

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210251Orig1s000

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

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
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Reviewer Name(s)	Naomi Redd, PharmD
Team Leader	Elizabeth Everhart, RN, MSN, ACNP
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	November 9, 2017
Subject	Evaluation of the Need for a REMS
Established Name	bictegravir(BIC)/emtricitabine(FTC)/tenofovir alanfenamide(TAF)
Trade Name	Biktarvy
Name of Applicant	Gilead Sciences
Therapeutic class	Antiretroviral
Formulation	50mg BIC/200mg FTC/25mg TAF Fixed-dose combination tablet
Dosing Regimen	One tablet orally by mouth daily for HIV-1 infection

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Biktarvy (bictegravir (BIC) 50mg/ emtricitabine (FTC) 200mg/ tenofovir alanfenamide (TAF) 25mg) is necessary to ensure the benefits outweigh its risks. Gilead Sciences submitted a New Drug Application (NDA) 210251 for Biktarvy with the proposed indications:

- For the treatment of HIV-1 infection in adults who have no antiretroviral treatment history, or
- To replace the current antiretroviral regimen in those patients who are virologically suppressed (HIV-1 RNA less than 50 copies/ml) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of bicetgravir (BIC) 50mg/ emtricitabine (FTC) 200mg/ tenofovir alanfenamide (TAF) 25mg)

The risks associated with Biktarvy include post treatment acute exacerbation of hepatitis B (included in a Boxed Warning), immune reconstitution syndrome, new onset or worsening renal impairment, and lactic acidosis/severe hepatomegaly with steatosis. The applicant did not submit a proposed REMS or risk management plan with this application.

The adverse events reported in the clinical trials for Biktarvy were similar to the currently approved drugs used in the treatment for HIV infection, and have been well described in the literature for HIV treatment for several years. In addition, a REMS is not required for the indication of treatment of HIV-1 infection for any antiretroviral on the market, nor for any of the risks of acute exacerbation of hepatitis B, immune reconstitution syndrome, new onset or worsening renal impairment or lactic acidosis. Because of these reasons, DRISK and the Division of Antiviral Products (DAVP) determined that a REMS is not needed to ensure the benefits of Biktarvy outweigh its risks.

1 Introduction

This review by the DRISK evaluates whether a REMS for the NME Biktarvy (bictegravir (BIC) 50 mg/ emtricitabine (FTC) 200mg/ tenofovir alanfenamide (TAF) 25 mg) is necessary to ensure the benefits outweigh its risks. Gilead Sciences submitted a NDA 210251 for BIC 50 mg/FTC 200 mg/TAF 2 5mg with the following proposed indications:

- For the treatment of HIV-1 infection in adults who have no antiretroviral treatment history, or
- To replace the current antiretroviral regimen in those patients who are virologically suppressed (HIV-1 RNA less than 50 copies/ml) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of bicetgravir (BIC) 50 mg/ emtricitabine (FTC) 200 mg/ tenofovir alanfenamide (TAF) 25 mg)

This application is under review in the Division of Antiviral Products (DAVP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Biktarvy is an antiretroviral, fixed dose combination (FDC) tablet proposed for the use of HIV-1 infection in treatment naïve adults, those stable on an antiretroviral regimen, or in patients with no evidence of resistance to any of its drugs in the combination tablet, taken orally once daily. ^a Emtricitabine 200 mg (approved in July 2003) and tenofovir alafenamide 25 mg (approved in November 2016) comprise the nucleoside (NRTI) and nucleotide (NtRTI) backbone of the regimen, and bictegravir, an integrase strand inhibitor (INSTI) comprises the third drug to make this fixed dose tablet a complete antiretroviral regimen. While FTC and TAF have been on the market for quite some time (TAF being a pro-drug of tenofovir disoproxil fumarate, approved in October 2001), the INSTI bictegravir has not been approved in any jurisdiction. The combination of these ingredients, including the addition of the investigational drug bictegravir, qualifies this drug as an NME. ^b

The mechanism of action of BIC involves inhibition of HIV-1 integrase; a specific HIV enzyme required for successful viral replication. Emtricitabine and TAF inhibit HIV transcriptase, another HIV-specific enzyme, which inhibits HIV from incorporating its viral DNA into the host cells. HIV disease is a chronic condition; therefore, treatment is expected indefinitely or until the patient experiences drug resistance to any of Biktarvy's components or unacceptable toxicity.

Biktarvy is likely to be prescribed by a wide variety of healthcare practitioners, including infectious disease specialists and midlevel providers such as physician's assistants and nurse practitioners who are in an ambulatory care setting and directly involved in the treatment and management of HIV patients.

Tenofovir alafenamide is a prodrug of tenofovir disoproxil, and its combination product emtricitabine/tenofovir disoproxil fumarate (Truvada[®]) has a Boxed Warning and REMS for the pre-exposure prophylaxis (PrEP) indication. The goal of the REMS for emtricitabine/tenofovir disoproxil fumarate are to inform and educate prescribers and uninfected individuals at high risk for acquiring HIV-1 infection about:

- The importance of strict adherence to the recommended dosing regimen
- The importance of regular monitoring of HIV-1 serostatus to avoid continuing to take emtricitabine/tenofovir disoproxil fumarate for a PrEP indication, if seroconversion has occurred, to reduce the risk of development of resistant HIV-1 variants
- The fact that emtricitabine/tenofovir disoproxil fumarate for a PrEP indication must be considered as only part of a comprehensive prevention strategy to reduce the risk of HIV-1 infection and that other preventive measures should also be used

Tenofovir alafenamide, or the FDC of Biktarvy, is not under review for pre-exposure prophylaxis. However, tenofovir alafenamide, like tenofovir disoproxil, emtricitabine, and lamivudine (another nucleoside reverse transcriptase inhibitor with hepatitis B activity) contain an additional Boxed Warning for monitoring of acute exacerbations of hepatitis B in patients co-infected with HIV-1, including the risk of lactic acidosis and severe hepatomegaly with steatosis for emtricitabine and lamivudine.

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

This NME application is under Priority Review with a Prescription Drug User Fee Act (PDUFA) date of February 28, 2018.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210251 relevant to this review:

- 06/12/2017: NDA 210251 submission for BIC/F/TAF received
- 09/27/2017: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for BIC/FTC/TAF
- 02/28/2018: expected PDUFA date

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

HIV-1 infection is a life threatening and serious disease that affects approximately 37 million people globally, with an estimated 1.1 million persons aged 13 and older living in the United States. This number also includes approximately 15% (166,000 people) whose infections had not been diagnosed. Undiagnosed and poorly treated HIV-1 infection can lead to severe outcomes, not only including the spread of this infection, but also debilitating, sometimes fatal, co-infections with other diseases, and multi-organ damage from metabolic issues that may arise from the inflammatory nature of HIV infection.^{1,c,d}

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The current standard of care for treatment of HIV-1 is focused on preventing the spread of disease by suppressing the patient's HIV-1 RNA (viral load) to less than 50 copies/ml; with additional non-pharmacological measures that focus on education of decreasing risky behaviors that may help preclude one to encountering the virus from an infected person(s).

More than 25 antiretroviral drugs in six mechanistic drug classes have been approved for the treatment of HIV-1 infection.² These six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), a fusion inhibitor (FI), a CCR5 antagonist, and integrase strand transfer inhibitors (INSTIs). In addition, two drugs, ritonavir (RTV or r) and cobicistat (COBI or c) are used solely as pharmacokinetic (PK) enhancers (or

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

boosters) to improve the PK profiles of some antiretroviral drugs (e.g., PIs and the INSTI elvitegravir [EVG]).²

Current United States Antiretroviral treatment guidelines recommend that an initial antiretroviral regimen consists of two NRTIs plus a drug from one of three drug classes: an INSTI, an NNRTI, or a PK-enhanced PI, with INSTI-based regimens recommended as initial therapy for most people with HIV due to high rates of virologic suppression, favorable tolerability and toxicity profiles, and ease of use.²

Adverse reactions are varied in each of the classes of antiretrovirals, in addition, there is variation individually in drugs within the same drug class. These adverse reactions range from lipid effects, hepatic and renal effects, as well as serious warnings on drug interaction potential amongst antiretrovirals and other drugs that are used in the management of HIV or its co-morbid conditions, including some which have had Boxed Warnings for several years, as well as being highlighted in the United States Treatment Guidelines for HIV. As described in section 2.1 in this review, the only antiretroviral drug that contains a REMS is Truvada® and its generic emtricitabine/tenofovir disoproxil fumarate for the risks outlined for PrEP in uninfected individuals.

Antiretroviral combination therapy has steadily improved since its advent in 1996, which has dramatically reduced HIV-associated morbidity and mortality into a manageable chronic condition in those patients who remain adherent to therapy. However, despite the improvement in antiretroviral drug combinations, only 55% of people living with HIV in the United States can achieve and maintain a suppressed viral load.² This is due mostly from undiagnosed HIV infection, failure to link and retain patients in care, and for those who are in care, failure of those patients to remain adherent to antiretroviral drug therapy due to either adverse effects or in some cases pill size and pill burden. Not only can failure to achieve a suppressed viral load result in the spread of the disease, but also in resistance; and in many cases, multi-drug resistance to many of the antiretroviral drugs that are available for treatment of this disease, thus limiting options available for the patient to use in the future. There remains a medical need for antiretroviral therapies that are potent, safe, and effective in this patient population.

4 Benefit Assessment

The following table is a summary of the clinical trials that support the efficacy and safety of BIC/FTC/TAF (Biktarvy) in adult patients with no antiretroviral treatment history, and those who were virologically suppressed on a former antiretroviral regimen. Please see the full review of these trials written by the clinical reviewer, Dr. Bell, for more information on these trials.

Of note, demographics across all trials presented were similar, and equally stratified amongst baseline CD4 cell counts and viral loads.

Table 1: Summary of Trials conducted with Biktarvy in Patients with HIV-1 infection³:

Trial	Population	Trial Arms (N)	Timepoint (Week)
Trial1489 ^a (NCT 02607930)	Adults with no antiretroviral treatment history	BIKTARVY (314) ABC/DTG/3TC (315)	48
Trial 1490 ^a (NCT 02607956)		BIKTARVY (320) DTG + FTC/TAF (325)	48
Trial 1844 ^a (NCT02603120)	Virologically-suppressed ^c adults	BIKTARVY (282) DTG+ABC/3TC or ABC/DTG/3TC (281)	48
Trial 1878 ^b (NCT 02603107)		BIKTARVY (290) ATV or DRV (with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC (287)	48

a. Randomized, double blind, active controlled trial.

b. Randomized, open label, active controlled trial.

c. HIV-1 RNA less than 50 copies per mL at baseline.

ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir; DRV = darunavir; ATV = atazanavir; NCT = National Clinical Trial

Virological outcomes were favorable in all treatment arms in adults with no previous antiretroviral therapy, and in those who were virologically suppressed on a previous antiretroviral regimen as represented below:

Table 2: Summary of Virological Outcomes at 48 weeks in HIV Patients with no Antiretroviral Treatment History receiving Biktarvy³

	Trial 1489		Trial 1490	
	BIKTARVY (N=314)	ABC/DTG/3TC (N=315)	BIKTARVY (N=320)	DTG + FTC/TAF (N=325)
HIV-1 RNA < 50 copies/mL	92%	93%	89%	93%
Treatment Difference (95% CI) BIKTARVY vs. Comparator	-0.6% (-4.8% to 3.6%)		-3.5% (-7.9% to 1.0%)	

ABC = abacavir; DTG = dolutegravir

Table 3: Summary of Virological Outcomes at 48 weeks in Virologically Suppressed HIV Patients who Switched to Biktarvy³

	Trial 1844		Trial 1878	
	BIKTARVY (N=282)	ABC/DTG/3TC (N=281)	BIKTARVY (N=290)	ATV- or DRV- based regimen (N=287)
HIV-1 RNA \geq 50 copies/mL^b	1%	<1%	2%	2%
Treatment Difference (95% CI)	0.7% (-1.0% to 2.8%)		0.0% (-2.5% to 2.5%)	
HIV-1 RNA < 50 copies/mL	94%	95%	92%	89%

ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir; DRV = darunavir; ATV = atazanavir

As presented at the midcycle clinical meeting for this NDA, the clinical reviewer concluded that the Applicant provided evidence of effectiveness based on suppression of viral load at the 48th week primary endpoint.

5 Risk Assessment & Safe-Use Conditions

Adverse reactions that will be as described in the Biktarvy include: severe acute exacerbation of hepatitis B in patients co-infected with HIV-1 and HBV (section 5.1 and the Box Warning), immune reconstitution syndrome (section 5.2), new onset or worsening renal impairment (section 5.3), and lactic acidosis/severe hepatomegaly with steatosis (section 5.4). Tenofovir alafenamide and emtricitabine are part of a drug class that has been used in antiretroviral therapy for nearly 20 years, and its adverse events are well described in literature² as well as in labeling.

6 Expected Postmarket Use

Biktarvy is likely to be prescribed primarily in outpatient, ambulatory care settings by a wide variety of healthcare practitioners who are actively involved in the management and treatment of patients infected with HIV. In the clinical trial setting, there were no new adverse reactions that practitioners in the HIV field were not already familiar with. Additionally, Biktarvy is not expected to be used for any off-labeled conditions.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Biktarvy beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

With over 1 million people being diagnosed in the United States each year, and 55% who are in care still unable to achieve suppressed viral loads, there is still a need for effective therapies for HIV patients that are efficacious and have safe and tolerable drug profiles.

If approved, Biktarvy would become the second FDC tablet co-formulated with an INSTI, NRTI, and NtRTI. The prescribing information⁴ for another FDC tablet with an INSTI, Triumeq® (abacavir/dolutegravir/lamivudine), contains Boxed Warnings in relationship to hypersensitivity reactions for abacavir, as well as lactic acidosis and severe hepatomegaly with steatosis and exacerbations of hepatitis B for lamivudine. Like adverse events described for tenofovir and emtricitabine containing regimens, these adverse events and the management thereof for Triumeq have been well described in the prescribing information of these antiretrovirals, and antiretroviral treatment guidelines for several years. None of these adverse reactions have required a REMS. Biktarvy will likely be prescribed by healthcare practitioners who are actively involved and aware of the management of drugs for HIV infection.

The Clinical Reviewer recommends approval of Biktarvy based on the efficacy and safety information currently available. Because the adverse events of Biktarvy are well known in various antiretroviral drug treatment literature, and there were no new safety adverse events seen in the clinical trials, this DRISK reviewer does not recommend a REMS for Biktarvy, as it is not necessary to ensure the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable, therefore, a REMS is not necessary for Biktarvy to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile so that this recommendation can be reevaluated.

10 References

¹ www.cdc.gov/hiv/statistic/overview/index.html accessed October 12, 2017

² Adult and Adolescent HIV Treatment Guidelines, Updated October 17, 2017 www.aidsinfo.nih.gov accessed October 19, 2017

³ Biktarvy Draft Prescribing Information November 3, 2017

⁴ Triumeq US Prescribing Information, Revised March 2017

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/s/

NAOMI B REDD
11/09/2017

CYNTHIA L LACIVITA
11/09/2017