

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207561Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: August 17, 2015

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Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir
alafenamide)

Therapeutic Class: Integrase inhibitor, Pharmacokinetic enhancer, Nucleoside reverse
transcriptase inhibitor, Nucleotide reverse transcriptase inhibitor

Dosage and Route: 150 mg/150 mg/200 mg/10 mg tablets

Indication: Treatment of HIV-1 infection in adults and pediatric patients 12
years of age and older

Application Type/Number: NDA 207561

Applicant/sponsor: Gilead

OSE RCM #: 2014-2302

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1 INTRODUCTION

The purpose of this review is provide the Division of Risk Management's (DRISK) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for the 4-drug fixed-dose combination (FDC) tablet, Genvoya (elvitegravir (E)/cobicistat (C)/emtricitabine (F)/tenofovir alafenamide (TAF)). A new drug application (NDA 207561) for Genvoya was received by the Division of Antiviral Products on November 5, 2014, from Gilead Sciences, Inc. (Gilead). The new molecular entity in the 4-drug FDC tablet is TAF. Stribild (E/C/F/tenofovir disoproxil fumarate), NDA 203100, was approved on August 27, 2012 for the treatment of HIV-1 infection in adult patients. Tenofovir disoproxil fumarate (TDF) in Stribild is the component proposed by Gilead to be replaced by TAF in Genvoya. The proposed indication for Genvoya is treatment of HIV-1infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed for at least 6 months with no history of treatment failure. The Sponsor did not submit a proposed REMS or risk management plan for Genvoya.

1.1 BACKGROUND OF CONDITION¹⁻³

Human Immunodeficiency Virus (HIV) is a ribonucleic acid (RNA)-containing virus that uses the enzyme reverse transcriptase to copy its RNA into the host cell DNA. It attacks the immune system by destroying the body's immune system (CD4 cells). HIV progressively destroys the body's ability to fight infections and certain cancers. An estimated 1.1 million people in the United States are living with HIV. Worldwide, an estimated 35.5 million people are living with HIV. Early diagnosis of HIV infection and antiretroviral therapy are associated with reduced morbidity and mortality as well as reduced transmission.

Reducing the level of HIV in a person's body to a very low or undetectable viral load (<200 copies/mL) is a primary goal of HIV treatment. The goal is best accomplished by using effective antiretroviral replacement therapy (ART) to maximally inhibit HIV replication. Durable viral suppression improves immune function and overall quality of life, lowers the risk of both AIDS-defining and non-AIDS-defining complications, and prolongs life. Additionally, effective ART can reduce viremia and transmission of HIV by more than 96%.

The recommendation for the optimal initial ART regimen for a treatment-naïve patient consists of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a drug from one of the three drug classes: a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase-strand transfer inhibitor (INSTI).

¹ Turning the Tide on HIV, Division of HIV/AIDS Prevention, Annual Report 2013. CDC, National Center for HIV/AIDS, Viral Hepatitis STD and TB Prevention, July 2014.

² Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Section accessed August 18, 2014.

³ Maartens,G., Celum, C., and Lewin, S. HIV infection: Epidemiology, Pathogenesis, Treatment and Prevention. The Lancet, 2014; vol 384, Issue 9939 (July 19-25): 258-271.

1.2 PRODUCT BACKGROUND

Genvoya is a FDC of antiretroviral drugs E 150mg/C 150mg/F 200mg/TAF 10mg taken once daily, with a proposed indication as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure. Each FDC contains the same active ingredients as the currently approved product, Stribild (STB), with the exception of the tenofovir (TFV) component. STB contains TDF whereas Genvoya contains TAF.

TFV is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. TDF, an oral prodrug of TFV, is a preferred nucleotide reverse transcriptase inhibitor (NRTI) for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. While TDF is used broadly in the treatment of HIV-1 infection, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs. TAF is also an oral prodrug of TFV. TAF is expected to be more stable in plasma than TDF, provide higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF⁴. The lower systemic circulating levels of TFV are expected to result in an enhanced safety profile as compared to TDF, particularly in regard to a reduced potential for adverse renal and bone effects. Additionally, virologically suppressed HIV-1 infected patients may switch from STB to Genvoya without any necessary washout/transition phase.

1.3 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 207561 relevant to this review:

January 29, 2013: The Sponsor was granted Fast Track Designation.

November 5, 2014: The Agency received an original NDA submission from Gilead for Genvoya (E/C/F/TAF) for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. The Sponsor did not submit a proposed REMS.

April 13, 2015: A Mid-Cycle meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that based on the currently available data a REMS was not needed for Genvoya.

2 MATERIALS REVIEWED

The following is a list of materials that informed our review:

- Gilead. Clinical Overview for Genvoya (E/C/F/TAF), received November 5, 2014.
- Gilead. Summary of Clinical Efficacy for Genvoya (E/C/F/TAF), received November 5, 2014.
- Gilead. Summary of Clinical Safety for Genvoya (E/C/F/TAF), received November 5, 2014.
- Gilead. Proposed Package Insert Labeling for Genvoya (E/C/F/TAF), received November 5, 2014, updated May 29, 2015 and August 7, 2015.

⁴ Gilead. Summary of Clinical Efficacy for Genvoya (E/C/F/TAF), dated October 4, 2014.

- Tauber W. DAVP. Mid-cycle Meeting slides for NDA 207561, dated March 31, 2015.
- Miele P. DAVP. Mid-cycle Meeting slides for Study GS-US-292-109 for NDA 207561, dated March 31, 2015.
- Kelsey JV. DDDP. DDDP Consult #1643 – DAVP NDA 207561 Genvoya, dated June 4, 2015.
- Tauber W, Miele P, Alarcon A. DAVP. Clinical Review for Genvoya (E/C/F/TAF), NDA 207561, dated July 29, 2015.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The safety and efficacy of Genvoya was evaluated in six clinical studies in HIV-1 infected subjects. The study populations in five Phase 3 trials providing safety and efficacy data included:

- **Study 104 and Study 111:** Treatment-naïve, adults with screening HIV-1 RNA ≥ 1000 copies/mL
- **Study 102:** Data from Study 104 and Study 111 was supported by this Phase 2 trial in treatment-naïve, HIV-1 infected adults with screening HIV-1 RNA ≥ 5000 copies/mL
- **Study 109:** Virologically suppressed adults taking a TDF-based regimen for 48 to >144 weeks
- **Study 112:** Adults with mild to moderate renal impairment
- **Study 106:** Treatment-naïve, adolescents between the ages of 12 to <18 years of age with screening HIV-1 RNA ≥ 1000 copies/mL or HIV-1 RNA

The primary efficacy endpoint for these pivotal studies was the proportion of subjects who achieved HIV-1 RNA <50 copies/mL at Week 48 for treatment-naïve and virologically suppressed patients (Study 104, Study 111, Study 109) and at Week 24 for subjects with renal impairment (Study 112), adolescent patients (Study 106) and for the randomized portion of Study 102. Secondary efficacy analyses included the percentage of subjects with HIV-1 RNA <50 copies/mL using the missing=failure (M=F) method, the percentage of subjects with HIV-1 RNA <20 copies/mL, and changes in CD4 cell count.

The Phase 3 studies in treatment-naïve adults (Studies 104, 111, 102, and 106) were multi-centered, double-blind, randomized studies, whereas the other Phase 3 studies (Studies 109 and 112) were open-label studies.

Study 104 and Study 111 were identical in design with the exception of the location of the study sites, and subjects were randomized 1:1 to receive either once daily Genvoya or STB. Genvoya was non-inferior when compared to STB in achieving HIV-1 RNA <50 copies/mL, with 92.4% of subjects in the Genvoya group and 90.4% in the STB group achieving virological success ($p=0.13$).

Study 109 was conducted to evaluate the efficacy, safety, and tolerability of switching to a FDC tablet of E/C/F/TAF from regimens containing TDF in virologically suppressed HIV-1 infected subjects. Eligible subjects were HIV-infect receiving ART regimens consisting of F/TDF and a third agent(s); either E/C (STB), efavirenz (Atripla, ATR), atazanavir/C (ATV/C), atazanavir/ritonavir (ATV/r), for at least 6 consecutive months. Subjects were randomized in a 2:1 ratio to switch to open-label Genvoya or remain on their prior regimen consisting of F/TDF+3rd Agent. Switching to Genvoya was non-inferior in achieving HIV-1 RNA <50

copies/mL when compared to maintaining F/TDF+3rd Agent with 95.6% of subjects in the Genvoya group and 92.9% in the F/TDF+3rd Agency group achieving virological success (p=0.051).

The efficacy of Genvoya in adult subjects with mild to moderate renal impairment (creatinine clearance 30 to 69 mL/min) was evaluated in Study 112, that enrolled both treatment-experienced and treatment-naïve subjects. The virologic success rate at Week 24, among virologically suppressed subjects (Cohort 1) with mild to moderate renal impairment who switched treatment to Genvoya was 95.0% and was maintained through Week 48, 93.7%. Cohort 2 included patients that were treatment-naïve. Data from this study indicated that daily dosing with Genvoya in individuals with baseline creatinine clearances of ≥ 50 mL/min was well tolerated.

Data from Study 106 supported the efficacy of Genvoya in adolescent subjects. The virologic success rate at Week 24 was 91.3% for the Genvoya treated group.

3.2 SAFETY CONCERNS

A total of 2394 subjects received E/C/F/TAF in Phase 2 and Phase 3 studies at the proposed commercial dose of 150/150/200/10mg. Most subjects across all studies reported at least 1 adverse event (AE). The most commonly reported AEs reported for subjects participating in the five Phase 3 trials were gastrointestinal disorders (diarrhea and nausea) and infections and infestations (upper respiratory infections).

3.2.1 Serious Adverse Events (SAEs)

The incidence of SAEs were <10% in the E/C/F/TAF groups for each study. SAEs were reported for a similar percentage of subjects in both treatment groups in the comparative studies (Study 104, Study 111, and Study 109). In the pooled Phase 3 analysis, 9% of subjects in the Genvoya group compared to 7% in the control arm had SAEs. No individual SAE occurred in >1% of subjects in either treatment group.

In Study 104 and Study 111, 8.5% and 7.7% in the Genvoya group reported SAEs compared to 6.7% and 6.9% in the STB group, respectively. Those considered related to study drug was low, 0.7% and 0%, in Study 104 and Study 111 respectively, for Genvoya treated group and 0.2% (for both trials) for the STB treated group. After considering the safety update, the clinical reviewer notes that there may be an imbalance in the incidence of infection (predominantly upper respiratory infections) SAEs, which may be due to the possibility of an immunologic impact of Genvoya.⁵ In Study 112, SAEs were similar across renal functional levels, although cardiovascular disorders were increased in the moderate renal impairment group compared to the mild renal impairment group.

Across all studies, AEs leading to study drug discontinuation were uncommon, and the percentages were generally similar between treatment groups within each study (1.5% in the Genvoya group and 1.6% in the comparator groups). All cases leading to discontinuation were considered related to the study drugs by the investigator.

⁵ Tauber W, Miele P, Alarcon A. DAVP. Clinical Review for Genvoya (E/C/F/TAF), NDA 207561, dated July 29, 2015.

In the pooled Phase 3 studies there were a total of 10 deaths. In treatment-naïve subjects, there were 2 deaths in the E/C/F/TAF group and 3 deaths in the STB group. There was one additional death reported from the STB group in the 120 day safety update. In virologically suppressed subjects, there were 3 deaths in the E/C/F/TAF group and death in the renal impairment group. None of these events were considered by the investigator as related to the study drug.

3.2.2 Severe Adverse Events

The incidences of Grade 3 or 4 AEs and of SAEs were low and generally similar across all of the studies and treatment arms, and few were considered related to study drug. The events were reported as not related to study drug in all but 1 subject who experienced Grade 3 diarrhea lasting 1 day.

3.2.3 Adverse events of interest

3.2.3.1 Lactic acidosis/severe hepatomegaly with steatosis and post treatment acute exacerbation of Hepatitis B

STB contains a boxed warning for this risk in the prescribing information; therefore, this risk is of interest for Genvoya. The safety and efficacy of Genvoya has not been established in patients co-infected with HIV-1 and HBV. Discontinuation of Genvoya in patients co-infected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC or TAF components of Genvoya. Patients co-infected with HIV-1 and HBV who discontinue Genvoya should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. No cases of lactic acidosis/severe hepatomegaly with steatosis have been observed with Genvoya, at this time.

3.2.3.2 Serum lipids

Genvoya was associated with increases in serum lipids greater than those associated with STB in the clinical trials. In the treatment naïve population, the median and mean increases in total cholesterol of 29mg/dL and 31mg/dL were seen compared to 15mg/dL and 23mg/dL with STB; and LDL – median and mean – 14mg/dL and 16mg/dL for Genvoya and 3mg/dL and 4mg/dL with STB. Forty percent of patients receiving Genvoya vs 20% of patients receiving STB went from normal total cholesterol to Grade 1 or higher. The use of lipid modifying medications although minimal, was balanced between arms. Based on an assessment of having a LDL cholesterol of > 190mg/dL 27 (3.1%) Genvoya subjects and 13 (1.5%) STB subjects would be candidates for lipid modifying agents independent of their HIV therapy based on guidelines for initiating lipid lowering therapy. Lipid changes are frequently seen in patients on ART-treatment and current HIV guidelines recommend monitoring lipid profiles before initiating or changing therapy and then, if levels are stable, every 6–12 months.⁶ However, increases with Genvoya were significantly greater than those seen with STB, and may require a larger percentage of patients to start lipid-lowering therapy. The clinical reviewer noted this may prompt ongoing

⁶ Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed August 11, 2015.

discussion between patients and their providers regarding the impact of elevated lipids. Based on results of Study 112, it may be advisable to caution older individuals with baseline renal impairment to monitor their lipids closely.⁶

4 DISCUSSION

HIV is a progressive disease that affects about 35.5 million people and initiation of antiretroviral therapy is critical to reduce morbidity and mortality, as well as reduce transmission. Based on results of the Phase 3 trials, Genvoya was found to be efficacious with an acceptable safety profile for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and in patients with an estimated creatinine clearance >30mL/minute.

The most important safety concern associated with Genvoya include lactic acidosis/severe hepatomegaly with steatosis and post treatment acute exacerbation of Hepatitis B, which is based on the risk for STB and is reflected in the Boxed Warning for Genvoya.

The most likely prescribers of Genvoya are specialists who are familiar with the management of HIV infection, frequently monitor patients, and understand the risks of treatment. The FDC tablet offers a comparable safety profile (including new onset or worsening renal failure and decreases in BMD) to STB, which is identical to Genvoya in all components except for TAF, and also used to treat patients with HIV (albeit patients with an estimated creatinine clearance >50mL/min). Genvoya is prescribed by a similar prescriber population as STB, which currently does not require a REMS.

In addition, safety concerns associated with Genvoya will be adequately addressed through the prescribing information. Genvoya will contain a Boxed Warning comparable to STB and the proposed Warnings and Precautions section of the prescribing information for Genvoya includes the additional safety issues surrounding use in patients with new onset or worsening renal impairment and decreases in BMD that are also seen with STB. Also, the proposed Genvoya label includes increased serum lipids as a common adverse event. Monitoring for an increase in serum lipids is also recommended in current HIV guidelines, as ART-treatment frequently causes lipid alterations.⁶

Therefore, based on the currently available data, DRISK does not recommend a REMS as necessary to ensure the benefits of Genvoya outweigh the risks.

5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Genvoya (E/C/F/TAF). Based on the currently available data, the benefit-risk profile for Genvoya is acceptable for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed on a stable antiretroviral regimen for at least 6 months with no history of treatment failure. Therefore, based on the

currently available data, DRISK does not recommend a REMS as necessary to ensure the benefits of Genvoya outweigh the risks at this time.

Should DAVP have any concerns or questions, feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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/s/

JASMINDER N KUMAR
08/17/2015

REEMA J MEHTA
08/17/2015
I concur.