PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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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 phosphonamidate 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 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 exposure in rats and rabbits were 54 and 85 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 \( N-[(S)-{[(2R)-1-(6-amino-9H-purin-9-yl)propan-2-yl]-oxy\}}\)methyl)(phenoxy) phosphoryl]-lalaninate,\( (2E)\)-but-2-enedioate (2:1)

Molecular Formula/Molecular Weight: \( C_{23}H_{31}O_7N_6P/534.50 \)

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 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 “GST” 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

<table>
<thead>
<tr>
<th>Component</th>
<th>Quality Standard</th>
<th>Function</th>
<th>Quantity per Tablet (mg)</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir Alafenamide Fumarate</td>
<td>In-house</td>
<td>Active Ingredient</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>NF, Ph. Eur.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>NF, Ph. Eur.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>NF, Ph. Eur.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>NF, Ph. Eur.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Tablet Core Weight</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Film Coat:

- In-house
- USP, Ph. Eur.
- ---
- ---

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 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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Species</th>
<th>Study/Dose Duration</th>
<th>TAF NOAEL (mg/kg/day)</th>
<th>AUCss (μg·h/mL) NOAEL</th>
<th>Margin Relative to Human AUCss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TFV/TAF</td>
</tr>
<tr>
<td>Overall NOAEL</td>
<td>Rat</td>
<td>26 Weeks</td>
<td>25</td>
<td>3.8/NC</td>
<td>12/NA</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>39 Weeks</td>
<td>2</td>
<td>1.2/0.08</td>
<td>4/0.4</td>
</tr>
<tr>
<td></td>
<td>Monkey</td>
<td>4 Weeks</td>
<td>≥30</td>
<td>≥5.9/1.0</td>
<td>&gt;18/5</td>
</tr>
<tr>
<td>Renal Toxicity</td>
<td>Rat</td>
<td>26 Weeks</td>
<td>25</td>
<td>3.8/NC</td>
<td>12/NA</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>39 Weeks</td>
<td>2</td>
<td>1.2/0.08</td>
<td>4/0.4</td>
</tr>
<tr>
<td></td>
<td>Monkey</td>
<td>4 Weeks</td>
<td>≥30</td>
<td>≥5.9/1.0</td>
<td>&gt;18/5</td>
</tr>
<tr>
<td>Bone Mineral Loss</td>
<td>Rat</td>
<td>26 Weeks</td>
<td>25</td>
<td>3.8/NC</td>
<td>12/NA</td>
</tr>
<tr>
<td></td>
<td>Dog</td>
<td>39 Weeks</td>
<td>2</td>
<td>1.2/0.08</td>
<td>4/0.4</td>
</tr>
<tr>
<td></td>
<td>Monkey</td>
<td>4 Weeks</td>
<td>≥30</td>
<td>≥5.9/1.0</td>
<td>&gt;18/5</td>
</tr>
<tr>
<td>Ocular toxicity</td>
<td>Dog</td>
<td>39 Weeks</td>
<td>6</td>
<td>4.45/1.03</td>
<td>14/5</td>
</tr>
<tr>
<td>Nasal Turbinate Toxicity</td>
<td>Mouse</td>
<td>13 Weeks</td>
<td>&lt;10</td>
<td>&lt;0.213/NC</td>
<td>&lt;1/NA</td>
</tr>
<tr>
<td>Fertility(^c)</td>
<td>Rat</td>
<td>Up to 10 weeks</td>
<td>160</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Embryo fetal Development</td>
<td>Rat</td>
<td>12 days</td>
<td>100</td>
<td>17.4/0.2</td>
<td>54/1</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>14 days</td>
<td>100</td>
<td>27.3/11</td>
<td>85/51</td>
</tr>
<tr>
<td>Perinatal/postnatal(^c)</td>
<td>Rat</td>
<td>27 days (Gestation day 7 to Lactation day 20)</td>
<td>Developmental NOAEL: 150 (TDF)</td>
<td>7.84 (GD7), 11.7(LD20)/NA</td>
<td>24 (GD7), 36 (LD20)/NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F1 NOAEL: 50</td>
<td>3.81(GD7), 5.88(LD20)/NA</td>
</tr>
</tbody>
</table>

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 μ g·h/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 μ g·h/mL

c) The peri/postnatal study was conducted with TDF not TAF
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CLAUDIA WRZESINSKI
10/07/2016

HANAN N GHANTOUS
10/11/2016

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