

**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 Review

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Product Name: Descovy[®] (emtricitabine and tenofovir alafenamide)
oral tablets

**Pediatric Labeling
Approval Date:** April 4, 2016

Application Type/Number: NDA 208215

Applicant/Sponsor: Gilead Sciences Inc.

OSE RCM #: 2018-277

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with Descovy® (emtricitabine and tenofovir alafenamide) in pediatric patients.

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 HIV-1 infection in adults and pediatric patients weighing at least 35 kg. In September 2017, Descovy 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.

There were no serious pediatric cases identified in this search. No new safety signals were identified, there was no increase in severity or frequency of any labeled adverse events, and no deaths were reported. There is no evidence from these data that there are pediatric safety concerns with Descovy. DPV recommends no regulatory action at this time and will continue to monitor adverse events associated with the use of Descovy.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Descovy is a two-drug fixed dose combination product containing a nucleoside reverse transcriptase inhibitor, emtricitabine, and a 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 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.

In September 2017, the FDA expanded the pediatric indication 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. This was based on the results of Trial GS-US-292-0106, which was a pediatric trial evaluating the use of Genvoya[®].¹ 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 on this regimen. The most commonly reported adverse events in pediatric patients were respiratory tract infection, abdominal pain, vomiting, and headache.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

BOXED WARNING

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

¹ <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm580375.pdf>

DESCOVY is not approved for the treatment of chronic hepatitis B virus (HBV) infection. Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HIV-1 and HBV and 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 patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

-----**CONTRAINDICATIONS**-----

- None.

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

- Immune reconstitution syndrome: May necessitate further evaluation and treatment.
- New onset or worsening renal impairment: Assess creatinine clearance, urine glucose, and urine protein in all patients before initiating DESCOVY therapy and monitor during therapy. Monitor serum phosphorus in patients with chronic kidney disease.
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

-----**ADVERSE REACTIONS**-----

- Most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea.

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

- Pediatrics: Not recommended for patients weighing less than 25 kg.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

<i>Table 2.1.1 FAERS Search Strategy</i>	
Date of Search	January 29, 2018
Time Period of Search	April 4, 2016* through January 29, 2018
Search Type	FAERS Business Intelligence Solution (FBIS)
Product Names	Product Name: Descovy Product Active Ingredient: emtricitabine/tenofovir alafenamide fumarate NDA: 208215
Search Parameters	All ages, all outcomes, worldwide
<i>*U.S. Approval date and approval date of pediatric labeling</i>	

2.2 RESULTS

2.2.1 Total number of FAERS reports by Age

Table 2.2.1 Total Adult and pediatric FAERS reports* from April 4, 2016 through January 29, 2018 with Descovy

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	197 (138)	118 (56)	6 (2)
Pediatrics (0 - <17 years)	3 (3)	1 (1)	0 (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, and other serious important medical events.

2.2.2 Selection of Serious Pediatric Cases in FAERS

We did not identify any pediatric reports with a serious outcome from April 4, 2016 through January 29, 2018 associated with the use of Descovy.

There was one case in a 16-year-old male that was coded as being serious; however, the adverse events (blood creatinine of 1.6, 2-plus glycosuria, and 2-plus proteinuria) occurred while the patient was taking Truvada. These laboratory values returned to normal when Truvada was replaced with Descovy.

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

We did not identify any fatal pediatric adverse event cases.

2.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASE (N=0)

We did not identify any non-fatal pediatric serious adverse event cases.

3 DISCUSSION

There were no serious pediatric cases identified in this search. No new safety signals were identified, there was no increase in severity or frequency of any labeled adverse events, and no deaths were reported.

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with Descovy.

5 RECOMMENDATIONS

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

6 APPENDICES

6.1 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 spontaneous adverse event reports that are submitted to FDA from the product manufacturer or directly from the consumer, healthcare professional, or other reporter. The database supports the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products.

FAERS is particularly useful for identifying new (i.e., unexpected or unlabeled), rare, serious adverse events that are temporally associated with a product for which the background rate of events is low. Examples of these adverse events include Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anemia, and liver injury. Such adverse events are often not observed in the premarketing trials because these trials are limited in the number of patients, the types of patients included, and the duration of treatment. In addition, the spontaneous adverse event reports in FAERS can further refine or characterize a known adverse event.

There are inherent limitations to FAERS. FAERS data are rarely reliable for analyzing adverse events that have a delayed time to onset (e.g., effects on bone metabolism leading to osteoporosis) or a delayed time to detection (e.g., cancers). This limitation also applies to events that are not unusual in the underlying population (e.g., myocardial infarction in the older adult population). Additionally, FAERS cannot be used to quantify a risk or calculate the incidence of an adverse event because FAERS does not collect information about the total number of persons exposed to a product. Under-reporting of adverse events, as a result of the voluntary nature of spontaneous reporting, further limits the feasibility of using FAERS data to determine the incidence of an adverse event associated with a product. Because of these limitations, FAERS data should not be used to make comparisons between drugs or biologic products in an effort to identify differential risk. Specific limitations that may lead to differential reporting for one product over another may include the time the product has been on the market, publication of literature reports related to the adverse event, and publicity.

Spontaneous adverse event reports are frequently missing complete information necessary for determining whether there is a causal relationship between a product and an adverse event. For example, the reports may lack information about product exposure (e.g., timing of treatment, duration of treatment, actual dose(s) taken, or concomitant products used); baseline patient characteristics; outcomes following product dechallenge, rechallenge, or both; and information about the adverse event (e.g., relevant laboratory or radiologic information, timing, duration, and seriousness). Because of these limitations, FAERS data alone cannot often be relied upon for definitive causality determinations.

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