Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

Date:	April 15, 2020
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Product Name:	Descovy® (emtricitabine and tenofovir alafenamide)
Pediatric Labeling Approval Date:	September 28, 2017
Application Type/Number:	NDA 208215
Applicant:	Gilead Sciences Inc.
OSE RCM #:	2020-176

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Descovy (emtricitabine, and tenofovir alafenamide) in pediatric patients through age 16 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) and focuses on serious unlabeled adverse events reported in pediatric patients using Descovy. This review was triggered by approval of new pediatric labeling on September 28, 2017.

Descovy is a two-drug fixed dose combination product containing 200 mg of emtricitabine and 25 mg of tenofovir alafenamide. It was first approved in April 2016 and was 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 updated to "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. Descovy is not recommended for individuals weighing less than 35 kg for HIV-1 PrEP. During the supplement review for HIV-1 PrEP indication, postmarketing adverse drug reactions of angioedema, urticaria and rash as supported by the cumulative safety review across tenofovir alafenamide (TAF)-containing products was added to the Descovy label.

There were no serious pediatric cases identified in this review. No new safety signals were identified, no increase in severity or frequency of any labeled adverse events, and no deaths were reported. DPV recommends no regulatory action at this time 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, and tenofovir alafenamide) in pediatric patients through age 16 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) and focuses on serious unlabeled adverse events reported in pediatric patients using Descovy. This review was triggered by approval of new pediatric labeling on September 28, 2017.

1.1 PEDIATRIC REGULATORY HISTORY

Descovy is a two-drug fixed dose combination product containing the nucleoside reverse transcriptase inhibitor emtricitabine and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide. Descovy was initially approved in April 2016 and was 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 of at least 35 kg and a creatinine clearance greater than or equal to 30 mL per minute. Prior to starting Descovy, patients should be tested for hepatitis B virus infection. In addition, estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating therapy and should be monitored during therapy in all patients. Each Descovy tablet contains 200 mg of emtricitabine and 25 mg of tenofovir alafenamide. The recommended dose is one tablet taken orally once daily with or without food in adult and pediatric patients. This combination product is not a complete regimen for the treatment of HIV-1; Descovy must be combined with a third drug to form a complete regimen.

DPV previously evaluated postmarketing adverse event reports with a serious outcome for Descovy in pediatric patients.[1] On September 28, 2017 Descovy's original pediatric indication was updated to "Descovy is indicated in pediatric patients weighing at least 35 kg" and the pediatric indication was expanded to include the use of Descovy, 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. DPV's evaluation, dated March 6, 2018, was prompted by the pediatric labeling changes on September 28, 2017, which was based on the results of Trial GS-US-292-0106, a pediatric trial evaluating the use of Genvoya.[2] Genvoya is a four-drug fixed dose combination product containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide. The efficacy assessment of Descovy was based on the demonstration of bioequivalence to Genvoya, which contains two of the ingredients in Genvoya, emtricitabine and tenofovir alafenamide. Because bioequivalence was demonstrated for emtricitabine and tenofovir alafenamide in Descovy, two of the components of Genvoya, the results of the pediatric study of Genvoya were used to support the safety and antiviral activity of Descovy. The safety profile in pediatric patients was similar to that of HIV-1 infected adults receiving this regimen. The most commonly reported adverse events in pediatric patients were respiratory tract infection, abdominal pain, vomiting, and headache.[2] FDA presented DPV's evaluation to the Pediatric Advisory Committee (PAC) on June 13, 2018. DPV's evaluation did not identify any new safety concerns, and recommended return to routine surveillance for adverse events with Descovy.

In October 2019, Descovy received approval for a new indication. Descovy's new indication is to treat 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. Descovy is not recommended for individuals weighing less than 35 kg for HIV-1 PrEP. The safety profile of Descovy for HIV-1 PrEP was comparable to that observed in clinical trials of HIV-infected subjects based on a double-blind, randomized, active-controlled trial (DISCOVER)[a] in which a total of 5,387 HIV-1 uninfected adult men and transgender women who have sex with men received Descovy (emtricitabine/tenofovir alafenamide) (N=2,694) or Truvada (emtricitabine/tenofovir disoproxil fumarate) (N=2,693) once daily for HIV-1 PrEP. 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.[4] Adult HIV-1 PrEP efficacy data from DISCOVER in men who have sex with men and transgender women and available safety and pharmacokinetic data with emtricitabine and tenofovir alafenamide in HIV infected pediatric subjects was used to support an adolescent indication.[5] During the supplement review for HIV-1 PrEP indication, postmarketing adverse drug reactions of angioedema, urticaria and rash as supported by the cumulative safety review across tenofovir alafenamide (TAF)-containing products was added to the Descovy label.[6]

1.2 RELEVANT LABELED SAFETY INFORMATION

The Descovy labeling has the following safety information under HIGHLIGHTS OF PRESCRIBING INFORMATION. Please refer to the full prescribing information for additional information.[3]

BOXED WARNING

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B and RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR HIV-1 PRE-EXPOSURE PROPHYLAXIS (PrEP) IN UNDIAGNOSED EARLY HIV-1 INFECTION

See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B (HBV) have been reported in HBV-infected individuals who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of DESCOVY. Hepatic function should be monitored closely in these individuals. If appropriate, anti-hepatitis B therapy may be warranted.

DESCOVY used for HIV-1 PrEP must only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of FTC/TDF for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate DESCOVY for HIV-1 PrEP if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed.

[a] DISCOVER = Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre- Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are at Risk of HIV-1 Infection (Study GS-US-412-2055). NCT02842086.

----------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.
- Immune reconstitution syndrome during treatment of HIV-1 infection: May necessitate further evaluation and treatment.
- 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.

----------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.

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

Consult the Full Prescribing Information prior to and during use for potential drug interactions.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Mothers infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV transmission.
- Pediatrics:
    - Treatment of HIV-1 Infection: Not recommended for patients weighing less than 25 kg.
    - HIV-1 PrEP: Not recommended for individuals weighing less than 35 kg.

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	January 29, 2020
Time period of search	January 29, 2018[†] through January 28, 2020
Search type	FAERS Business Intelligence Solutions (FBIS) Quick Query, Product-Manufacturer Reporting Summary

Table 1. FAERS Search Strategy*	
Product terms	Product Name: Descovy Product Active Ingredient: emtricitabine/tenofovir alafenamide fumarate NDA #: 208215
MedDRA search terms (Version 22.1)	All terms
* See Appendix A for a description of the FAERS database. † Data lock date of prior DPV pediatric review for Descovy dated March 6, 2018 (RCM # 2018-277)	

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 from January 29, 2018 through January 28, 2020 with Descovy.

Table 2. Total Adult and Pediatric FAERS Reports* with Age Received by FDA From January 29, 2018 through January 28, 2020 With Descovy

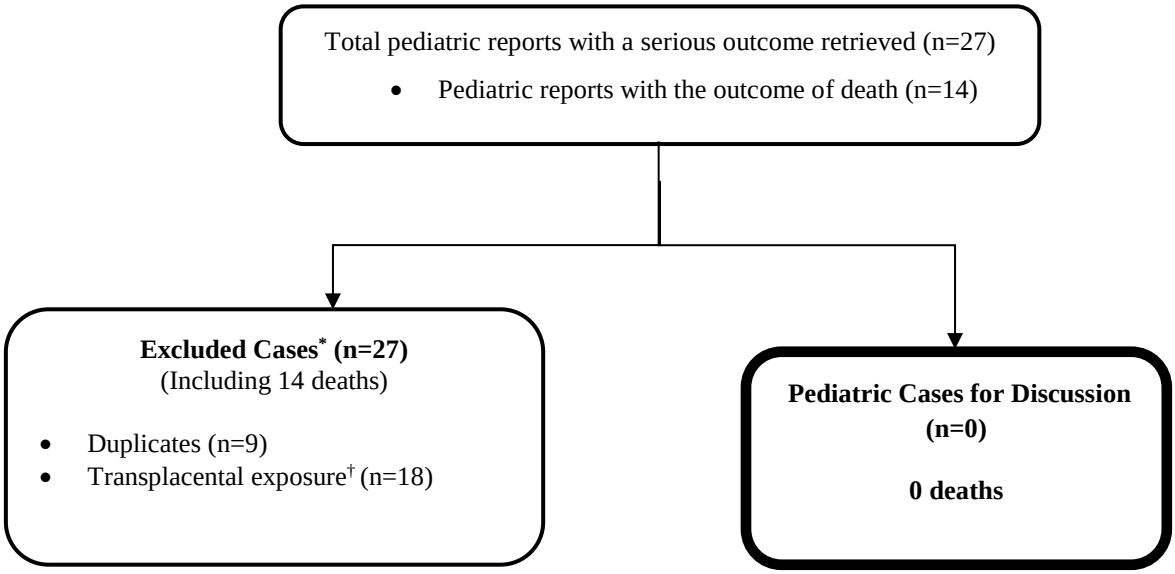
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	687 (434)	450 (201)	40 (20)
Pediatrics (0 - <17 years)	28 (20)	**27‡ (19)**	**14‡** (11)

* 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.
‡ See Figure 1, 11 additional reports of pediatric deaths were identified among reports not reporting an age and all 11 were transplacental exposure. The 14 pediatric death reports reflect these 11 additional reports.

3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved 27 serious pediatric reports received from January 29, 2018 through January 28, 2020. DPV reviewed the 27 FAERS pediatric reports with a serious outcome but all were excluded from further discussion because they were duplicate reports or reported exposure to Descovy through transplacental route. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Descovy



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

† DPV reviewed all transplacental reports and identified no evidence of new safety signals or worsening of known labeled adverse reactions within these cases.

3.1.3 Summary of Fatal Pediatric Cases (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)

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

4 DISCUSSION

There were no serious pediatric cases identified in this review for further discussion. No new safety signals were identified, no increase in severity or frequency of any labeled adverse events, and no deaths were reported.

5 CONCLUSION

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

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Descovy.

7 REFERENCES

1. Boxwell D. March 6, 2018. OSE RCM # 2018-277. DARRTS Reference ID: 4230398,
2. Baylor M. Clinical and Cross-Discipline Team Leader Review. NDA 207561 Supplement 014. September 10, 2017. Accessed February 25, 20120 at: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm580375.pdf
3. Descovy (emtricitabine, and tenofovir alafenamide) [product label]. Foster City, CA: Gilead Sciences Inc.; Revised December 2019.
4. Miele P, Carter W. Clinical Review and Summary CDTL NDA 208215/S-012 for HIV-1 PrEP in adults and adolescents weighing at least 35kg. DARRTS Reference ID: 4500037. October 2, 2019.
5. Gilead Sciences. Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex With Men and Are At Risk of HIV-1 Infection (DISCOVER). NCT02842086
6. Murray JS. Descovy, NDA 208215 Supplement 12 Approval letter for HIV-1 PrEP and changes to US prescribing information. Accessed on February 25, 20120 at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/208215Orig1s012ltr.pdf

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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