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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: 208,464  
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Product: Vemlidy (Tenofovir Alafenamide)  
Indication: Treatment of HBV infection in adults  
Applicant: Gilead Sciences Inc.  
Review Division: Division of Antiviral Products  
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# 1 Executive Summary

## 1.1 Introduction

This application is being submitted in support of a new drug application (NDA) for tenofovir alafenamide (TAF, GS-7340) 25 mg tablets for the treatment of chronic hepatitis B (CHB) with the tradename Vemlidy. TAF is a phosphoramidate prodrug of tenofovir (TFV) that is under evaluation for the treatment of CHB and is approved as a component of the fixed-dose combination (FDC) product, Genvoya, Descovy and Odefsey for the treatment of HIV-1 infection. Tenofovir disoproxil fumarate (TDF) is another prodrug of TFV that is approved for the treatment of CHB and HIV-1 infection. Vemlidy is indicated for the treatment of CHB in adults. TAF 25 mg tablets are for oral administration and one tablet is given once daily, with (b) (4) food.

A comprehensive review of the non-clinical studies for TAF has been performed under NDA 207,561 (Genvoya, E/C/F/TAF FDC).

## 1.2 Brief Discussion of Nonclinical Findings

Ample nonclinical safety information is available for TAF from previous NDAs. 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 Vemlidy be approved.

### 1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

### 1.3.3 Labeling

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 VEMLIDY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

#### Risk Summary

There are no human data on the use of VEMLIDY in pregnant women to inform a drug-associated risks of adverse fetal developmental outcome. In animal studies, no adverse developmental effects were observed when tenofovir alafenamide was administered during the period of organogenesis at exposure equal to or 51 times (rats and rabbits, respectively) the tenofovir alafenamide exposure at the recommended daily dose of VEMLIDY, [see Data]. No adverse effects were observed in the offspring when TDF (tenofovir disoproxil fumarate) was administered through lactation at tenofovir exposures of approximately 12 times the exposure at the recommended daily dosage of VEMLIDY.

The background risk of major birth defects and miscarriage for the indicated population 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*

Embryonic fetal development studies performed in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. The embryo-fetal NOAELs (no observed adverse effect level) in rats and rabbits occurred at tenofovir alafenamide exposures similar to and 51 times higher than, respectively, the exposure in humans at the recommended daily dose. Tenofovir alafenamide is rapidly converted to tenofovir, the observed tenofovir exposure in rats and rabbits were 54 and 85 times higher than human tenofovir exposures at the recommended daily doses, respectively.

Tenofovir alafenamide was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at tenofovir alafenamide exposures approximately similar to (rats) and 51 (rabbits) times higher than the exposure in humans at the recommended daily dose of VEMLIDY. Tenofovir alafenamide is rapidly converted to tenofovir; the observed tenofovir exposures in rats and rabbits were 54 (rats) and 85 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Since tenofovir alafenamide is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after tenofovir alafenamide administration compared to TDF, another prodrug for tenofovir administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation

day 7 [and lactation day 20] at tenofovir exposures of approximately 12 [18] times higher than the exposures in humans at the recommended daily dose of VEMLIDY.

## 8.2 Lactation

### Risk Summary

It is not known whether VEMLIDY and its metabolites are present in human breast milk, affects human milk production, or have effects on the breastfed infant. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF [see Data]. It is not known if tenofovir alafenamide can be present in animal milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VEMLIDY and any potential adverse effects on the breastfed infant from VEMLIDY or from the underlying maternal condition.

### Data

#### *Animal Data*

Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11 [see Data (8.1)]. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Since tenofovir alafenamide is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after tenofovir alafenamide administration compared to tenofovir disoproxil fumarate administration, carcinogenicity studies were conducted only with tenofovir disoproxil fumarate. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate 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 tenofovir disoproxil fumarate for chronic hepatitis B. The tenofovir exposure in these studies was approximately 151 times (mice) and 50 times (rat) those observed in humans after administration of VEMLIDY treatment. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 151 times those observed after VEMLIDY administration 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 7 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 14 (tenofovir) times the exposure seen in humans at the recommended daily VEMLIDY dosage.

## Drug Information

### 2.1 Drug

**CAS Registry Number:** 379270-37-8

**Generic Name:** Tenofovir alafenamide fumarate

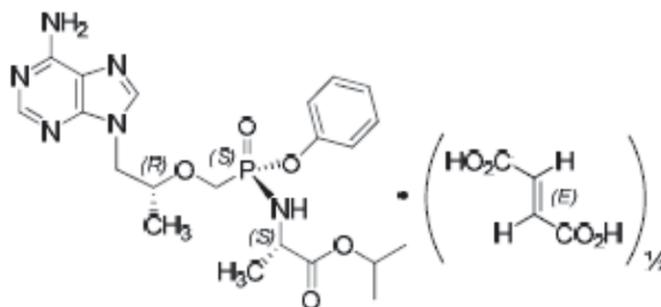
**Code Name:** GS-7340-03, TAF

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

**Molecular Formula/Molecular Weight:** C<sub>23</sub>H<sub>31</sub> O<sub>7</sub>N<sub>6</sub>P/534.50

**Structure or Biochemical Description:**

Figure 1: 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 IND 63,737 for TAF as well as Gilead’s IND 103,093 and NDA 203,100 for Stribild, Gilead’s (b) (4) NDA 21,356 for Viread, Gilead’s IND 111,077 and NDA 207,561 for Genvoya.

**2.3 Drug Formulation**

Tenofovir alafenamide (TAF) tablets are an immediate-release dosage form containing 25 mg of TAF as TAF fumarate. TAF tablets are yellow, round, film-coated tablets debossed with “GSI” on one side and “25” on the other side. The tablet is approximately 7.9 mm in diameter.

**Table 1: Quantitative Composition of TAF tablets**

Component	Quality Standard	Function	Quantity per Tablet (mg)	% w/w
Tenofovir Alafenamide Fumarate <sup>a</sup>	In-house	Active Ingredient	28 (b) (4)	(b) (4)
Lactose Monohydrate <sup>a</sup>	NF, Ph. Eur.			
Microcrystalline Cellulose	NF, Ph. Eur.			
Croscarmellose Sodium	NF, Ph. Eur.			
Magnesium Stearate	NF, Ph. Eur.			
Total Tablet Core Weight	---			
<b>Film Coat</b>				
(b) (4) Yellow (b) (4)	In-house			(b) (4)
(b) (4)	USP, Ph. Eur.	(b) (4)	---	---
a	(b) (4)			
b	28 (b) (4) mg of tenofovir alafenamide fumarate corresponds to 25 mg of tenofovir alafenamide free base.			
c	(b) (4) Yellow (b) (4) contains (b) (4) Polyvinyl Alcohol (USP, Ph. Eur.), (b) (4) Titanium Dioxide (USP, Ph. Eur.), (b) (4) PEG (NF, Ph. Eur.), (b) (4) Talc (USP, Ph. Eur.), and (b) (4) Iron Oxide Yellow (NF).			
d	(b) (4)			
e	(b) (4)			

**2.4 Comments on Novel Excipients**

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

**2.5 Comments on Impurities/Degradants of Concern**

Proposed TAF drug substance and drug product specifications are considered acceptable from a pharmacology/toxicology perspective. Detailed safety assessments for organic impurities, residual solvents, heavy metals, and degradants are described in NDA#207-561 and NDA#208-215.

## 2.6 Proposed Clinical Population and Dosing Regimen

Vemlidy is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease. The recommended dosage of Vemlidy is 25 mg (one tablet) taken orally once daily with food.

## 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 substance Tenofovir Alafenamide Fumarate (TAF). All toxicological 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 tablets contain the same dosages of TAF that is currently approved within Descovy (FTC/TAF) and Odefsey (FTC / RPF /TAF) for use in adults.

## 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 IND 63,737 for TAF as well as Gilead's IND 103,093 and NDA 203,100 for Stribild, Gilead's IND (b) (4)/52,849 and NDA 21,356 for Viread, Gilead's IND 111,077 and NDA 207,561 for Genvoya.

## 11 Integrated Summary and Safety Evaluation

**Table 2: Estimated safety margins of TAF based on AUCss when comparing animal NOAELs to human exposures**

Toxicity	Species	Study/Dose Duration	TAF NOAEL (mg/kg/day)	AUCss ( $\mu\text{g}\cdot\text{h}/\text{mL}$ ) NOAEL	Margin Relative to Human AUCss
				TFV/ TAF	TFV <sup>a</sup> /TAF <sup>b</sup>
Overall NOAEL	Rat	26 Weeks	25	3.8/NC	12/NA
	Dog	39 Weeks	2	1.2/0.08	4/0.4
	Monkey	4 Weeks	$\geq 30$	$\geq 5.9/1.0$	$>18/5$
Renal Toxicity	Rat	26 Weeks	25	3.8/NC	12/NA
	Dog	39 Weeks	2	1.2/0.08	4/0.4
	Monkey	4 Weeks	$\geq 30$	$\geq 5.9/1.0$	$>18/5$
Bone Mineral Loss	Rat	26 Weeks	25	3.8/NC	12/NA
	Dog	39 Weeks	2	1.2/0.08	4/0.4
	Monkey	4 Weeks	$\geq 30$	$\geq 5.9/1.0$	$>18/5$
Ocular toxicity	Dog	39 Weeks	6	4.45/1.03	14/5
Nasal Turbinate Toxicity	Mouse	13 Weeks	$<10$	$<0.213/\text{NC}$	$<1/\text{NA}$
Fertility <sup>c</sup>	Rat	Up to 10 weeks	160	NA	NA
Embryo fetal <sup>c</sup> Development	Rat	12 days	100	17.4/0.2	54/1
	Rabbit	14 days	100	27.3/11	85/51
Perinatal/postnatal <sup>c</sup>	Rat	27 days (Gestation day 7 to Lactation day 20)	Developmental NOAEL: 150 (TDF)	7.84 (GD7), 11.7(LD20)/NA	24 (GD7), 36 (LD20)/NA
			F1 NOAEL: 50	3.81(GD7), 5.88(LD20)/NA	12 (GD7), 18 (LD20)/NA

NA = not applicable; NC = insufficient data to calculate

a) Predicted safety margin for TFV human exposure is based on pooled PK data from TAF Phase 3 pivotal studies GS-US-320-0108 and GS-US-320-0110 where the mean TFV AUCss =  $0.322 \mu\text{g}\cdot\text{h}/\text{mL}$

b) Predicted safety margin for TAF human exposure is based on pooled PK data from TAF Phase 3 pivotal studies GS-US-320-0108 and GS-US-320-0110 where the mean TAF AUCss =  $0.216 \mu\text{g}\cdot\text{h}/\text{mL}$

c) The peri/postnatal study was conducted with TDF not TAF

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/s/  
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CLAUDIA WRZESINSKI  
10/07/2016

HANAN N GHANTOUS  
10/11/2016

I agree with Dr. Wrzesinski recommendation that Vemlidy be approved.