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

Date:	December 20, 2017
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Product Name:	Genvoya® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) oral tablets
Pediatric Labeling Approval Date:	November 05, 2015
Application Type/Number:	NDA 207561
Applicant/Sponsor:	Gilead Sciences Inc.
OSE RCM #:	2017-2415

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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 Genvoya® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) in pediatric patients.

Genvoya is a four-drug fixed dose combination product initially approved in 2015. Genvoya is indicated as a complete regimen for the treatment of HIV-1 infection in patients 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 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya. At the time of initial approval, Genvoya was indicated in adults and pediatric patients 12 years of age and older with body weight of at least 35 kg.

Although we reviewed all FDA Adverse Event Reporting System (FAERS) reports with Genvoya in the pediatric population (ages 0 - < 17 years) during the period November 05, 2015 (initial U.S. approval) through September 24, 2017, only two cases were included in our case series. The events described in the two cases (i.e., abdominal pain, headache, dizziness and tremor) contained limited information which precluded a meaningful causality assessment and were possibly attributed to other causes. Of the overall reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths reported with Genvoya in the pediatric population.

There is no evidence from these data that there are new pediatric safety concerns with Genvoya at this time.

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

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Genvoya is a four-drug fixed dose combination product containing elvitegravir, an HIV-1 integrase strand transfer inhibitor, cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir alafenamide, both HIV-1 nucleoside analog reverse transcriptase inhibitors. Genvoya is indicated as a complete regimen for the treatment of HIV-1 infection in patients 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 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya. Each Genvoya tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide. The recommended dosage of Genvoya is one tablet taken orally once daily with food.[1]

Genvoya was initially approved in November 2015 in adults and pediatric patients 12 years of age and older with body weight at least 35 kg and a creatinine clearance greater than or equal to 30 mL per minute. In September 2017, the FDA approved a supplement to extend the Genvoya indication to include the pediatric population of patients weighing at least 25 kg. The use of Genvoya in the pediatric population was supported by studies in adults and by an open-label trial of antiretroviral treatment-naïve HIV-1 infected pediatric subjects receiving Genvoya (Study GS-US-292-0106; Identification No. NCT01854775).[2-3] The safety profile of Genvoya in pediatric patients was similar to that in adults; the most common adverse events considered related to Genvoya in pediatric patients were abdominal pain, vomiting, and nausea.[2-5]

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

At the time of the September 2017 pediatric labeling change, the pertinent excerpted sections of the approved labeling for Genvoya were identical to the ones from November 2017:

BOXED WARNING

GENVOYA 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 coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of GENVOYA. Hepatic function should be monitored closely in these patients. If appropriate, anti-hepatitis B therapy may be warranted.

CONTRAINDICATIONS

Coadministration of GENVOYA is contraindicated with drugs that:

- Are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious adverse events.
- Strongly induce CYP3A, which may lead to lower exposure of one or more components and loss of efficacy of GENVOYA and possible resistance.

WARNINGS AND PRECAUTIONS

- Risk of adverse reactions or loss of virologic response due to drug interactions: The concomitant use of GENVOYA and other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of GENVOYA and possible development of resistance; and possible clinically significant adverse reactions from greater exposures of concomitant drugs.
- Immune reconstitution syndrome: May necessitate further evaluation and treatment.
- New onset or worsening renal impairment: Prior to and during therapy, as clinically appropriate, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients, and also assess 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.

DRUG INTERACTIONS

- GENVOYA should not be administered with other antiretroviral medications for treatment of HIV-1 infection.
- GENVOYA can alter the concentration of drugs metabolized by CYP3A or CYP2D6. Drugs that induce CYP3A can alter the concentrations of one or more components of GENVOYA. Consult the full prescribing information prior to and during treatment for potential drug-drug interactions.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System Search Strategy

The Division of Pharmacovigilance (DPV) searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

Date of Search	November 17, 2017
Time Period of Search	November 05, 2015* through September 24, 2017
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query Product-Manufacturer Reporting Summary
Product Names	Product Name: Genvoya Product Active Ingredient: Cobicistat\Elvitegravir\Emtricitabine\Tenofovir Alafenamide Fumarate NDA: 207561
Search Parameters	All ages, all outcomes, worldwide

** U.S. Approval date and approval date of pediatric labeling*

We reviewed all FAERS pediatric reports from November 05, 2015 through September 24, 2017 and included reports in our case series if an adverse event was reported.

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 presents the number of adult and pediatric FAERS reports from November 05, 2015 through September 24, 2017 with Genvoya.

Table 2.2.1 Total Adult and Pediatric FAERS Reports* from November 05, 2015 through September 24, 2017 with Genvoya

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	346 (276)	159 (90)	5 (2)
Pediatrics (0 - <17 years)	4 (3)	2‡ (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.*

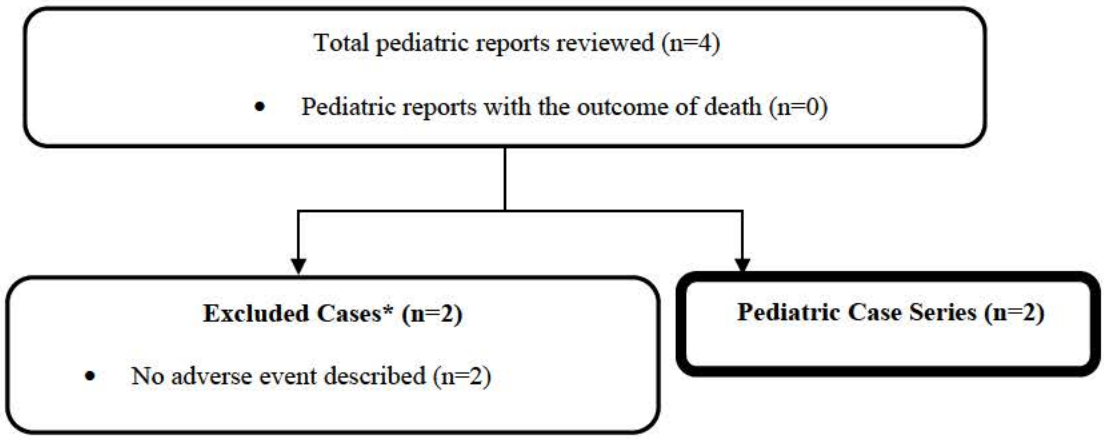
‡ *See Figure 2.2.2*

2.2.2 Selection of Pediatric Cases in FAERS

We identified four pediatric reports with Genvoya from November 05, 2015 through September 24, 2017. Our pediatric case series included two cases.

Figure 2.2.2 presents the specific selection of cases to be summarized in **Section 2.4**.

Figure 2.2.2 Selection of Pediatric Cases with Genvoya



* DPV reviewed these cases, but they were excluded from the case series for the reason listed above

2.3 SUMMARY OF FATAL PEDIATRIC CASES (N=0)

We did not identify any fatal pediatric adverse event cases.

2.4 SUMMARY OF ALL PEDIATRIC CASES (N=2)

Appendix B contains a line listing of all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the two cases in this case series.

FAERS Case Number	**13006806**
Initial FDA Received Date	December 07, 2016
Country	USA

A 15-year-old female received Genvoya and darunavir (dose and frequency not reported) because of the development of resistance associated with medication non-adherence. It was reported the patient's mother crushed the Genvoya tablets and placed the contents in gel capsules. After the first dose of Genvoya and darunavir, the patient stated she could not tolerate it due to upset stomach and was placed on another unspecified regimen. Approximately 6 to 7 months later, the patient re-started Genvoya (without darunavir); however, it was not reported if the patient experienced upset stomach when Genvoya was administered without darunavir. The patient's past medical history, relevant laboratory/diagnostic tests, and causality assessment were not reported.

Reviewer's Comments: This case contains limited information which precluded a meaningful causality assessment. The Genvoya label does not state if the tablets can be crushed or split. Darunavir is labeled for abdominal pain.[6]

FAERS Case Number **13627464**

Initial FDA Received Date	June 08, 2017
Country	Great Britain

A 12-year-old male received Genvoya and approximately 5 months later, the patient fainted while at church. The patient was taken to the emergency room and experienced intermittent headache and felt dizzy. The patient's mother stated that the patient was shaking; however, the emergency room report stated there was no seizure activity. An electrocardiogram was performed and results were reported as normal; the results of magnetic resonance imaging of the brain and spine were not reported. The patient's past medical history and concomitant medications were not reported. Although a clinical outcome for the reported events was not reported, the patient was not hospitalized and remained on Genvoya. The reporter's causality assessment for fainting was due to prolonged standing and not related to Genvoya.
Reviewer's Comments: This case contains limited information which precluded a meaningful causality assessment. The events of headache, dizziness, and tremor were possible symptoms of syncope, which was attributed to prolonged standing by the reporting pharmacist.

3 DISCUSSION

Of the two cases of pediatric patients included in this case series, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths reported with Genvoya in the pediatric population. The events described in the two cases (i.e., abdominal pain, headache, dizziness and tremor) contained limited information which precluded a meaningful causality assessment and were possibly attributed to other causes.

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with Genvoya at this time.

5 RECOMMENDATIONS

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

6 REFERENCES

1) Genvoya® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets for oral use, NDA 207561 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207561s013lbl.pdf. Accessed: November 2017.
2) U.S. Food & Drug Administration, New Pediatric Labeling Information Database. Available at: https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase. Accessed: November 2017.
3) Development Resources for Medical, Statistical, and Clinical Pharmacology Reviews of Pediatric Studies Conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA Safety and Innovation Act of 2012 (FDASIA). Available at: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm316937.htm. Accessed: November 2017.
4) Gaur AH, Kizito H, Prasitsueubsai W, et al. Safety, efficacy, and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in treatment-naive, HIV-infected adolescents: a single-arm, open-label trial. *Lancet HIV*. 2016;3:e561-e568.
5) Natukunda E, Gaur AH, Kosalaraksa P, et al. Safety, efficacy, and pharmacokinetics of single-tablet elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in virologically suppressed, HIV-infected children: a single-arm, open-label trial. *Lancet Child and Adolesc Health*. 2017;1:27-34.
6) Prezista® (darunavir), NDA 021976 – Approved Product Label. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021976s045_202895s020lbl.pdf. Accessed: November 2017.

7 APPENDICES

7.1 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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference 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.

7.2 APPENDIX B. FAERS LINE LISTING OF THE GENVOYA PEDIATRIC CASE SERIES (N=2)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome*
1	December 07, 2016	13006806	1	US-GILEAD-2016-0247127	Non-Expedited	15	Female	USA	
2	June 08, 2017	13627464	2	GB-GILEAD-2017-0276642	Expedited (15-day)	12	Male	Great Britain	OT

*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, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.

Abbreviations: OT, Other serious medical event

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