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, 2022
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Product Name:	Descovy® (emtricitabine and tenofovir alafenamide)
Pediatric Labeling Approval Date:	October 3, 2019
Application Type/Number:	NDA 208215
Applicant:	Gilead Sciences, Inc.
OSE RCM #:	2022-1027
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Descovy (emtricitabine/tenofovir alafenamide) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Descovy in pediatric patients and was prompted by the approval of new pediatric labeling on October 3, 2019.

Descovy is a fixed-dose combination tablet of emtricitabine and tenofovir alafenamide. It was first FDA approved in April 2016 and indicated, in combination with other antiretroviral agents, for the treatment of human immunodeficiency virus (HIV)-1 infection in adults and pediatric patients 12 years of age and older with a body weight at least 35 kg and a creatinine clearance greater than or equal to 30 mL per minute. In September 2017, Descovy's original pediatric indication was expanded to include any "pediatric patients weighing at least 35 kg" and was also approved, in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg. In October 2019, Descovy was approved for use in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. In January 2022, the label was expanded to include pediatric patients weighing at least 14 kg to less than 25 kg for use in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection. Pediatric patients not receiving a protease inhibitor administered with ritonavir or cobicistat and weighing at least 25 kg to less than 35 kg will take one 200 mg/25 mg (emtricitabine/tenofovir alafenamide) tablet, whereas those weighing at least 14 kg to less than 25 kg will take one 120 mg/15 mg (emtricitabine/tenofovir alafenamide) tablet once daily.

We searched the medical literature and reviewed all FAERS reports with Descovy in the pediatric population (ages 0 - <18 years) from January 29, 2020 through May 29, 2022 and did not identify any cases for inclusion in our case series. DPV did not identify any new pediatric safety concerns for Descovy and will continue to monitor all adverse events associated with the use of Descovy.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Descovy (emtricitabine/tenofovir alafenamide) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Descovy in pediatric patients and was prompted by the approval of new pediatric labeling on October 3, 2019.

1.1 PEDIATRIC REGULATORY HISTORY

Descovy is a fixed-dose combination tablet of emtricitabine and tenofovir alafenamide with two dosage strengths: 200 mg/25 mg and 120 mg/15 mg of emtricitabine and tenofovir alafenamide, respectively. Descovy is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg or in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing at least 14 kg and less than 35 kg.[1] Descovy is also indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex.[1] This current indication for Descovy was last updated on January 21, 2022. Before January 21, 2022, labeling changes pertaining to the pediatric population occurred in September 2017 and October 2019. See **Table 1** for indication updates pertaining to the pediatric population for Descovy from initial approval in April 2016 through January 2022.

This review was triggered by the approval of a new indication for Descovy on October 3, 2019, for use in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex.[2] The approval of this indication was based on demonstrated noninferiority of Descovy in comparison to Truvada (emtricitabine/tenofovir disoproxil fumarate), which has an approval for PrEP.[3] The double-blind, randomized clinical trial GS-US-412-2055 (DISCOVER) treated 5,387 HIV-1 uninfected adult men and transgender women who have sex with men; 2,694 participants received Descovy and 2,693 participants received Truvada once daily for HIV-1 PrEP with a median duration of 86 and 87 weeks, respectively.[3] The most common adverse reactions in adult participants who received Descovy were diarrhea (5%), nausea (4%), headache (2%), fatigue (2%) and abdominal pain (2%).[3] Clinical trials to evaluate the safety and efficacy of Descovy for a PrEP indication have not been conducted in adolescents. Instead, the adult HIV-1 PrEP efficacy data from DISCOVER, and available safety and pharmacokinetic data with emtricitabine/tenofovir alafenamide in HIV-1 infected pediatric subjects, of age 12 to less than 18 years, were used to support the adolescent indication.[1,3] During the supplement review for the HIV-1 PrEP indication, postmarketing adverse drug reactions of angioedema, urticaria and rash, as supported by the cumulative safety review across tenofovir alafenamide containing products, were added to the Descovy label.[4]

DPV previously completed two Pediatric Postmarketing Pharmacovigilance Reviews for Descovy. The first review[5], dated March 6, 2018, was prompted by the initial approval for

Descovy on April 4, 2016. The second DPV Pediatric Postmarketing Pharmacovigilance Review [6], dated April 15, 2020, was prompted by approval of the new pediatric labeling on September 28, 2017. Neither review identified new safety concerns, and both recommended ongoing routine monitoring for adverse events with Descovy.

Table 1 presents indication updates pertaining to the pediatric population for Descovy from initial approval in April 2016 through January 2022.[1,2,7,8]

Table 1. Relevant pediatric indication updates in the Descovy product labeling	
Date of Approval	Indication
April 4, 2016	Descovy is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. Limitations of Use: Descovy is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.
September 28, 2017	Descovy is indicated: • in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg. OR • in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg. Limitations of Use: Descovy is not indicated for use as pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.
October 3, 2019	Descovy is indicated: • in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg. OR • in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg. HIV-1 PrEP: Descovy is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating Descovy for HIV-1 PrEP. Limitations of Use: The indication does not include use of Descovy in

	individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.
January 21, 2022	Descovy is indicated: • in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg. OR • in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing at least 14 kg and less than 35 kg. HIV-1 PrEP: Descovy is indicated in at-risk adults and adolescents weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating Descovy for HIV-1 PrEP. Limitations of Use: The indication does not include use of Descovy in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions, and Use in Specific Populations (from the Highlights of Prescribing Information) of the Descovy product labeling are reproduced below.[1] Please refer to the full prescribing information for additional information. [1]

---------- CONTRAINDICATIONS ----------

- DESCOVY for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Comprehensive management to reduce the risk of sexually transmitted infections (STIs), including HIV- 1, when DESCOVY is used for HIV-1 PrEP: Counsel on adherence to daily dosing and safer sex practices, including condoms, to reduce the risk of STIs. (5.2)
- Management to reduce the risk of acquiring HIV-1 drug resistance when DESCOVY is used for HIV-1 PrEP: refer to full prescribing information for additional detail. (5.2)
- Immune reconstitution syndrome during treatment of HIV-1 infection: May necessitate further evaluation and treatment. (5.3)
- New onset or worsening renal impairment: Assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein when initiating

DESCOVY and during use on a clinically appropriate schedule in all individuals. Also assess serum phosphorus in individuals with chronic kidney disease. (5.4)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue DESCOVY in individuals who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)

---------- ADVERSE REACTIONS ----------

- In HIV-1 infected patients, the most common adverse reaction (incidence greater than or equal to 10%, all grades) was nausea. (6.1)
- In HIV-1 uninfected adults in a PrEP trial, the most common adverse reaction (incidence greater than or equal to 5%, all grades) was diarrhea. (6.1)

---------- DRUG INTERACTIONS ----------

- Consult the Full Prescribing Information prior to and during use for potential drug interactions. (7, 12.3)

---------- USE IN SPECIFIC POPULATION ----------

- Lactation: Mothers infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV transmission. (8.2)
- Pediatrics:
    - Treatment of HIV-1 Infection: Not recommended for patients weighing less than 14 kg. (8.4)
    - HIV-1 PrEP: Not recommended for individuals weighing less than 35 kg. (8.4)

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*	
Date of search	May 30, 2022
Time period of search	January 29, 2020† - May 29, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: Emtricitabine\Tenofovir Alafenamide Fumarate
MedDRA search terms (Version 25.0)	All PT terms

* See Appendix A for a description of the FAERS database.
† Continuation date of the most recent previous DPV pediatric review for Descovy dated April 15, 2020 (RCM # 2020-176)[6]
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

2.2 LITERATURE SEARCH STRATEGY

DPV searched the literature with the strategy described in **Table 3**.

Table 3. Descovy Literature Search Strategy		
Database	Embase	PubMed
Date of search	June 13, 2022	
Search terms	'emtricitabine plus tenofovir alafenamide'/exp	Descovy OR emtricitabine plus tenofovir alafenamide
Limits	English, humans, case reports, publication years 2020-2022, Neonate, Child, Adolescent	English, humans, case reports, publication years 2020-2022, child (birth-18 years)

3 RESULTS

3.1 FAERS AND THE MEDICAL LITERATURE

3.1.1 Total Number of FAERS Reports by Age

Table 4 presents the number of adult and pediatric FAERS reports from January 29, 2020, through May 29, 2022, with Descovy.

Table 4. Total Adult and Pediatric FAERS Reports* with Age Received by FDA From January 29, 2020 through May 29, 2022 with Descovy			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	417 (279)	244 (109)	37 (24)
Pediatrics (0 - <18 years)	15‡ (2)	14‡ (1)	13‡ (0)

* 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.

‡ We identified six additional reports of pediatric deaths among reports not reporting an age and one additional death report that was not coded for death as an outcome. These reports are reflected in the pediatric report counts.

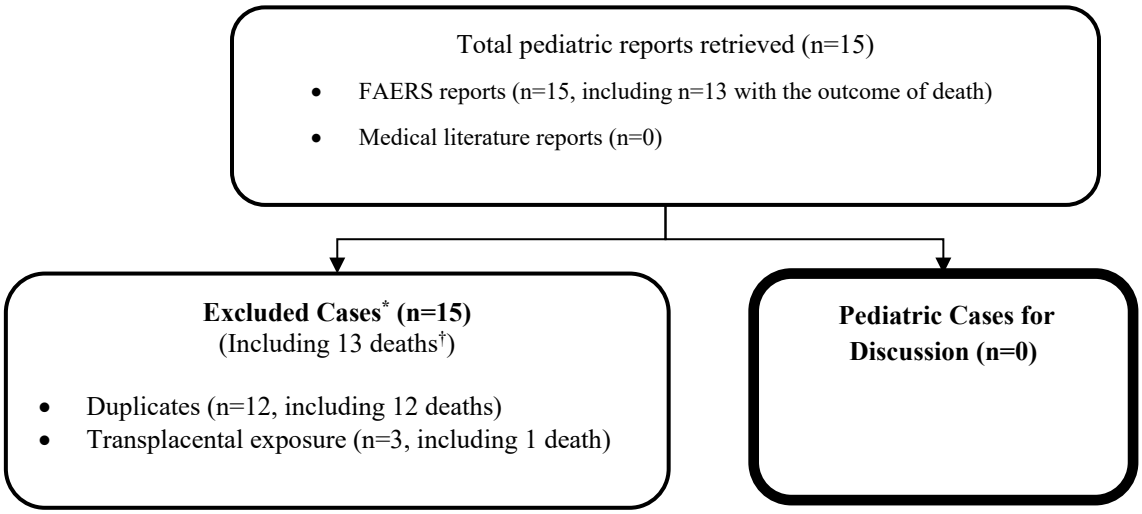
3.1.2 Selection of Pediatric Cases in FAERS and the Medical Literature

Our FAERS search retrieved 15 pediatric reports from January 29, 2020, through May 29, 2022.

After accounting for duplicate reports, we identified three unique patient cases. **Figure 1** presents cases for the pediatric case series.

The search of the medical literature retrieved no additional pediatric adverse event reports with Descovy.

Figure 1. Selection of Pediatric Cases with Descovy



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

† After accounting for duplicate reporting, we identified one case describing a fatal outcome in a premature neonate with a history of transplacental exposure to Descovy and other antiretroviral therapies throughout gestation. The patient was born with multiple congenital anomalies and died at an unspecified time due to unspecified reasons.

3.1.3 Summary of Fatal Pediatric Cases (N=0) and the Medical Literature (N=0)

We did not identify any fatal pediatric adverse event cases for further discussion.

3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=0) and the Medical Literature (N=0)

We did not identify any non-fatal pediatric adverse event cases for further discussion.

4 DISCUSSION

We searched FAERS and the medical literature and identified 15 FAERS reports with Descovy in the pediatric population (ages 0 - <18 years) from January 29, 2020, through May 29, 2022. We excluded all reports from our case series. We did not identify new safety signals, increase in severity or frequency of any labeled adverse events, or any deaths directly associated with Descovy.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for Descovy at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of Descovy.

7 REFERENCES

1. Descovy (emtricitabine and tenofovir alafenamide) [product label]. Foster City, CA: Gilead Sciences Inc.; Revised January 2022.

2. Descovy (emtricitabine and tenofovir alafenamide) [product label]. Foster City, CA: Gilead Sciences Inc.; Revised October 2019.

3. Miele P. Descovy Clinical Review and Summary CDTL. NDA 208215 Supplement 012. September 27, 2019. Accessed on May 27, 2022: https://www.fda.gov/media/135237/download

4. Murray JS. Descovy, NDA 208215 Supplement 012 Approval Letter. October 3, 2019. Accessed on June 29, 2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/208215Orig1s012ltr.pdf

5. Boxwell D. Descovy Pediatric Postmarketing Pharmacovigilance Review. March 6, 2018. Accessed on May 27, 2022: https://www.fda.gov/media/114073/download

6. Chamberlain C. Descovy Pediatric Postmarketing Pharmacovigilance Review. April 15, 2020. Accessed on May 27, 2022: https://www.fda.gov/media/141740/download

7. Descovy (emtricitabine and tenofovir alafenamide) [product label]. Foster City, CA: Gilead Sciences Inc.; Revised April 2016.

8. Descovy (emtricitabine and tenofovir alafenamide) [product label]. Foster City, CA: Gilead Sciences Inc.; Revised September 2017.

8 APPENDICES

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

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 or not 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.

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