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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 REVIEW AND EVALUATION

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Product: Emtricitabine/rilpivirine/tenofovir alafenamide fumarate fixed dose combination tablet, 200 mg FTC/25 mg RPV/ (b) (4) mg TAF
Indication: HIV-1 infection
Applicant: Gilead Sciences
Review Division: Division of Antiviral Products
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1 Executive Summary

1.1 Introduction

Gilead Science has submitted an NDA for ODEFSEY, a new combination drug product for HIV infection. The proposed fixed dose combination includes three approved drug products (emtricitabine (FTC)/rilpivirine (RPV)/tenofovir alafenamide (TAF) fixed-dose combination tablet, 200 mg FTC/25 mg RPV/ (b) (4) mg TAF). All nonclinical information is cross-referenced to the original NDAs and INDs cited below and no additional nonclinical toxicology information is included in the package.

1.2 Brief Discussion of Nonclinical Findings

Sufficient nonclinical safety information is available for FTC, RPV, and TAF individually, and in combination toxicity studies (FTC+TDF) from previous NDAs. The target organs of toxicity are different for the three drugs; therefore, administration of FTC, RPV and TAF in combination is unlikely to exacerbate known toxicities of the individual agents. The only notable effect of FTC was a minor anemia identified at dose levels associated with large clinical exposure multiples. The primary toxicity findings in nonclinical studies with RPV were adrenal effects, generally characterized by increased serum progesterone and decreased cortisol levels, observed in rats, dogs, Cynomolgus monkeys, and possibly mice. 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 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.

A comprehensive review of the non-clinical studies for TAF has been performed under NDA 207,561 (GENVOYA, E/C/F/TAF FDC), for RPV under NDA 202022 (EDURANT) and for FTC under NDA 21,500 (EMTRIVA). NDA 207,561 (GENVOYA, E/C/F/TAF FDC) also includes the comprehensive clinical safety evaluation of TAF.

1.3 Recommendations

1.3.1 Approvability

It is recommended that ODEFSEY be approved.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

FTC and TAF exposures were bioequivalent when comparing ODEFSEY (FTC/RPV/TAF; 200/25/25 mg) to GENVOYA (EVG/COBI/FTC/TAF; 150/150/200/10 mg) following single-dose administration to healthy subjects (N=95).

RPV exposures were bioequivalent when comparing ODEFSEY (FTC/RPV/TAF; 200/25/25 mg) to EDURANT (25 mg) following single-dose administration to healthy subjects (N=95),

Exposure margins in the ODEFSEY label will be calculated using human AUCs from GENVOYA and EDURANT.

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 ODEFSEY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry 1-800-258-4263.

Risk Summary

There are (b) (4) ODEFSEY (b) (4) human (b) (4) during pregnancy (b) (4). In animal studies, no adverse developmental effects were observed when the components of ODEFSEY were administered separately during the period of organogenesis at exposures up to 60 and 108 times (mice and rabbits, respectively; (b) (4) 15 and 70 times (rats and rabbits, respectively; (b) (4) and equal to and 53 times (rats and rabbits, respectively; (b) (4) the exposure at the recommended daily dose of ODEFSEY. Likewise, no adverse developmental effects were seen when (b) (4) was administered to mice and (b) (4) was administered to rats through lactation at exposures up to 60 and 63 times, respectively, the exposure at the recommended daily dose of ODEFSEY.

The background (b) (4) major birth defects (b) (4) miscarriage (b) (4) of (b) (4) In the U.S. general population, the estimated background (b) (4) of (b) (4) miscarriage in clinically recognized pregnancies (b) (4) 15-20%, (b) (4).

Data

Animal Data

Emtricitabine: (b) (4) (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). (b) (4) (b) (4) 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, (b) (4) mice were administered doses up to 1000 mg/kg/day through lactation, no significant adverse effects directly related to drug were (b) (4) in the offspring.

Rilpivirine: (b) (4) (RPV) was administered orally to pregnant rats (40, 120, or 400 mg/kg/day) and rabbits (5, 10, or 20 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 6 through 19, respectively). (b) (4) (b) (4) (b) (4) with RPV (b) (4) (b) (4) embryo-fetal (b) (4) (b) (4) 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily. In a pre/postnatal development study with RPV, where rats were administered up to 400 mg/kg/day through lactation, no significant adverse effects directly related to drug were noted in the offspring.

Tenofovir Alafenamide: (b) (4) (b) (4) embryo-fetal (b) (4) in rats and rabbits (b) (4) at TAF exposures similar to and 53 times higher than, (b) (4) 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, (b) (4)

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 (b) (4) mothers (b) (4) not to breastfeed if they are receiving ODEFSEY.

Data

Emtricitabine: Samples of breast milk obtained from (b) (4) HIV-1-infected mothers show that (b) (4) is (b) (4) in human milk. Breastfeeding infants whose mothers are being treated

with emtricitabine may be at risk for developing viral resistance to (b) (4). Other (b) (4) associated risks in infants breastfed by mothers being treated with (b) (4) are unknown.

Rilpivirine: (b) (4) studies have (b) (4) been conducted to assess (b) (4) of Rilpivirine (b) (4)

Tenofovir Alafenamide: (b) (4)

(b) (4). Studies in rats have demonstrated that tenofovir is secreted in milk. (b) (4) excreted (b) (4) milk.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Emtricitabine: In long-term carcinogenicity studies of FTC, 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 (b) (4) 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).

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

FTC did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times 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 times higher than human exposures at the recommended 200 mg daily dose.

Rilpivirine: RPV was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60, and 160 mg per kg per day were administered to mice and doses of 40, 200, 500, and 1500 mg per kg per day were administered to rats. In rats, there were no drug-related neoplasms. In mice, RPV was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent specific. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to RPV were 21 times (mice) and 3 times (rats) relative to those observed in humans at the recommended dose (25 mg once daily).

RPV has tested negative in the absence and presence of a metabolic activation system, in the in vitro Ames reverse mutation assay and in vitro clastogenicity mouse lymphoma assay. RPV did not induce chromosomal damage in the in vivo micronucleus test in mice.

In a study conducted in rats, there were no effects on mating or fertility with RPV up to 400 mg per kg per day, a dose of RPV that showed maternal toxicity. This dose is associated with an exposure that is approximately 40 times higher than the exposure in humans at the recommended dose of 25 mg once daily.

Tenofovir Alafenamide: Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice is observed after TAF administration compared to 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 (b)(4) dose of TDF for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and (b)(4) times (rat) those observed in humans after administration of (b)(4). At the high dose in female mice, liver adenomas were increased at tenofovir exposures 10 times (300 mg TDF) and 167 times (b)(4) in humans. In rats, the study was negative for carcinogenic findings.

TAF 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 TAF was administered to male rats at a dose equivalent to (b)(4) 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 TAF, reversibility was seen after a three month recovery period. (b)(4) eye toxicity, the systemic exposure in (b)(4) 5 (TAF) and 15 (tenofovir) times the exposure seen in humans at the recommended daily ODEFSEY (b)(4).

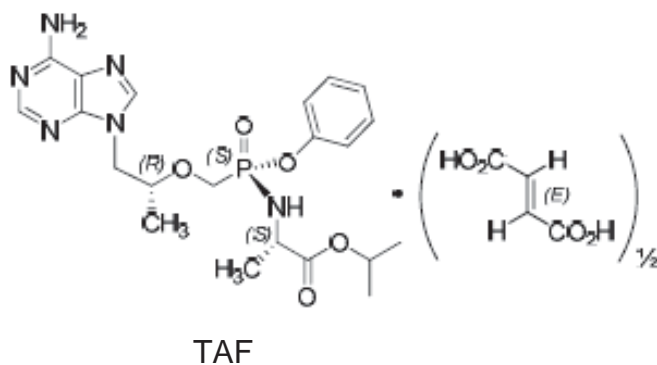
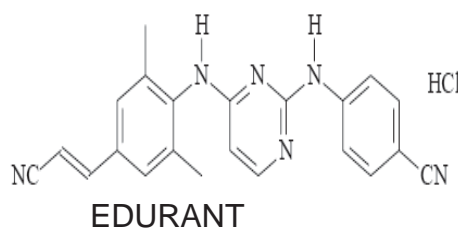
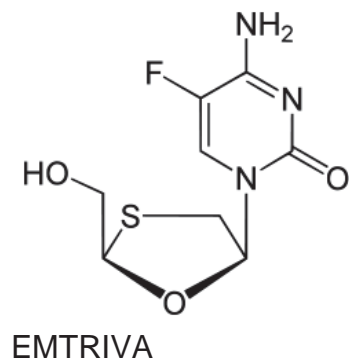
2 Drug Information

2.1 Drug

EMTRIVA (emtricitabine, FTC): CAS number 143491-57-0; chemical name 2'-deoxy-5-fluoro-3'-thiacytidine

EDURANT (rilpivirine, RPV): CAS number 700361-47-3; chemical name (E)-4-[[4-[[4-(2-cyanoethenyl)-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile hydrochloride

Tenofovir alafenamide (TAF): CAS number 379270-37-8; 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)



Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI). Rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Tenofovir alafenamide is a nucleotide reverse transcriptase inhibitor (NtRTI).

2.2 Relevant INDs, NDAs, BLAs and DMFs

This NDA is supported by right of reference to applicable sections of Gilead's applications: NDA 021500, NDA 021896, and IND 053971 for FTC (Emtriva®); NDA 021356 and IND 052849 for TDF (Viread®); NDA 021752 and IND 067671 for TVD (Truvada®); NDA 202123 and IND 106252 for Complera, NDA 203100 and IND 103093 for E/C/F/TDF (Stribild®); NDA 207561 and IND 111007 for E/C/F/TAF, in addition to Janssen's NDA 202022 and IND 67699 for Edurant, and Janssen's IND 075391 for simeprevir.

2.3 Drug Formulation

Emtricitabine/rilpivirine/tenofovir alafenamide (F/R/TAF; ODEFSEY) fixed-dose combination (FDC) tablets are an immediate-release tablet dosage form containing 200 mg of emtricitabine (FTC), 25 mg of rilpivirine (RPV), and 25 mg of tenofovir alafenamide (TAF, GS-7340). F/R/TAF tablets are gray, capsule-shaped, film-coated tablets debossed with "GSI" on one side and "255" on the other side.

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

There are no unique impurities or degradants in the FTC/RPV/TAF tablets. The impurities and degradation products present in FTC, RPV, and TAF and in FTC/RPV/TAF tablets have been qualified through toxicology studies.

2.6 Proposed Clinical Population and Dosing Regimen

Gilead is pursuing registration of the FTC/RPV/TAF fixed-dose combination as a complete regimen for treatment of HIV-1 infection in (b) (4) patients 12 years of age and older without any known mutations associated with resistance to the individual components of FTC/RPV/TAF. FTC/RPV/TAF will be administered orally, once daily, with (b) (4)

2.7 Regulatory Background

Emtricitabine and rilpivirine have been approved for the treatment of HIV-1 infection in adults as stand-alone agents EMTRIVA® (Emtricitabine, NDAs 21-500 for the capsule formulation approved on 2 July 2003 and 21-896 for an oral solution approved on 28 September 2005), and EDURANT® (Rilpivirine, NDA 202022 for 25 mg tablets approved May 20, 2011). In the United States, emtricitabine is approved for use in adolescents. An oral solution of emtricitabine is approved in the United States and may be administered to newborns. Tenofovir Alafenamide was approved as part of the FDC drug GENVOYA (NDA 207561 for tablet formulation approved on 5 November 2015).

3 Studies Submitted

3.1 Studies Reviewed

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 Gilead's applications: NDA 021500, NDA 021896, and IND 053971 for FTC (EMTRIVA®); NDA 021356 and IND 052849 for TDF (VIREAD®); NDA 021752 and IND 067671 for TVD (TRUVADA®); NDA 202123 and IND 106252 for COMPLERA, NDA 203100 and IND 103093 for E/C/F/TDF (STRIBILD®); NDA 207561 and IND 111007 for GENVOYA. In addition, refer to Janssen's NDA 202022 and IND 67699 for EDURANT.

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/s/

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