in the strengths 100/150 mg, 133/200 mg and 167/250 mg.

1.2 Risk-Benefit Assessment

Very few, if any, FDC products are available for HIV infected pediatric patients, particularly for patients younger than 12 years of age. There are many benefits to having FDC products available. Most importantly, FDC products reduce pill-burden and thus increase the likelihood of adherence; adherence is an important factor in achieving HIV viral suppression. Early adherence is essential, as it contributes to a good initial response, which can determine long-term success or failure of the regimen[1]. A weight-band based FDC tablet administered once a day may also decrease patient-related dosing errors by avoiding the need for measuring liquid formulations. Truvada will provide an FDC product for 2 NRTIs, though tenofovir is not the preferred NRTI for pediatric patients. Nonetheless, the development of 2-NRTIs FDC product for US, HIV-infected pediatric patient is a step in the right direction.

Tenofovir
The recommended dose for Viread for the treatment of HIV in pediatric patients 2 to 12 years of age is 8mg/kg (up to a maximum of 300 mg) once daily administered as oral powder or tablets. Viread is available as tablets in 150, 200, 250 and 300 mg strengths for pediatric patients who weigh greater than or equal to 17 kg and who are able to swallow tablets.

Body Weight	Tablets Once Daily
17 to <22	150 mg
22 to <28	200 mg
28 to <35	250 mg
≥35	300 mg

Source: VIREAD USPI

The proposed dosing regimen for the TDF component of Truvada is (b) (4) already approved dosing recommendation with the individual drug product, tenofovir; thus no additional evidence is required to support approval of the proposed dosing for the TDF component of Truvada. Therefore, this review focuses on evaluating the data to support the proposed dosing regimen for the FTC component of Truvada.

Emtricitabine
The approved recommended dose of emtricitabine for pediatric patients is 6 mg per kg up to a maximum of 240 mg (24 mL) daily with the oral solution and 200mg capsule (adult dose) for patients weighing more than 33kg and able to swallow capsule.

The primary objectives when considering a weight-band dosing approach is to minimize under- or over- dosing while aiming to create a more convenient and simplified FDC dosing regimen. The proposed weight-band dosing are 150mg, 200mg and 250 mg for patients weighing 17 to < 22kg, 23 to <28kg, and 28 to <35kg, respectively.

One potential risk associated with the proposed dosing with Truvada is that most weight categories will have higher dose (thus exposure) for emtricitabine compared to the approved

dosing regimen. The highest dose-increase (thus exposure) is predicted to be in patients weighing 22 kg and 28 kg (Table 2). In both weight categories, the proposed doses would lead to a 20% higher dose than the currently approved dosing regimen. The predicted exposure (AUC) range for these weight categories based on age is 10.9 to 13.9 ug/ml*hr. In fact, this exposure range falls in the AUC ranges previously observed during pediatric clinical trials conducted with the individual drug product, FTC (i.e. 10.9±4.0 and 12.6 ±3.5 ug/ml*hr for the 22-<28kg and 28 -<35kg weight bands, respectively). Therefore, no significant changes are expected in the overall safety and tolerability profile of FTC when the FDC product is administer to pediatric patients.

Table 2: Predicted AUC Exposure for the proposed Weight-Band Dosing, Compared to the AUC from the Approved Dosing Regimen

Weight (kg)	Age; years (median) (range: 5% to 95%)	FTC dose (mg/kg)	Predicted AUC ranges (ug/ml*hr)	FTC AUC and ranges from the approved dose (ug/ml*hr)
17-< 22	~4.5 to ~6.5 (range: ~3 to ~8.5)	4.5 to 5.9	10.5 -13.4	9±3
22-<28	~7 to ~8.5 (range: ~4.5 to~11)	4.8 to 6.0	10.9 -13.9	10.9 ± 4.0
28-<35	~9 to ~10.5 (range: ~6 to ~13)	4.8 to 6.0	10.9 -13.7	12.6 ±3.5

*The predicted and approved AUC values were extrapolated for the current weight bands using historical AUC data based on age bands. Extrapolation from age bands to weight bands was done using the CDC growth chart for the 50th percentile weight for each of the corresponding age bands.

Source: Gilead, Submission sNDA 021752 (Reviewer's Guide for Truvada Low-Strength Tablets), 05/05/2015; Emtriva USPI; Gilead, NDA 021896, Submission: 02/28/2005

In summary, the anticipated increased dose (exposure) is unlikely to lead to new or increased frequency in safety signals because the increase is within an acceptable range. The two weights with the highest exposure increases are 22 kg and 28 kg (a 20% increase in dose). Such an increase is within a reasonable bound; for example, in renally-impaired adult patients, no dose adjustment is required for patients with CrCL 50-80 cc/min, despite an AUC increase by almost 60%. In addition, an increase in FTC exposure by approximately 20% may be observed during drug-drug interaction and no dose adjustment would be recommended. This is likely due to a wide therapeutic range for FTC where dose adjustments are not required due to anticipated safety reasons. Importantly, post-marketing safety reporting will be systematically reviewed by the Agency 18 months after the approval of the current supplement.

Conversely, some weight categories are expected to have lower-than approved doses. The weight categories of 21 kg, 27 kg, 34 kg, and 35 kg will experience minimal dose decreases. The lowest dose-decrease of 4% was calculated for the weight category 21 kg. Such a dose decrease is not expected to have a clinically significant impact on the exposure of FTC, and thus on the effectiveness of FTC. In fact, the predicted exposures still remain within the range of the observed AUC during the pediatric clinical trial with FTC single agent (see Table 2).

In summary, the favorable safety profile of emtricitabine in both adults and pediatric patients and exposure-response relationship for safety support the use of Truvada despite anticipated ~ 20% exposures.

2. Introduction/Background

With the introduction of highly active antiretroviral therapy (HAART) in 1996, morbidity and mortality secondary to AIDS in the developed world has decreased. Unfortunately the prevalence and incidence of HIV infection continues to be a global issue. Of concern is that the CDC estimates that young persons (age 13-29 years old) accounted for a significant portion of all the new HIV infections in the U.S. For example, in 2009, 39% of all new HIV infections in the US were among the 13 to 29 year old age group. From a global perspective, the UNAIDS, as of 2013, estimated that the number of people infected with HIV or AIDS is approximately 35 million, 3.2 million (9%) are children from birth to 14 years of age. Therefore, the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) encourage pharmaceutical industries to innovate new dosage forms (i.e. scored tables or low strength tablets) for use and accessibility in pediatric patients with HIV both domestically and abroad. The WHO published a document in 2007 "Preferred antiretroviral medicines for treating and preventing HIV infection in younger children"[6] that provides recommendations on FDC drug development.

Currently available HIV treatments includes six different antiretroviral drug classes- comprised of over 27 approved single agents (not including FDC products). The drug classes include: nucleoside reverse transcriptase inhibitors (NRTI), non- nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors, CCR5 receptor antagonists, and integrase strand transfer inhibitors (INSTI). Most approved ARVs have dosing recommendations approved in at least one subset of pediatric age range.

The purpose of the current supplemental NDA is to provide weight-band dosing in pediatric patients weighing at least 17 kg, and able to swallow pills; three new low-strength Truvada® tablets have been formulated --100/150 mg, 133/200 mg and 167/250 mg. The sponsor did not conduct a pediatric trial to evaluate the pharmacokinetics (PK), safety, tolerability, and efficacy of the proposed Truvada low strength tablets. The proposed dosing is supported by historical PK, safety and efficacy data from pediatric (and adult) trials with the individual drug agents – Emtriva (emtricitabine, FTC) and Viread (tenofovir, TDF). Using the existing PK data, the Sponsor performed modeling to predict exposures with the proposed low-strength tablets. The proposed weight-band dosing is expected to have generally similar PK profile compared to the individual drug products.

2.1 Regulatory Background

TVD was originally approved in 2004 as a FDC for adults in use in combination with other ARVs. In 2011 it was approved as an FDC for use in patients from 12 years of age to less than <18 years of age in combination with other ARVs. On November 26, 2014, the applicant was notified that pediatric studies with Truvada®, for patients aged 0 to 6 years would be waived as it was noted that development of Truvada® for use in this age group would not represent a meaningful therapeutic benefit over existing therapies nor was it likely to be used in a substantial number of pediatric patients. In this same communication to the applicant, a new pediatric assessment under PREA, was requested for pediatric patients between the ages of 6 to less than 12 years of age as follows:

PMR 2833-1: Deferred pediatric assessment under PREA for Truvada (emtricitabine/tenofovir disoproxil fumarate) for the treatment of HIV-1 infection in pediatric subjects from ages 6 years to less than 12 years, weighing at least 17 kg. **(**Final Report Submission: June 30, 2015)

The current sNDA submission is in response the PREA PMR study mentioned above. In the support of this sNDA, no new safety or efficacy data was submitted by the sponsor; the Sponsor and FDA relied on previous findings from the original NDA approval and subsequent studies conducted by Gilead in pediatric subjects. The PK, safety and antiviral activity of TDF and FTC have been previously evaluated in children from birth (FTC) and 2 years of age (TDF).

3. Ethics and Good Clinical Practice

No new clinical data was submitted; therefore, this section is not applicable.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 CMC

Please refer to Biopharmaceutics review by Dr. Gerlie Gieser and CMC review by Dr. Allan Fenselau for complete details. In summary, both reviewers recommend approval of this sNDA.

The three low strength tablets are produced using (b) (4) the FTC/TDF 200/300 mg formulation, and manufactured in a similar process, (b) (4) the 200/300 mg dosage strength.

Dr. Fenselau's review of chemistry, manufacturing, and controls concludes that the CMC information presented in the submission is sufficient to recommend APPROVAL. Biopharmaceutics evaluation of the dissolution test data concluded that the already approved dissolution method for the 200/300 mg FDC/TDF tablet can be used for the analysis of the three new lower strength TRUVADA tablets; in addition, the same dissolution acceptance criterion (i.e., USP criteria of Q= (b) (4) % at 30 minutes) as that used routinely for the dissolution testing of the already approved TRUVADA tablet can be used. Therefore, a biowaiver request to eliminate conducting BE studies for the new lower strength tablets can be granted, "based on evidence that these three new lower strength tablets are compositionally proportional to and have *in vitro* dissolution profiles that are considered not clinically different from that of the approved 200/300 mg tablet". Please refer to Dr. Gieser for further detail.

4.2 Pharmacology/Toxicology

No new data were submitted. Please refer to the original NDA review submitted on 3/11/204 and approved on 08/02/2015 under NDA 21-752.

4.3 Microbiology

No new data were submitted. Refer to original NDA review submitted on 3/11/204 and approved on 08/02/2015 under NDA 21-752.

4.5 Clinical Pharmacology

The proposed dosing recommendation with TVD in pediatric patients weighing at least 17 kg is summarized below. The dosing recommendations are further discussed below for the individual drug products within the FDC and are compared to the approved doses with the single drug products, tenofovir and emtricitabine.

Weight Band in kg	FTC/TDF Strength (mg)	FTC (mg/kg)	TDF (mg/kg)
17 to < 22 kg	100/150	4.6 to 5.9	6.8 to 8.8
22 to < 28 kg	133/200	4.8 to 6.1	7.2 to 9.1
28 to < 35 kg	167/250	4.8 to 6.0	7.2 to 8.9

Source: Gilead, Submission sNDA 021752 (Reviewer's Guide for Truvada Low-Strength Tablets), 05/05/2015

Tenofovir

Table 3: Values for Emtricitabine Pharmacokinetic Parameters at Steady-State by Age Group for All Patients Receiving Capsule and Solution Formulations

	HIV-1-infected Pediatric Subjects			
Age	**3–24 mo (N=14)**	**25 mo–6 yr (N=19)**	**7–12yr (N=17)**	**13–17 yr (N=27)**
Formulation Capsule (n) Oral Solution (n)	 0 14	 0 19	 1 0	 26 1
Dose (mg/kg)[a]	6.1 (5.5−6.8)	6.1 (5.6−6.7)	5.6 (3.1−6.6)	4.4 (1.8−7.0)
C_{max} (µg/mL)	1.9 ± 0.6	1.9 ± 0.7	2.7 ± 0.8	2.7 ± 0.9
AUC (µg·hr/mL)	8.7 ± 3.2	9.0 ± 3.0	12.6 ± 3.5	12.6 ± 5.4
$T_{1/2}$ (hr)	8.9 ± 3.2	11.3 ± 6.4	8.2 ± 3.2	8.9 ± 3.3

a. Mean (range)
Source: USPI Emtriva

Methods for reviewing the current sNDA: FTC is dose proportional, following linear pharmacokinetics, from 25 mg up to 200 mg; thus, dose predicts changes in exposure. Therefore, we evaluated the percent difference in dose between the approved FTC oral solution to the proposed weight-band low strength Truvada tablets to analyze the predicted exposures. First, the weight-band dosing was expanded to provide the individual weight category dosing in mg/kg. Next, to determine the Emtriva solution equivalent dose, the proposed dose in mg/kg/day was multiplied by a factor of 1.2 since the relative bioavailability of the FTC capsule versus oral solution is 124%. Thereafter, a direct dose difference was determined between the proposed Truvada weight-based tablets to the approved 6 mg/kg/day oral solution. The AUC range (ug/ml*hr) for each weight band category was predicted using modeling based on historical PK data from pediatric trials (as discussed above).

The table below summarizes the percent difference between the proposed Gilead weight based doses and the FDA approved emtricitabine oral formulation. Additionally, the predicted AUCs are described for each proposed weight-band based low-strength tablet formulation.
As discussed previously, because of the linear PK of emtricitabine, exposures can be calculated based on dosing information.

Table 4: Percent Differences in Daily Doses and Predicted AUC for each Weight Band Category: Proposed Gilead Doses vs. FDA Approved Emtriva oral solution

Weight (kg)	**Approved Emtriva solution dose (A)**	**Proposed Truvada dose (emtricitabine portion) (B)**	**Emtriva-solution equivalent dose (C)**	**Dose difference (%)**	**Predicted AUC Range (ug/ml * hr)**
	6mg/kg/day	Weight band *17-<22 (100mg/day) *22- <28 (133mg/day) *28- <35 (167mg/day)	C=1.2xB (mg/kg/day)	C vs. A	
17	102 mg/day	5.9 mg/kg/day	7.08 mg/kg/day	↑18%	10.5-13.4
18	108 mg/day	5.6 mg/kg/day	6.72 mg/kg/day	↑12%	
19	114 mg/day	5.3 mg/ kg/day	6.36 mg/kg/day	↑6%	
20	120mg/day	5 mg/ kg/day	6.00mg/kg/day	0%	
21	126 mg/day	4.8 mg/ kg/day	5.76 mg/kg/day	↓4%	
22	132 mg/day	6.0 mg/ kg/day	7.2 mg/kg/day	↑20%	10.9-13.9
23	138 mg/day	5.8 mg/ kg/day	6.96 mg/kg/day	↑16%	
24	144 mg/day	5.5 mg/ kg/day	6.6 mg/kg/day	↑10%	
25	150 mg/day	5.3 mg/ kg/day	6.36 mg/kg/day	↑6%	
26	156 mg/day	5.1 mg/ kg/day	6.12 mg/kg/day	↑2%	
27	162 mg/day	4.9 mg/ kg/day	5.88 mg/kg/day	↓2%	
28	168 mg/day	6.0 mg/ kg/day	7.2 mg/kg/day	↑20%	10.9-13.7
29	174 mg/day	5.8 mg/kg/day	6.96 mg/kg/day	↑16%	
30	180 mg/day	5.6 mg/ kg/day	6.72 mg/kg/day	↑12%	
31	186 mg/day	5.4 mg/ kg/day	6.48 mg/kg/day	↑8%	
32	192 mg/day	5.2 mg/ kg/day	6.24 mg/kg/day	↑4%	
33	198 mg/day	5.1 mg/ kg/day	6.12 mg/kg/day	↑2%	
34	204 mg/day	4.9 mg/kg/day	5.88mg/kg/day	↓2%	
35	210 mg/day	4.8 mg/kg/day	5.76mg/kg/day	↓4%	

Table 5 and 6 describes the observed FTC AUC values and predicted AUC values based on dosing or proposed dosing; Table 5 highlights exposure based on age while Table 6 summarizes exposure based on approximate age plus weight (Table 5).

The lowest dose decrease that would result from the proposed dosing regimen is 4% (for the 22 kg, and 35 kg child) and the highest dose increase is 20% (for the 22 kg, and 28 kg child). The FTC predicted AUC range following Truvada reduced strength tablet administration is 10.5-13.9 ug/ml*hr. The established adult FTC AUC is 10.0 ±3.1 ug/ml*hr, thus achieving the goal of having pediatric dosing with similar concentrations to adults. Additionally, the predicted FTC AUC is similar to the FTC AUC in the pediatric FTC trial. In NDA 021896, the observed AUC of 10.9 (±4.0) for solution only, and 12.6 (± 3.5) ug/ml * hr for all patients in the ages 7 years to 12 years old is in harmony with the FTC AUC predicted range of the current submission (10.5-13.9 ug/ml*hr).

Table 5: Observed FTC AUC Values in Various Populations from Pediatric Clinical Trials (FTC-203, FTC-202, FTC-203), and Adult Clinical Trial (FTC-106)

Population (Patients, years)	Formulation	FTC AUC (ug/ml *hr) Mean ± SD
Adults	Capsule	10.0 ± 3.1
13-17 yr (n=27)	Capsule	12.6 ± 5.4
7-12 years (n=17)	Capsule + Solution	12.6 ± 3.5
7-12 years (n=17)	Solution	11.0 ± 4.1
25 months to 6 years (n=19)	Solution	9.0 ± 3.0
3 month to 24 month (n=14	Solution	8.7 ± 3.2
17-35 kg	Truvada Reduced Strength Tablets	Predicted at 4.5 mg/kg 10.5 ± 4.0 at 6.0 mg/kg 13.9 ± 5.1

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

Table 6: Predicted AUC Exposure for the proposed Weight-Band Dosing, Compared to the AUC from the Approved Dosing Regimen

Weight (kg)	Age; years (median) (range: 5% to 95%)	FTC dose (mg/kg)	Predicted AUC ranges (ug/ml*hr)	FTC AUC and ranges from the approved dose (ug/ml*hr)
17 -<22	~4.5 to ~6.5 (range: ~3 to ~8.5)	4.8 to 5.9	10.5 -13.4	9±3
22-<28	~7 to ~8.5 (range: ~4.5 to~11)	4.9 to 6.0	10.9 -13.9	10.9 ± 4.0
28-<35	~9 to ~10.5 (range: ~6 to ~13)	4.9 to 6.0	10.9 -13.7	12.6 ±3.5

Source: Gilead, Submission sNDA 021752 (Reviewer's Guide for Truvada Low-Strength Tablets), 05/05/2015; Emtriva USPI; Gilead, Submission NDA 021896, 02/28/2005

5. Source of Clinical Data

No new clinical trials were conducted with Truvada. The data from the individual drug products, Emtriva and Viread were referenced to support the dosing recommendation for Truvada in pediatric patients weighing at least 17kg. For details on the clinical trials, refer to NDAs 021896 and 021356 and the USPI respectively for Emtriva and Viread.

The goal of the current sNDA submission is to demonstrate that the proposed dosing regimens are similar to the approved regimens in children.

Emtriva and Viread were approved for use in pediatric patients on the bases of establishment of comparable pharmacokinetic exposure in children and adults. In addition Emtriva and Viread were evaluated to assess their safety when administered in children. Supportive antiviral activity data were also collected.

The extrapolation of efficacy for antiretroviral drugs is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c)**.** DAVP agrees that HIV disease in pediatric subjects is similar but not identical to adult HIV disease, noting that the routes of transmissions may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age in contrast to adolescent and adult subjects in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric subjects. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in HIV-infected adults.

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two parameters, CD4 count and HIV RNA viral load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) and protease inhibitors (PIs) are shown to lower HIV RNA, improve CD4 counts (or percentage) and improve general clinical outcome in adult and pediatric subjects and treatment recommendations are very similar across all age groups [see US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents; Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection]. Available at http://aidsinfo.nih.gov/guidelines

6. Review of Efficacy

No additional discussion is necessary to support the proposed dosing for the TDF component of Truvada as the proposed dose is identical to the approved dose.

Extrapolation from previously conducted adult and pediatric trials was relied upon to support the proposed dosing regimen for the FTC component of Truvada. This is possible because of the established bioequivalency and because of dose proportionality and linear pharmacokinetics of FTC. The proposed Truvada doses for the varying weight bands among children weighing at least 17kg is generally similar but not identical to the mg/kg dosing regimens approved with the individual drug, FTC.

The lowest dose decrease of 4% was calculated for the weight category 21 kg. Such a decrease is not expected to have a meaningful impact on the efficacy of FTC, which is administered in combination with other ARVs. More importantly, the predicted AUC for a 21kg

child would fall within the acceptable range of the previously observed AUC exposures during pediatric clinical trials as observed in Table 7 below.

Table 7: Predicted AUC Exposure for the FTC Weight-Band Dosing of 17 kg to less than 22 kg, Compared to the AUC from the FTC Approved Dosing Regimen:

Weight (kg)	Age; years (median) (range: 5% to 95%)	FTC dose (mg/kg)	Predicted AUC ranges (ug/ml*hr)	FTC AUC and ranges from the approved dose (ug/ml*hr)
17 - < 22	~4.5 to ~6.5 (range: ~3 to ~8.5)	4.8 to 5.9	10.5 -13.4	9±3

Source: Gilead, Submission sNDA 021752 (Reviewer's Guide for Truvada Low-Strength Tablets), 05/05/2015; Emtriva USPI; Gilead, Submission NDA 021896, 02/28/2005

7. Review of Safety

As described above, the PK, safety and antiviral activity of TDF and FTC have been previously evaluated in children from birth in FTC, and as young as 2 years of age for TDF. Although, no clinical trials have been conducted with Truvada in children 6 years of age to less than 12 years of age, the safety profile can be extrapolated from the trials conducted with the individual drug products. For tenofovir, the proposed weight-band dosing regimen for the TDF component of Truvada is identical to the already approved dosing recommendation with the individual drug product, TDF. Thus, no further supportive evidence is required to approve the proposed dosing regimen.

The safety characteristics of emtricitabine have been well described in adults and children. Although children may receive a higher exposure to adults when compared on mg/kg basis, the safety profile of FTC in pediatrics remains similar to adults after 96 weeks of exposure to emtricitabine in FTC-203 and FTC-202. When combining the 169 pediatric patients in the three clinical trials (FTC-203, FTC-202, and FTC-211) and comparing the adverse event profile to the 580 adult patients in two pivotal studies (FTC-301A and FTC 303), the adverse profile is similar with the exception of higher adverse event rates in pediatrics for emesis, gastroenteritis, cough, and hyperpigmentation. Cough and gastroenteritis (which likely includes emesis) were likely reported more frequently in children as part of typical childhood illnesses. Emesis was reported as an adverse event in 23% of the pediatric population versus 9% in the adult population. Hyperpigmentation was reported in 32% of patients in pediatric studies versus 13% in adult studies. In comparison to adult trials, pediatric trials had no major differences in regards to serious adverse events; grade 3 adverse events, deaths, treatment discontinuations, treatment-related adverse events and laboratory toxicities.

As mentioned previously, the highest dose increase is anticipated to be approximately 20% in the 22 kg- and 28 kg- weight child. The anticipated increased dose is unlikely to lead to new or increased frequency in safety signals. FTC has a wide therapeutic range and dose adjustment would not be recommended for such dose/exposure increase. For example, an increase in FTC exposure by approximately 20% may be observed during a drug-drug interaction for which no dose adjustment would be recommended. Another example can be found in the renally-impaired adult patients. No dose adjustment is required for patients with CrCL 50-80 cc/min despite an AUC increase by almost 60%. With respect to the predicted exposures for the 22- and 28- kg weighing child, the exposures are expected to fall in the exposure range previously

observed during pediatric clinical trial. Finally, the anticipated dose increase for a child weighing 22 kg or 28 kg is temporary, averaging a 6-month period for those tracking medially on the CDC-growth chart.

Table 8: Predicted AUC Exposure for the FTC Weight-Band Dosing of 22 to less than 28 kg, Compared to the AUC from the FTC Approved Dosing Regimen

Weight (kg)	Age; years (median) (range: 5% to 95%)	FTC dose (mg/kg)	Predicted AUC ranges (ug/ml*hr)	FTC AUC and ranges from the approved dose (ug/ml*hr)
22-<28	~7 to ~8.5 (range: ~4.5 to~11)	4.9 to 6.0	10.9 -13.9	10.9 ± 4.0
28-<35	~9 to ~10.5 (range: ~6 to ~13)	4.9 to 6.0	10.9 -13.7	12.6 ±3.5

Source: Gilead, Submission sNDA 021752 (Reviewer's Guide for Truvada Low-Strength Tablets), 05/05/2015; Emtriva USPI; Gilead, Submission NDA 021896, 02/28/2005

8.0 Pediatric Review

This submission is in response to the Pediatric PMR. After approval of this submission, Truvada will be available and labeled for use in pediatric patients weighing at least 17kg and who are able to swallow tablets. No additional pediatric trials are required for Truvada to establish dosing recommendations.

9.0 Postmarketing Experience

Postmarketing adverse reactions have not been identified for Emtriva; however, adverse reactions have been identified for Viread, as described in section 6.3 of the postmarketing experience for Truvada label, and includes the following: immune system disorders: allergic reactions, angioedema; metabolism and nutrition disorders: lactic acidosis, hypokalemia, hypophosphatemia; thoracic, and mediastinal disorders: including dyspnea; gastrointestinal disorders: pancreatitis, increased amylase, and abdominal pain; hepatobiliary disorders: hepatic steatosis, hepatitis, and transaminitis (elevated AST, ALT, GGT); skin and subcutaneous tissue disorders: rash; musculoskeletal and connective disorders: rhabdomyolysis, osteomalacia, muscular weakness, myopathy; renal and urinary disorders: acute renal failure, acute tubular necrosis, fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus, renal insufficiency, increased creatine, proteinuria, polyuria.

Eighteen months post approval of the current sNDA, a post marketing safety analyses will be conducted for the pediatric population by the Agency, led by the Office of Surveillance and Epidemiology (OSE), Office of Pediatric Therapeutics (OPT), Division of Pediatric and Maternal Health (DPMH), and supported by DAVP.

10. Other Outstanding Issues

There are no current outstanding issues with the current supplemental NDA submission.

11. Labeling

The following is the proposed dosing regimen by Gilead. Based on the historical pharmacokinetic and safety analysis in pediatric and adults, the proposed recommendations are acceptable.

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

Source: Gilead, Submission sNDA 021752 (Reviewer's Guide for Truvada Low-Strength Tablets), 05/05/2015

12. Appendix

12.1 Literature Review and References (See below)

12.2 Financial Disclosure
N/A

12.3 Advisory Committee Meeting
N/A

References

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/s/

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02/05/2016
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