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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	021-752; Amendment
Supporting document/s:	S-30 # 760
Applicant's letter date:	July 10, 2012
CDER stamp date:	July 11, 2012
Product:	TRUVADA (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg)
Indication:	Pre-exposure prophylaxis of HIV-1 infection (PrEP).
Applicant:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
Review Division:	DAVP
Reviewer:	Pritam Verma, Ph.D.
Supervisor/Team Leader:	Hanan Ghantous, Ph.D.
Division Director:	Debra Birnkrant, M.D.
Project Manager:	Katherine Schumann, M.S.

Disclaimer

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Introduction

Truvada, an approved drug, is a fixed-dose combination of the nucleoside analogue emtricitabine 200 mg and the acyclic nucleotide analogue tenofovir disoproxil fumarate 300 mg. It is indicated for the treatment of HIV-1 infected adults over 18 years of age, in combination with other antiretroviral products. The sponsor has submitted an Efficacy Supplement in support of the use of Truvada for pre-exposure prophylaxis of HIV-1 infection (PrEP) to reduce the risk of acquiring HIV-1.

TOXICOLOGY

LABEL

Pregnancy section of Truvada label has been amended as follows:

8.1 Pregnancy

Pregnancy Category B

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to TRUVADA, an Antiretroviral Pregnancy Registry (APR) has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Risk Summary

TRUVADA has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that TRUVADA does not increase the risk of major birth defects overall compared to the background rate. There are, however, no adequate and well-controlled trials in pregnant women. Because the studies in humans cannot rule out the possibility of harm, TRUVADA should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking TRUVADA for a PrEP indication, careful consideration should be given to whether use of TRUVADA should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy.

Clinical Considerations

As of July 2011, the APR has received prospective reports of 764 and 1219 exposures to emtricitabine- and tenofovir- containing regimens, respectively in the first trimester, 321 and 455 exposures, respectively, in second trimester, and 140 and 257 exposures, respectively, in the third trimester. Birth defects occurred in 18 of 764 (2.4%) live births for emtricitabine-containing regimens and 27 of 1219 (2.2%) live births for tenofovir-containing regimens (first trimester exposure) and 10 of 461 (2.2%) live births for emtricitabine-containing regimens and 15 of 714 (2.1%) live births for tenofovir-containing regimens (second/third trimester exposure). Among pregnant women in the U.S. reference population, the background rate of birth defects is 2.7%. There was no association between emtricitabine or tenofovir and overall birth defects observed in the APR.

Animal Data

Emtricitabine:

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

Tenofovir Disoproxil Fumarate:

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

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/s/

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07/16/2012

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07/16/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	021-752
Supporting document/s:	S-30 # 704
Applicant's letter date:	December 14, 2011
CDER stamp date:	December 15, 2011
Product:	TRUVADA (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg)
Indication:	Pre-exposure prophylaxis of HIV-1 infection (PrEP).
Applicant:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
Review Division:	DAVP
Reviewer:	Pritam Verma, Ph.D.
Supervisor/Team Leader:	Hanan Ghantous, Ph.D.
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Introduction

Truvada, an approved drug, is a fixed-dose combination of the nucleoside analogue emtricitabine 200 mg and the acyclic nucleotide analogue tenofovir disoproxil fumarate 300 mg. It is indicated for the treatment of HIV-1 infected adults over 18 years of age, in combination with other antiretroviral products. The sponsor has submitted an Efficacy Supplement in support of the use of Truvada for pre-exposure prophylaxis of HIV-1 infection (PrEP) to reduce the risk of acquiring HIV-1.

TOXICOLOGY

Truvada (FTC/TDF): Correlation of Nonclinical and Clinical Findings: Based on findings in the nonclinical studies, the key safety points for consideration related to FTC or TDF for both the treatment of HIV-1 infection in adult males and females and for the prevention of HIV-1 acquisition in adult men who have sex with men and who are at high risk for HIV infection include: (1) potential for bone loss upon chronic dosing due to TDF, (2) potential for renal toxicity due to TDF, especially related to use with other drugs that have been shown to cause renal toxicity and in patients with renal impairment, (3) use in patients with hepatic impairment, (4) potential for mitochondrial toxicity, and (5) potential for carcinogenicity.

In regard to these possible concerns, the following should be considered:

1. A reduction in bone mineral density has been observed in nonclinical and clinical studies with TDF. A statement has been included in the section on "Animal Toxicology and/or Pharmacology" to highlight that nonclinical studies of TDF revealed effects on bone and that the mechanisms are not completely understood.

2. As nephrotoxicity has been seen nonclinically and there have been post-marketing reports of renal toxicity with TDF, warnings regarding these reports and appropriate monitoring guidance is included in the proposed Prescribing Information.

3. There was no substantive hepatotoxicity identified in the nonclinical studies with either FTC or TDF. The pharmacokinetics of FTC has not been studied in patients with hepatic impairment, but because FTC is not metabolized by liver enzymes, the impact of liver impairment should be limited.

4. FTC and TDF are considered to have a low potential for mitochondrial toxicity, as demonstrated by enzyme and cell analyses *in vitro* and by markers of mitochondrial injury *in vivo*. Ongoing assessment of clinical safety data from company-sponsored clinical studies and post-marketing experience has shown that the risk of mitochondrial toxicity with FTC and TDF is low.

5. In carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice or rats. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in

female mice, liver adenomas were increased at exposures 16 times those in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

The toxicities of potential concern outlined above are adequately highlighted and addressed in the current Prescribing Information for the individual agents and the proposed Prescribing Information for the combination tablet. The proposed dose of the combination tablet for the new indication is the same as the approved dose (200 mg/day FTC/300 mg/day TDF) for HIV-1 infection in adults and is justified from a safety perspective based on the nonclinical data presented in this dossier.

Overall Conclusions: The pharmacokinetic and toxicological profiles of FTC and TDF/TFV are well-characterized in multiple animal species and the findings are applicable for consideration of the use of these agents in combination. Data from controlled clinical studies and extensive post-marketing experience of combination regimens of FTC and TDF demonstrates acceptable tolerability and safety profiles to support use in the adult population.

Toxicology studies submitted:

In Silico Toxicology Prediction for [redacted] (b) (4) (TX-162-2008)
A 14-day Study of Non-degraded and Degraded TDF/FTC by Oral Gavage in Rats (TX-164-2005)

Toxicology studies reviewed:

In Silico Toxicology Prediction for [redacted] (b) (4) (TX-162-2008). The purpose of this evaluation was to predict the potential genotoxicity of isomers of [redacted] (b) (4) degradation products of emtricitabine (FTC) containing products (but not Emtriva). The [redacted] (b) (4) were evaluated *in silico* for potential toxicity using two predictive toxicity software programs, DEREK for Windows (Lhasa Ltd) and FDA Model Applier (Leadscope).

DEREK Evaluation: No structural matches to [redacted] (b) (4) were identified in the DEREK knowledge base; therefore, *in silico* results indicate no prediction for carcinogenicity, mutagenicity, chromosome damage, or genotoxicity (other genotoxic activity, e.g. Unscheduled DNA Synthesis).

Leadscope Model Applier Evaluation: The genetic toxicity suite of the Leadscope Model Applier software resulted in positive predictions in 11 of the 29 computational models (range 0.502-0.955) for various assay types of in vitro and in vivo genotoxicity models for [redacted] (b) (4). The substructures or structural features represented by example compounds of each structural feature contributing to the positive genetic toxicity predictions in the Leadscope Model Applier were evaluated in detail. The positive predictions were primarily based on the occurrence of structural features of primary or secondary [redacted] (b) (4)

(b) (4). Due to the absence of structural features in (b) (4) that contributed to the positive predictions, the likelihood of a true positive is low.

Related Structural Considerations: Neither (b) (4) in vitro tests have demonstrated that FTC and (b) (4) are nongenotoxic.

Based on the weight of evidence, (b) (4) do not appear to have the potential to be genotoxic.

A 14-day Study of Non-degraded and Degraded TDF/FTC by Oral Gavage in Rats (TX-164-2005). The objective of this study was to determine the potential toxicity of degraded TDF/FTC when compared to non-degraded material given by daily oral gavage for 14 days to rats. In addition, the toxicokinetic characteristics of non-degraded and degraded TDF/FTC were compared. Male Crl:CD(SD) rats were assigned to seven groups (10 animals/group for main study; 3 animals for the control toxicokinetic study; and nine animals/group for the FTC/TDF-treated toxicokinetic study). Each group received dose preparations containing the vehicle control article [Suspension vehicle (carboxymethylcellulose, 0.5% (w/v), benzyl alcohol, 0.9% (w/v), polysorbate 20, 0.5% (w/v) and sterile water for injection, USP] or non-degraded or degraded TDF/FTC at 30/20, 100/67 or 300/200 mg/kg/day. There were no preterminal deaths, or non-degraded or degraded TDF/FTC-related clinical observations or changes in body weights, food consumption, coagulation or urinalysis parameters. There were no gross necropsy findings or changes in organ weights.

Administration of non-degraded or degraded TDF/FTC at 300/200 mg/kg/day was associated with minimal, non-adverse, decreases in red cell mass parameters hemoglobin and hematocrit. These changes were associated with minimal, non-adverse, red cell indices (MCV, MCH and RDW) changes indicating microcytosis. Differences observed in animals given non-degraded TDF/FTC or degraded TDF/FTC regarding red cell mass parameters or indices were considered to be of comparable magnitude and had no microscopic correlates. Non-adverse, minimal, dose level-dependent increases in ALT activity were observed in rats given non-degraded TDF/FTC at ≥100/67 mg/kg/day and degraded TDF/FTC at 300/200 mg/kg/day. Increased ALT activity was not associated with histological findings.

In the duodenum, there was minimal cryptal epithelium hyperplasia and minimal single cell necrosis with both degraded and non-degraded formulations of TDF/FTC at 300/200 mg/kg/day.

Toxicokinetics: results are shown in Tables 1 &2. The $T_{1/2}$ of FTC was estimated to be between 3.14 and 6.73 hours, and was similar between 30/20 and 100/67 mg/kg/day dose levels but was higher at 300/200 mg/kg/day, for both non-degraded and degraded. The $T_{1/2}$ of tenofovir was estimated to be between 6.95 and 9.36 hours, and was similar across all dose levels. The exposure of FTC and tenofovir was similar on Days 1 and 14 for dose levels of 30/20 and 100/67 mg/kg/day but slight increases were observed for the 300/200 mg/kg/day dose level. The exposure of FTC was generally less than dose proportional on Day 1 but was generally dose

proportional on Day 14 within the dose range tested. The exposure of tenofovir was generally less than dose proportional on both Days 1 and 14 within the dose range tested. The exposure of FTC and tenofovir was similar for both non-degraded and degraded material for each dose group.

Table 1. Toxicokinetic Parameters of FTC in Male Sprague-Dawley Rat Plasma Following Oral Gavage Administration of Non-Degraded or Degraded TDF/FTC

Day 1

Group No.	Dose Level (mg/kg/day)	Test Article Specification	Tmax (h)	Cmax (ng/mL)	SE	AUC(0-t) (ng•h/mL)	SE	AUC(0-inf) (ng•h/mL)	T1/2 (h)
2	30/20*	Non-degraded	1	3213	248	14670	1194	14874	3.68
3	100/67*	Non-degraded	1	5540	484	40141	1796	40490	3.49
4	300/200*	Non-degraded	1	9160	340	88730	6818	RNR	RNR
5	30/20*	Degraded	1	2500	37.9	12360	1159	12432	3.14
6	100/67*	Degraded	1	5077	497	35656	2552	36133	3.84
7	300/200*	Degraded	1	9290	370	86880	8145	96374	6.73

Day 14

Group No.	Dose Level (mg/kg/day)	Test Article Specification	Tmax (h)	Cmax (ng/mL)	SE	AUC(0-t) (ng•h/mL)	SE	AUC(0-inf) (ng•h/mL)	T1/2 (h)
2	30/20*	Non-degraded	1	3087	212	17911	2370	18095	3.55
3	100/67*	Non-degraded	1	6057	766	55302	6069	55704	3.29
4	300/200*	Non-degraded	4	15767	1697	163317	12446	167010	4.24
5	30/20*	Degraded	1	2520	376	13446	678	13561	3.38
6	100/67*	Degraded	1	5340	147	39705	3034	40259	3.87
7	300/200*	Degraded	4	13367	1445	132591	11564	136376	4.46

* Dose level is expressed as mg/kg/day of non-degraded or degraded TDF/FTC.
RNR Result not reported because the AUC(0-inf) was extrapolated by more than 20% or Rsq was <0.800.

Table 2. Toxicokinetic Parameters of Tenofovir in Male Sprague-Dawley Rat Plasma Following Oral Gavage Administration of Non-Degraded or Degraded TDF/FTC

Day 1

Group No.	Dose Level (mg/kg/day)	Test Article Specification	Tmax (h)	Cmax (ng/mL)	SE	AUC(0-t) (ng•h/mL)	SE	AUC(0-inf) (ng•h/mL)	T1/2 (h)
2	30/20*	Non-degraded	0.5	450	85.5	2402	141	2702	8.51
3	100/67*	Non-degraded	0.5	1237	260	5187	293	5786	8.36
4	300/200*	Non-degraded	0.5	1360	290	8887	660	RNR	RNR
5	30/20*	Degraded	0.5	461	62.8	2194	180	2395	7.43
6	100/67*	Degraded	0.5	1103	43.3	4402	255	5060	9.36
7	300/200*	Degraded	0.5	1377	118	9095	867	RNR	RNR

Day 14

Group No.	Dose Level (mg/kg/day)	Test Article Specification	Tmax (h)	Cmax (ng/mL)	SE	AUC(0-t) (ng•h/mL)	SE	AUC(0-inf) (ng•h/mL)	T1/2 (h)
2	30/20*	Non-degraded	0.5	462	50.8	3056	173	3365	7.67
3	100/67*	Non-degraded	0.5	1317	252	6891	535	7544	6.95
4	300/200*	Non-degraded	1	1400	153	13625	1115	15953	8.85
5	30/20*	Degraded	0.5	538	16.4	2488	130	2767	8.19
6	100/67*	Degraded	0.5	828	18.4	5573	133	6279	8.08
7	300/200*	Degraded	1	1211	207	13695	1447	15426	7.59

* Dose level is expressed as mg/kg/day of non-degraded or degraded TDF/FTC.
RNR Result not reported because the AUC(0-inf) was extrapolated by more than 20% or Rsq was <0.800.

Administration of non-degraded or degraded TDF/FTC by once daily oral gavage was well tolerated in rats at levels of 30/20, 100/67 and 300/200 mg/kg/day. Minimal, non-adverse changes in red cell mass parameters and red cell indices were noted in animals given non-degraded or degraded TDF/FTC at 300/200 mg/kg/day. Non-adverse, minimal, dose level-dependent increases in ALT activity were observed in rats given non-degraded TDF/FTC at ≥100/67 mg/kg/day and degraded TDF/FTC at 300/200 mg/kg/day. Microscopically, minimal cryptal epithelium hyperplasia and minimal single cell necrosis were observed in the duodenum of animals given degraded or non-degraded formulations of TDF/FTC at 300/200 mg/kg/day

NOAEL was considered to be 300/200 mg/kg/day for both non-degraded and degraded TDF/FTC. No differences in toxicity were observed between non-degraded and degraded material. At all dose levels tested, exposure of FTC and tenofovir was similar for both non-degraded and degraded material.

LABEL

The Truvada label was rearranged; no changes were made to the label. Below is the final version of the label:

8.1 Pregnancy

Pregnancy Category B

(b) (4)

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to TRUVADA, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Animal Data

Emtricitabine:

The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with emtricitabine in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

Tenofovir Disoproxil Fumarate:

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Emtricitabine: In long-term oral carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose).

Tenofovir Disoproxil Fumarate: Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Mutagenesis

Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, tenofovir disoproxil fumarate was negative when administered to male mice.

Impairment of Fertility

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

13.2 Animal Toxicology and/or Pharmacology

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Approvability: There are no nonclinical pharmacology and toxicology issues which would preclude the approval of this NDA.

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/s/

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05/10/2012

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