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 Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	August 31, 2023
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Product Name:	Biktarvy (bictegravir sodium; emtricitabine; tenofovir alafenamide fumarate)
Pediatric Labeling Approval Dates:	June 18, 2019 (supplement 5); October 7, 2021 (supplement 14)
Application Type/Number:	NDA 210251
Applicant:	Gilead Sciences, Inc.
TTT Record ID:	2023-5449

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide) in pediatric patients through age <18. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Biktarvy in pediatric patients.

The FDA approved Biktarvy for adult patients on February 7, 2018, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy. On June 18, 2019, the Biktarvy indication was expanded to include use in pediatric patients weighing at least 25 kg. The indication was expanded again on October 7, 2021, to include pediatric patients weighing at least 14 kg.

We reviewed all serious U.S. FAERS reports with Biktarvy in the pediatric population (through age <18 years) received through July 9, 2023. We identified one case for discussion, but it had limited information which precluded a meaningful causality assessment. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with Biktarvy.

DPV will continue routine pharmacovigilance monitoring for Biktarvy.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide) in pediatric patients through age <18 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with Biktarvy in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Biktarvy was initially approved in adult patients as a fixed-dose combination oral tablet containing 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide on February 7, 2018. The original indication was for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per 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 Biktarvy.[1] The first pediatric approval was granted on June 18, 2019, for the same indication in pediatric patients weighing at least 25 kg at the same dose.[2] On October 7, 2021, the indication was expanded to include pediatric patients weighing at least 14 kg, and a new fixed-dose combination tablet containing 30 mg of bictegravir, 120 mg of emtricitabine, and 15 mg of tenofovir alafenamide was made available to provide the dose for patients weighing at least 14 kg but less than 25 kg.[3]

The initial pediatric approval in patients weighing at least 25 kg was based on the results of Trial GS-US-380-1474 (ClinicalTrials.gov Identifier: NCT02881320), which had initially enrolled virologically suppressed children and adolescents with HIV-1 infection in two age cohorts: 12 to 18 years old and weighing at least 35 kg; and 6 to <12 years old and weighing at least 25 kg. Safety data were available for 100 pediatric participants with at least 24 weeks of treatment and indicated that Biktarvy was generally safe and tolerated, adverse events were similar to those seen in adults, and no new safety issues were identified in this age and weight range.[4] The subsequent pediatric approval for patients weighing at least 14 kg was based on a third age cohort included in Trial GS-US-380-1474, with pediatric patients >2 years of age and weighing 14 kg to <25 kg. Safety data from 22 pediatric patients with at least 24 weeks of treatment were available and indicated that Biktarvy was safe and well tolerated in this age group as well, with adverse events generally mild and similar to those observed in adolescents and adults.[5]

This review was prompted by the pediatric labeling updates on June 18, 2019, and October 7, 2021. Biktarvy has not been previously presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION[6]

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY.

Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted [see Warnings and Precautions (5.1)].

4 CONTRAINDICATIONS

BIKTARVY is contraindicated to be co-administered with:

- dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events [see Drug Interactions (7.5)].
- rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY [see Drug Interactions (7.5)].

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV

Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) infection before or when initiating antiretroviral therapy [see Dosage and Administration (2.1)]. Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Patients coinfected with HIV-1 and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

5.2 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of BIKTARVY with certain other drugs may result in known or potentially significant drug interactions, some of which may lead to [see Contraindications (4) and Drug Interactions (7.5)]:

- Loss of therapeutic effect of BIKTARVY and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

See Table 3 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during BIKTARVY therapy; review concomitant medications during BIKTARVY therapy; and monitor for the adverse reactions associated with the concomitant drugs.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections [such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis], which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.4 New Onset or Worsening Renal Impairment

Postmarketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome, have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events [see Adverse Reactions (6.1, 6.2)]. BIKTARVY is not recommended in patients with severe renal impairment (estimated creatinine clearance of 15 to below 30 mL/min), or patients with ESRD (estimated creatinine clearance below 15 mL/min) who are not receiving chronic hemodialysis, or patients with no antiretroviral treatment history and ESRD who are receiving chronic hemodialysis [see Dosage and Administration (2.4), Use in Specific Populations (8.6)]. Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.5 Lactic Acidosis/Severe Hepatomegaly with Steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of BIKTARVY, and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with BIKTARVY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Clinical Trials in Pediatric Subjects
The safety of BIKTARVY was evaluated in HIV-1 infected virologically-suppressed subjects between the ages of 12 to less than 18 years and weighing at least 35 kg (N=50) through Week 48 (cohort 1), in virologically-suppressed subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (N=50) through Week 24 (cohort 2), and in virologically suppressed subjects at least 2 years of age and weighing at least 14 to less than 25 kg (N=22) through Week 24 (cohort 3) in an open label clinical trial (Trial 1474) [see Clinical Studies (14.4)]. No new adverse reactions or laboratory abnormalities were identified compared to those observed in adults. Adverse reactions were reported in 11% of pediatric subjects. The majority (76%) of adverse reactions were Grade 1. No Grade 3 or 4 adverse reactions were reported. The adverse reaction reported by more than one subject (regardless of severity) was abdominal discomfort (n=2). One subject (1%) had Grade 2 adverse reactions of insomnia and anxiety that led to discontinuation of BIKTARVY. The other adverse reactions that occurred in single subjects were similar to those seen in adults.

6.2 Postmarketing Experience
Renal and Urinary Disorders
Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

Skin and Subcutaneous Tissue Disorders
Angioedema, Stevens-Johnson syndrome/toxic epidermal necrolysis, and urticaria

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
The safety and effectiveness of BIKTARVY have been established as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in pediatric patients weighing at least 14 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY [see Indications and Usage (1) and Dosage and Administration (2.2, 2.3)]. Use of BIKTARVY in pediatric patients weighing at least 14 kg is supported by the following:

- trials in adults [see Clinical Studies (14.1)]
- an open-label trial in three age-based cohorts of virologically-suppressed pediatric subjects [see Clinical Studies (14.4)]
    - Cohort 1: 12 to less than 18 years of age and weighing at least 35 kg receiving BIKTARVY through Week 48 (N=50),
    - Cohort 2: 6 to less than 12 years of age and weighing at least 25 kg receiving BIKTARVY through Week 24 (N=50), and
    - Cohort 3: at least 2 years of age and weighing at least 14 to less than 25 kg through Week 24 (N=22).

No pediatric subjects 2 years of age were enrolled; of the 6 pediatric subjects who were 3 years of age at enrollment, 3 subjects weighed between 14 to less than 15 kg. The safety and efficacy of BIKTARVY in these pediatric subjects were similar to that in adults, and there was no clinically significant change in exposure for the components of BIKTARVY [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]. Safety and effectiveness of BIKTARVY in pediatric patients weighing less than 14 kg have not been established.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	July 10, 2023
Time period of search	All dates through July 9, 2023
Search type	RxLogix PV Reports Post-Market Cases
Product terms	Product Active Ingredient: bictegravir, bictegravir sodium, bictegravir sodium\emtricitabine\tenofovir alafenamide fumarate, bictegravir\emtricitabine\tenofovir alafenamide
MedDRA search terms (Version 26.0)	All PTs
* See Appendix A for a description of the FAERS database. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports through July 9, 2023, with Biktarvy.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through July 9, 2023, With Biktarvy			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	3,137 (2,119)	2,147 (1,142)	242 (174)
Pediatrics (0 - <18 years)	64 (44)	51 **(32)**	2 (1)
* May include duplicates and transplacental exposures, and have not been assessed for causality † For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.			

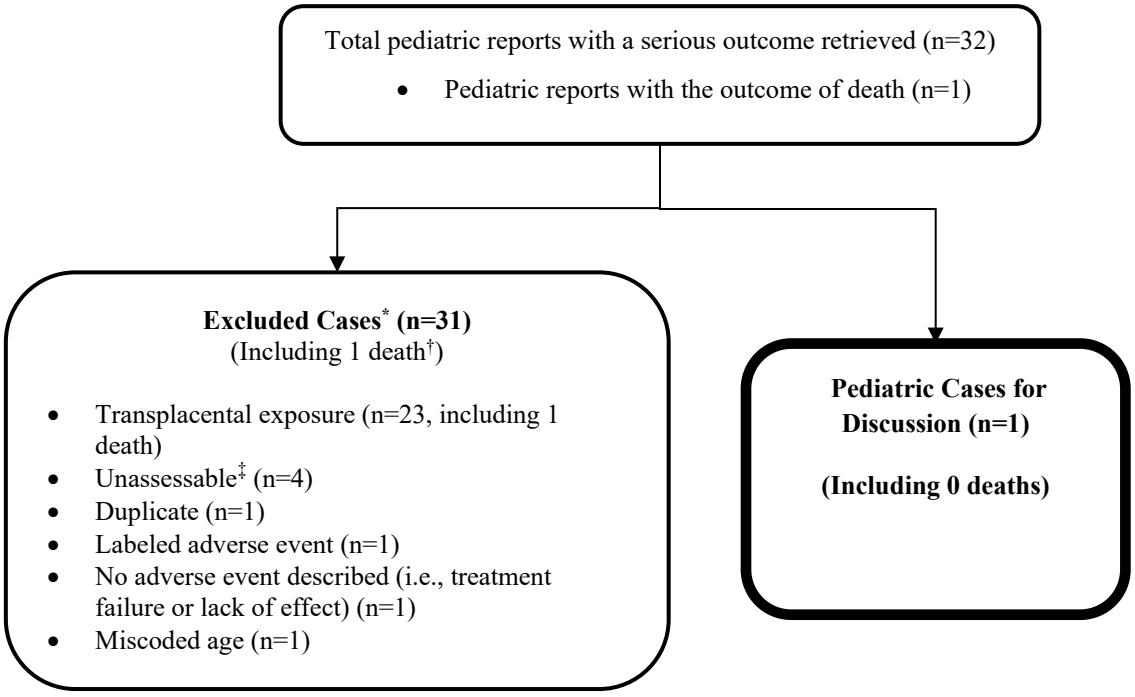
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 32 U.S. serious pediatric reports through July 9, 2023.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for the following reasons: transplacental exposure (n=23), unassessable (n=4), duplicate reports (n=1), labeled adverse event (n=1), no adverse event described (n=1) and miscoded age (n=1). We summarize the remaining case in the sections below.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Biktarvy



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above

† One excluded U.S. FAERS report described a fatal outcome. The case described a premature infant with transplacental exposure to Biktarvy. Death was secondary to intracerebral hemorrhage attributed to a traumatic delivery.

‡ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the case cannot be supplemented or verified.

3.1.3 Summary of U.S. Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event reports.

3.1.4 Summary of U.S. Serious Non-Fatal Cases (N=1)

We identified one serious FAERS case with Biktarvy in the U.S. pediatric population reporting a non-fatal serious outcome.

FAERS Case #20015868, Version #1, Initial FDA Received Date 11/2/2021, United States, Serious Outcome: Other

A 14-year-old female with an unknown past medical history experienced "fluttering in chest," insomnia, headache, abdominal discomfort, and "a hard time breathing" after starting Biktarvy. Her concomitant medications were gabapentin, trazodone, and ketoconazole. It was reported that she took ibuprofen for the headache and famotidine for the abdominal discomfort. The timing of

these medications relative to her other symptoms was not reported. The severity and clinical course of these events were not described in the narrative. The patient had received a total of "7 to 10 days" of Biktarvy before discontinuing Biktarvy and returning to her previous regimen. It was not reported if these symptoms resolved after discontinuation of Biktarvy.

Reviewers' comments: Insomnia, headache, and abdominal pain are labeled as events experienced by adult subjects in Section 6.1 Clinical Trials Experience while abdominal discomfort and insomnia are labeled as events experienced by pediatric subjects.[6] A causal association between Biktarvy and the patient's two unlabeled symptoms, "a hard time breathing" and "fluttering in chest" cannot be excluded based on the temporal association with Biktarvy. The patient's concomitant medications may provide an alternative explanation for the unlabeled symptoms. Gabapentin is labeled for dyspnea[7] and trazodone is labeled for palpitations,[8] however, no information about the temporal relationship between the concomitant medications and the adverse events was available. Additional clinical information needed for an adequate causality assessment was not available, such as the patient's past medical history, a diagnostic workup for additional alternative etiologies, and the effect of Biktarvy dechallenge on the symptoms. An exploratory search of the FAERS data for the PTs Palpitations and Dyspnoea did not identify evidence of a new safety signal for palpitations or dyspnea with Biktarvy in pediatric patients.

4 DISCUSSION

We reviewed all serious U.S. FAERS reports with Biktarvy in the pediatric population (through age <18 years) received through July 9, 2023 and identified one case for discussion. Although two unlabeled adverse events (palpitations and dyspnea) were reported in this case, it had limited information which precluded a meaningful causality assessment. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with Biktarvy.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Biktarvy at this time and will continue routine pharmacovigilance monitoring.

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6. Biktarvy (bictegravir, emtriciatbine, and tenofovir alafenamide) tablets, for oral use [package insert]. Foster City, CA: Gilead Sciences, Inc. Revised October 14, 2022.
7. Gabapentin capsule [package insert]. Coral Springs, FL: ACI Healthcare USA, Inc. Revised November 2022.
8. Trazodone hydrochloride tablet [package insert]. Durham, NC: Accord Healthcare, Inc. Revised December 2021.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 APPENDIX B. FAERS LINE LISTING OF THE BIKTARVY PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control # or Central Triage Unit #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	02-NOV-2021	20015868	1	FDA-CDER-CTU-2021-81540	Direct	14	Female	United States	Other

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. A case may have more than one serious outcome.

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