CENTER FOR DRUG EVALUATION AND RESEARCH

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:	208,215
Supporting document/s:	0000
Applicant's letter date:	04/07/2015
CDER stamp date:	04/07/2015
Product:	Emtricitabine/Tenofovir Alafenamide FDC
Indication:	Treatment of HIV-1 infection
Applicant:	Gilead Sciences Inc.
Review Division:	Division of Antiviral Products
Reviewer:	Claudia Wrzesinski, DVM, Ph.D.
Supervisor/Team Leader:	Hanan Ghantous, Ph.D., DABT
Division Director:	Debra B. Birnkrant, M.D.
Project Manager:	Myong-Joo Patricia Hong, M.S.

Disclaimer

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Reference ID: 3855297

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1 Executive Summary

1.1 Introduction

This application is being submitted in support of a new drug application (NDA) for a fixed dose combination (FDC), named Descovy, that contains the nucleoside reverse transcriptase inhibitor (NRTI) Emtricitabine (FTC, F, Emtriva), and the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir alafenamide (TAF, GS-7340) fumarate. Descovy is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and children 12 years of age and older. Gilead Sciences has coformulated TAF with FTC into an FDC tablet available in 2 dosage strengths, F/TAF (200/25 mg) (b) (4) [redacted] . (b) (4) [redacted] (b) (4) F/TAF 200/25 mg FDC will be given without boosting agents. [redacted] F/TAF 200/25 mg without a boosting agent showed similar systemic TAF exposures.

A comprehensive review of the non-clinical studies for TAF has been performed under NDA 207,561 (Genvoya, E/C/F/TAF FDC) and for FTC under NDA 21,500. Nonclinical studies on impurities of FTC and TAF for Descovy are reviewed in Appendix A.

1.2 Brief Discussion of Nonclinical Findings

Ample nonclinical safety information is available on FTC and TAF as well as combination toxicity studies (FTC+TDF) from previous NDAs. The two drugs exhibit different patterns of main target organ toxicity; therefore, administration of TAF in combination with FTC is unlikely to exacerbate known toxicities of the individual agents. The only notable effect of FTC was a minor anemia identified at dose levels constituting large clinical multiples. The main target organs for TAF were kidney and bone in rats and dogs, as well as eye (posterior uveitis) in dogs. Bone and kidney toxicities have also been seen with another Tenofovir (TFV)-prodrug (TDF) and are believed to be due to TFV exposure while uveitis has been seen after TAF administration, but not after TDF administration. Further, chronic administration of TAF showed reversible PR prolongation and a reversible reduction in heart rate associated with mild QT prolongation associated with decreased serum T3 levels in dogs.

1.3 Recommendations

1.3.1 Approvability

It is recommended that Descovy be approved.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

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1.3.3 Labeling

FTC and TAF exposures were bioequivalent when comparing F/TAF (200/25 mg, Descovy) versus E/C/F/TAF (Genvoya) [redacted] (b) (4) following single-dose administration to healthy subjects. Therefore, exposure margins in the Descovy label will be calculated using human AUCs from Genvoya.

The Reviewer's recommendation for the nonclinical portion of the drug product label is included below:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DESCOVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry 1-800-258-4263.

Risk Summary

There are no adequate and well-controlled studies with Descovy in pregnant women. Because animal reproduction studies are not always predictive of human response, Descovy should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal studies, no adverse developmental effects were observed when the components of Descovy were administered separately during the period of organogenesis at exposures up to 60 and 108 times (mice and rabbits, respectively; Emtricitabine, see Data), and equal to and 53 times (rats and rabbits, respectively; Tenofovir alafenamide, see Data) the exposure at the recommended daily dose of Descovy. Likewise, no adverse developmental effects were seen when Emtricitabine was administered to mice through lactation at exposures up to 60, the exposure at the recommended daily dose of Descovy.

The background risk of major birth defects and miscarriage for the indicated population(s) is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Emtricitabine: Emtricitabine (FTC) was administered orally to pregnant mice (250, 500, or 1000 mg/kg/day) and rabbits (100, 300, or 1000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). The incidence of fetal variations and malformations was not increased in embryo-fetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the recommended daily dose. In a pre/postnatal development study with FTC, where mice were administered doses up to 1000 mg/kg/day through lactation, no significant adverse

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effects directly related to drug were noted in the offspring.

Tenofovir Alafenamide: Embryonic fetal development studies performed in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus due to TAF. The embryo-fetal NOAELs in rats and rabbits occurred at TAF exposures similar to and 53 times higher than, respectively, the exposure in humans at the recommended daily dose. TAF is rapidly converted to tenofovir; the observed tenofovir exposure in rats and rabbits were 59 and 93 times higher than human tenofovir exposures at the recommended daily doses, respectively.

8.2 Lactation

Risk Summary
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.
Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving Descovy.

Data
Emtricitabine: Samples of breast milk obtained from 5 HIV-1-infected mothers show that FTC is secreted in human milk. Breastfeeding infants whose mothers are being treated with Emtricitabine may be at risk for developing viral resistance to FTC. Other FTC associated risks in infants breastfed by mothers being treated with FTC are unknown.

Tenofovir Alafenamide: Lactation studies have not been conducted to assess the presence of Tenofovir Alafenamide in human milk, the effects of Tenofovir Alafenamide on the breastfed infant, or the effects of Tenofovir Alafenamide on milk production. Tenofovir Alafenamide is present in rat milk. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether TAF is excreted in human milk.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine

In long-term carcinogenicity studies of Emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (23 times the human systemic exposure at the therapeutic dose of 200 mg per day) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the therapeutic dose).

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

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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.

Tenofovir Alafenamide

Since tenofovir alafenamide (TAF) is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice is observed after TAF administration compared to tenofovir disoproxil fumarate (TDF) administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of TDF for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 5 times (rat) those observed in humans after daily administration of TAF. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300 mg TDF) and 167 times (10 mg or 20 mg TAF in Descovy) that in humans. In rats, the study was negative for carcinogenic findings.

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

There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose equivalent to 155 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through day seven of gestation.

13.2 Animal Toxicology and/or Pharmacology

Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three and nine month administration of tenofovir alafenamide, reversibility was seen after a three month recovery period. At the NOAEL for eye toxicity, the systemic exposure in dogs was 5 (tenofovir alafenamide) and 15 (tenofovir) times the exposure seen in humans at the recommended daily dosage.

2 Drug Information

2.1 Drug

Emtricitabine (FTC)

CAS Registry Number: 143491-57-0

Generic Name: Emtricitabine

Code Name: [redacted] (b) (4) FTC

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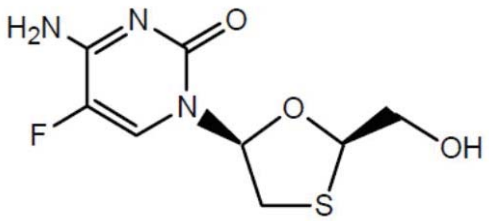
Chemical Name: 5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine

Molecular Formula/Molecular Weight: $C_8H_{10}FN_3O_3$/247.24

Structure or Biochemical Description:

Figure 1: FTC Structure



Pharmacologic Class: NRTI (Nucleoside Reverse Transcriptase Inhibitor)

Tenofovir Alafenamide (TAF)

CAS Registry Number: 379270-37-8

Generic Name: Tenofovir alafenamide fumarate

Code Name: GS-7340-03, TAF

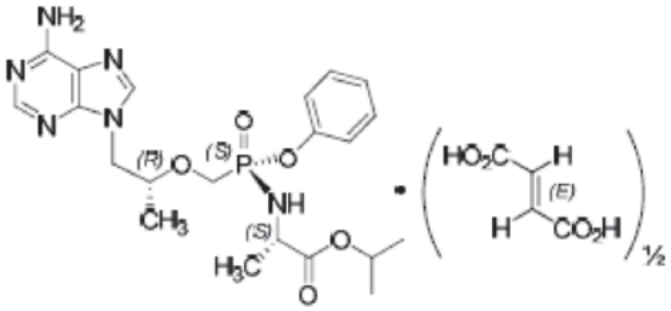
Chemical Name: Propan-2-yl *N*-[(*S*)-({[(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy) phosphoryl]-lalaninate,(2*E*)-but-2-enedioate (2:1)

Molecular Formula/Molecular Weight: (b) (4)

Structure or Biochemical Description:

Reference ID: 3855297

Figure 2: TAF Structure



Pharmacologic Class: NtRTI (Nucleotide reverse transcriptase inhibitors)

2.2 Relevant INDs, NDAs, BLAs and DMFs

This NDA is supported by right of reference to applicable sections of Gilead NDA 21,500, NDA 21,896 and Gilead IND 53,971 for FTC, Gilead NDA 207,561 and Gilead IND 63,737 for TAF as well as NDA 21,752 and IND 67,671 for Truvada and Gilead's IND 103,093 and NDA 203,100 for Stribild, Gilead's IND [redacted] (b) (4) and NDA 207,561 for Genvoya.

2.3 Drug Formulation

Emtricitabine/tenofovir alafenamide (F/TAF) FDC tablets are an immediate-release tablet dosage form containing either [redacted] (b) (4) 200 mg of FTC and 25 mg of TAF (F/TAF 200/25 mg tablets). Tablets are approximately 12.5 mm long and 6.4 mm wide. [redacted] (b) (4) the F/TAF 200/25 mg tablets are blue with "GSI" debossed on one side and "225" on the other side.

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Table 1: Quantitative Composition of FTC/TAF tablets *(excerpted from sponsor)*

Ingredient	(b) (4)	F/TAF 200/25 mg		Quality Standard	Function
		% w/w	mg/tablet		
Intragranular					
Emtricitabine[a]		57.14	200.0	In-house	Active Ingredient
Tenofovir Alafenamide Fumarate[a]		8.01	28.0[c]	In-house	Active Ingredient
Microcrystalline Cellulose[a]		25.34	88.7	NF, Ph. Eur.	Diluent/Filler
Croscarmellose Sodium		8.00	28.0	NF, Ph. Eur.	Disintegrant
Magnesium Stearate		0.75	2.625	NF, Ph. Eur.	Lubricant
Extragranular					
Magnesium Stearate		0.75	2.625	NF, Ph. Eur.	Lubricant
Total		100	350	--	--
Film-Coat					
(b) (4)				In-house	Film-coat
(b) (4) Blue (b) (4)		3.0	10.5	In-house	Film-coat
(b) (4)		--	--	USP, Ph. Eur.	Processing Aid

a The quantities of emtricitabine and tenofovir alafenamide fumarate drug substance (b) (4) (b) (4)

b (b) (4) of tenofovir alafenamide fumarate corresponds to (b) (4) of tenofovir alafenamide.

c of tenofovir alafenamide fumarate corresponds to 25 mg of tenofovir alafenamide.

d (b) (4)

e

f

2.4 Comments on Novel Excipients

No novel excipients are used to manufacture F/TAF tablets.

2.5 Comments on Impurities/Degradants of Concern

The proposed specifications are considered acceptable from a pharmacology/toxicology perspective. For more detail please refer to the review by Dr. Mark Powley.

2.6 Proposed Clinical Population and Dosing Regimen

The recommended dose of Descovy in adults and pediatric patients 12 years of age and older with body weight at least 35 kg is one tablet containing 200 mg FTC and 25 mg TAF taken orally once daily, with or without food. (b) (4)

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2.7 Regulatory Background

This application is being submitted in support of a NDA for a film-coated single tablet regimen that contains the active substances Emtricitabine (FTC), and Tenofovir Alafenamide Fumarate (TAF). All nonclinical information for the current NDA is cross-referenced to the original NDAs and INDs and no additional nonclinical toxicology information is included in the submission package. The F/TAF FDC tablets contains the same dosages of and FTC that is currently approved within Truvada (FTC/TDF), Stribild (E/C/F/TDF, STB) and Genvoya (E/C/F/TAF) for use in adults (200 mg of FTC). The F/TAF FDC tablet comes in (b) (4) different TAF dosages. (b) (4) F/TAF 200/25 mg FDC will be given without boosting agents. (b) (4) F/TAF 200/25 mg without a boosting agent showed similar systemic TAF exposures.

3 Studies Submitted

All nonclinical information for the current NDA is cross-referenced to the original NDAs and INDs and no additional nonclinical toxicology information is included in the submission package. Refer to applicable sections of NDA 21,500, NDA 21,896 and IND 53,971 for FTC; NDA 207,561 and IND 63,737 for TAF; NDA 21,752 and IND 67,671 for Truvada; IND 103,093 and NDA 203,100 for Stribild, IND (b) (4) and NDA 207,561 for Genvoya; NDA 21,356 and IND 52,849 for TDF (Viread); NDA 203,100 and IND 103,093 for STB (Stribild).

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/s/

CLAUDIA WRZESINSKI
12/03/2015

HANAN N GHANTOUS
12/03/2015

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 208-215

Supporting document/s:

Supporting Document	Sponsor Submission Date	CDER Received Date
1	4/07/15	4/07/15

Product: Emtricitabine/Tenofovir Alafenamide FDC

Indication: treatment of HIV-1 infection

Applicant: Gilead Sciences Inc.

Review Division: Division of Antiviral Products

Reviewer: Mark W. Powley, Ph.D.

Supervisor/Team Leader: Hanan Ghantous, Ph.D., DABT

Division Director: Debra B. Birnkrant, M.D.

Project Manager: Myong-Joo Patricia Hong, M.S.

Disclaimer

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Any information or data necessary for approval of NDA#208-215 that Gilead Sciences Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA#208-215.

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1 Executive Summary

1.1 Introduction

Gilead Science Inc. has submitted an NDA to support the fixed dose combination therapy of emtricitabine (FTC) and tenofovir alafenamide (TAF) for treating HIV-1 infection in adults and pediatric patients ≥ 12 years of age. The proposed dosing regimen includes 200 mg/day FTC + 25 mg TAF (unboosted 3rd agent) [redacted] (b) (4)

This review focuses on qualification of organic impurities, residual solvents, and elemental impurities. Regulatory decisions utilize recommendations from ICH M7 "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk", ICH Q3A(R2) "Impurities in New Drug Substances", ICH Q3B(R2) "Impurities in New Drug Products", ICH Q3C(R5) "Impurities: Guideline for Residual Solvents", and ICH Q3D "Guideline for Elemental Impurities".

Overall, proposed specifications are considered acceptable from a pharmacology/toxicology perspective.

2 Qualification of Emtricitabine Drug Substance

[redacted] (b) (4)

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/s/

MARK W POWLEY
12/01/2015

HANAN N GHANTOUS
12/02/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA/BLA Number: 208,215 **Applicant: Gilead** **Stamp Date:** April 7, 2015

Drug Name: Descovy **NDA Type: Original**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		Only summaries are submitted, TAF studies are under review of NDA 207-561, Emtricitabine has been already approved.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		Only summaries are submitted, TAF studies are under review of NDA 207-561, Emtricitabine has been already approved.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		Only summaries are submitted, TAF studies are under review of NDA 207-561, Emtricitabine has been already approved.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		Only summaries are submitted, TAF studies are under review of NDA 207-561, Emtricitabine has been already approved.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		Only summaries are submitted, TAF studies are under review of NDA 207-561, Emtricitabine has been already approved.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	x		Appropriateness of the content will be determined upon review and discussion at the labeling meeting.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		Evaluation of the sponsor's analyses is a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?	x		Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	x		Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes.

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Claudia Wrzesinski 05/18/2014

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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06/02/2015