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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	April 17, 2020
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Product Name:	Genvoya® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) oral tablets
Pediatric Labeling Approval Date:	September 25, 2017
Application Type/Number:	NDA 207561
Applicant/Sponsor:	Gilead Sciences Inc.
OSE RCM #:	2020-4

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Genvoya® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on all adverse events associated with Genvoya in pediatric patients.

FDA approved Genvoya on November 5, 2015 for adults and pediatric patients 12 years and older weighing at least 35 kg, and then extended the pediatric weight to at least 25 kg on September 25, 2017. Genvoya is indicated for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RINA 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.

DPV reviewed all FAERS reports with Genvoya use in the pediatric population (ages zero to <18 years), received by FDA from September 25, 2017 through December 17, 2019. After excluding duplicate reports, transplacental reports, and unassessable reports, DPV included four pediatric cases in the series.

Of the four cases reviewed in pediatric patients, there were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with Genvoya. No specific pattern of adverse events was noted; single reports of uveitis and weight gain, and two cases of suicide attempt were reported. These reports of adverse events are consistent with known adverse reactions described in the Genvoya labeling (uveitis, suicide attempt) or the literature (weight gain) or had limited information which precluded a meaningful causality assessment.

This review did not identify any new or unexpected pediatric safety concerns for Genvoya. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Genvoya through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Genvoya® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on all adverse events associated with Genvoya in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Genvoya is a four-drug combination of elvitegravir, an HIV-1 integrase strand transfer inhibitor (INSTI), cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir alafenamide (TAF), both HIV-1nucleoside analog reverse transcriptase inhibitors (NRTIs). Genvoya is indicated "as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RINA 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."[1]

On November 5, 2015, FDA first approved Genvoya for adults and pediatric patients 12 years and older weighing at least 35 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 adolescents (12-<18years) receiving Genvoya (Study GS-US-292-0106).[2,3] The safety profile of Genvoya in pediatric patients were comparable to those observed in adult studies.[2-5] The most common adverse events considered related to Genvoya in pediatric patients were nausea, abdominal pain, and vomiting.

On September 25, 2017, FDA approved a supplement (S014) to extend the Genvoya indication to include pediatric patients weighing at least 25 kg.[6] This pediatric supplement was in response to PREA postmarketing requirement 2971-1: *"Conduct your deferred pediatric study in HIV-infected patients 6 years to less than 12 years to assess the pharmacokinetics, safety, tolerability, and antiviral activity of age-appropriate doses of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide given in combination. At least some of the safety data must be derived from dosing as the Genvoya fixed dose combination"*

Genvoya use in pediatric patients weighing at least 25 kg is supported by studies in adults and by an open-label trial in virologically-suppressed pediatric patients 6 to less than 12 years and weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to Genvoya (Study GS-US-292-0106). The Division of Antiviral's (DAV) clinical review of the pediatric supplement (207561/S014) evaluated adverse events of interest of renal toxicity and bone toxicity (decrease in bone mineral density).[6] Findings related to renal toxicity were "consistent with those observed in adolescent and adult studies of Genvoya" and "there were no new or unexpected bone safety findings." Lastly, during the review of this pediatric supplement, DAV identified decrease in CD4 cell count as a safety issue. They noted that this finding was not observed in adolescents or adults and no mechanism has been identified. Decrease in CD4 count was included in the Genvoya labeling (**Section 6.1** under Clinical Trials in Pediatric

Subjects) and any post-marketing reports or publications discussing CD4 declines (or lack of anticipated CD4 increases) and/or reports of opportunistic infections are of interest.[1,6]

DPV previously evaluated postmarketing adverse event reports for Genvoya in pediatric patients. DPV's evaluation, dated December 20, 2017 and including cases through September 24, 2017, did not identify any new safety concerns and recommended routine monitoring for adverse events with Genvoya.[8]

At the time of writing this review, FDA is currently evaluating a safety issue of renal toxicity related to the TAF component of this combination product (TSI 2089).[7]

1.2 RELEVANT LABELED SAFETY INFORMATION

Genvoya labeling provides the following safety information (excerpted from the pertinent sections). For further Genvoya labeling information, please refer to the full prescribing information.[1]

BOXED WARNING

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. (5.1)

CONTRAINDICAITONS

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. (4)
- Strongly induce CYP3A, which may lead to lower exposure of one or more components and loss of efficacy of GENVOYA and possible resistance. (4)

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. (5.2)
- Immune reconstitution syndrome: 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 GENVOYA and during therapy on a clinically appropriate schedule in all patients. Also assess serum phosphorus in patients with chronic kidney disease. (5.4)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.5)

ADVERSE REACTIONS

Most common adverse reaction (incidence greater than or equal to 10%, all grades) is nausea. (6.1)

DRUG INTERACTIONS

- GENVOYA should not be administered with other antiretroviral medications for treatment of HIV-1 infection. (7.1)
- 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. (4, 7.2, 7.3, 12.3)

PEDIATRIC USE

The safety and effectiveness of GENVOYA for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg [see Indications and Usage (1) and Dosage and Administration (2.2)].

Use of GENVOYA in pediatric patients between the ages of 12 to less than 18 years and weighing at least 35 kg is supported by studies in adults and by a study in antiretroviral treatment-naïve HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 35 kg (cohort 1 of Study 106, N=50). The safety and efficacy of GENVOYA in these pediatric subjects was similar to that in adults [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)].

Use of GENVOYA in pediatric patients weighing at least 25 kg is supported by studies in adults and by an open-label trial in virologically-suppressed pediatric subjects ages 6 to less than 12 years and weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to GENVOYA (cohort 2 of Study 106, N=23). The safety in these subjects through 24 weeks was similar to that in antiretroviral treatment-naïve adults with the exception of a decrease in mean change from baseline in CD4+ cell count [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)].

Safety and effectiveness of GENVOYA in pediatric patients less than 25 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	December 18, 2019
Time Period of Search	September 25, 2017[†] - December 17, 2019
Search Type	*Quick Query*
Product Terms	• Product Name: Genvoya • Product Active Ingredient: cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide, cobicistat/elvitegravir/emtricitabine/tenofovir • NDA: 207561
MedDRA Search Terms (Version 22.1)	All preferred terms (PTs)
Search Parameters	Age < 18 years, all outcomes, worldwide
* See **Appendix A** for a description of the FAERS database. [†] End date of previous pediatric postmarketing adverse event review	

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 September 25, 2017 through December 17, 2019 with Genvoya.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from September 25, 2017 through December 17, 2019 with Genvoya

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	1248 (816)	699 (281)	35 (13)
Pediatrics (0 - <18 years)	24 (17)	17 (10)	2 (2)

* 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.

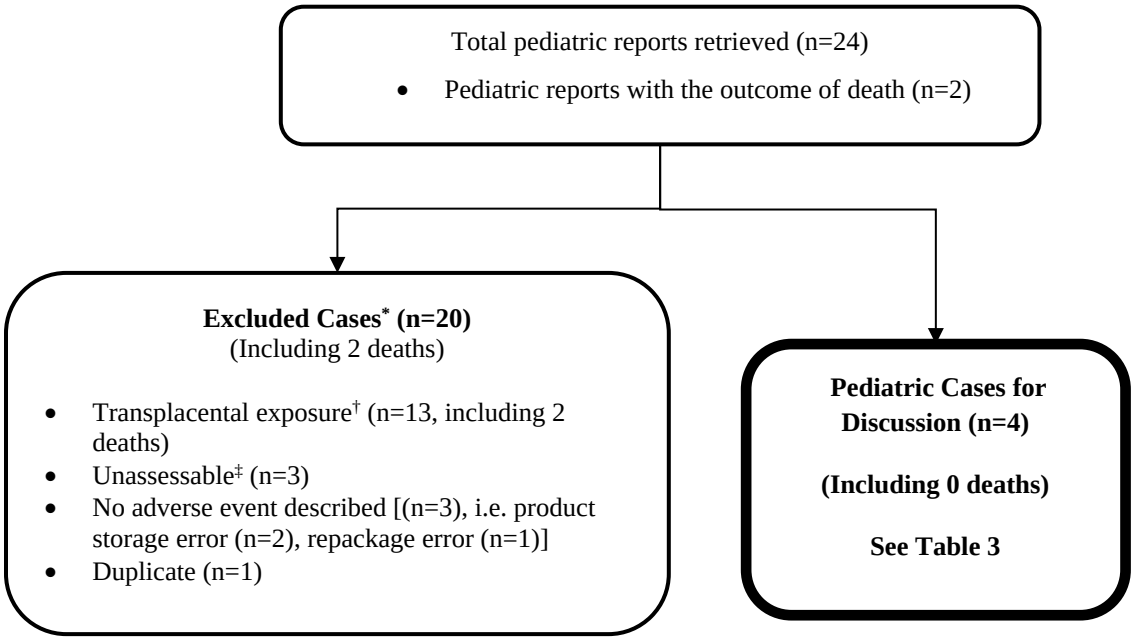
3.1.2 Selection of Pediatric Cases in FAERS

Our FAERS search retrieved 24 pediatric reports from September 25, 2017 through December 17, 2019.

We reviewed all FAERS pediatric reports. We excluded reports from the case series for various reasons, such as transplacental exposures, unassessable cases (e.g., report contained insufficient information), or if there was no adverse event described. We summarize the remaining cases in the sections below.

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

Figure 1. Selection of Pediatric Cases with Genvoya



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above. No new safety signals were identified among excluded cases.

† FDA evaluated a safety signal of neural tube defects (NTDs) with transplacental exposure to dolutegravir (an INSTI) and the dolutegravir label was updated in 2019.[9,10] Other drugs in the INSTI class, including elvitegravir, were also evaluated for this potential safety issue. Further information can be found under TSI 1898. Genvoya is not recommended for use during pregnancy because of substantially lower exposures of cobicistat and elvitegravir during pregnancy.[1] Of the transplacental cases reviewed, one case reported exencephaly but lacked additional details.

‡ 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) or the information is contradictory or information provided in the case cannot be supplemented or verified.

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the 4 pediatric cases.

Table 3 summarizes the 4 FAERS cases in pediatric patients with Genvoya received by FDA from September 25, 2017 through December 17, 2019.

Table 3. Characteristics of the FAERS Pediatric Cases with Genvoya Received by FDA from September 25, 2017 through December 17, 2019 (N=4)		
Age	12 - < 18 years	4
Sex	Male	2
	Female	2
Country	United States	2
	Foreign	2
Reported Reason for Use	HIV	4
Serious Outcome*	Life-threatening	1
	Hospitalization	2
	Other Serious	3
* 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. A case may have more than one serious outcome.		

3.1.4 Summary of Fatal Pediatric Cases (N=0)

We did not include any fatal pediatric adverse event cases in our case series.

3.1.5 Summary of Non-Fatal Pediatric Cases (N=4)

We identified four FAERS cases with Genvoya in the pediatric population reporting a non-fatal outcome. The cases are summarized below. No cases were identified of previously noted adverse events of interest of renal toxicity, bone toxicity, or decrease in CD4 count.[6]

Eye Disorders (n=1)

FAERS Case# 14496552 (Duplicate FAERS Case #14506647), USA, Direct

PTs: *Retinal detachment; Uveitis; Vitritis; Low vision, one eye; Menorrhagia; Prolactin increased; Pituitary adenoma; Blind*

- Case Description: A 14-year-old female developed acute, severe uveitis/vitritis of the left eye with visual impairment after being on Genvoya for approximately 1.5 years. Past medical history includes HIV well-controlled on antiretrovirals with undetectable viral load, long standing retinal detachment in right eye causing blindness, encephalomalacia, child abuse, post-traumatic stress disorder, mutism. Concomitant medication was Vitamin D3. She had diminished color vision with diminished visual acuity in both eyes. Ophthalmologic exam findings were consistent with chronic right retinal detachment and left eye acute uveitis, vitritis, retinal detachment, and swollen optic nerve. The reporter stated that the patient may have pars planitis. Complete blood count and differential analysis was normal and rapid plasma regain (RPR), "toxo" test, and antinuclear antibody (ANA) were negative. Three months after the patient experienced uveitis, she underwent a brain MRI due to menorrhagia and high prolactin. MRI noted "near total detachment of the right retina, partial left retinal detachment and left papilledema versus drusen. Left-sided pituitary microadenoma. Cystic encephalomalacia of the right temporal pole, chronic and Wallerian degeneration affecting the anterior commissure, right forn [sic]." The patient received steroid injections and her vision improved from only being able to count fingers to 20/160. She continued Genvoya.

Reviewer's comments:
The Genvoya package insert describes one case of uveitis in Section 6.1 Clinical Trials experience: a 13-year-old female in Study 106 who received Genvoya developed uveitis and the uveitis resolved without drug discontinuation.[1] Additionally, Section 5.3 Warnings and Precautions of the Genvoya package insert also describes immune reconstitution syndrome, which is a broad entity that encompasses immune recovery uveitis.[11] The differential for causes of uveitis is broad; the condition may be secondary to systemic inflammatory conditions, infections, or therapeutic drug products.[12] The diagnostic labs reported, although normal, are nonspecific and represent an incomplete evaluation for the etiology of uveitis. Similarly, the reported MRI findings confirm ophthalmologic findings but do not inform causality. In addition to uveitis, the narrative describes chronic and acute retinal detachment and pituitary adenoma, which are not described in the Genvoya label. Retinal detachment may be associated with uveitis but traumatic injury from the patient's history of child abuse is another plausible explanation. Pituitary adenoma may explain the patient's menorrhagia and high prolactin level, but the condition is not associated with uveitis or retinal detachment. The narrative lacks information to perform a robust causality assessment with uveitis, retinal detachment, or pituitary adenoma and Genvoya. An expanded FAERS database search for high level term (HLT) uveal tract infections, irritations, and inflammations; HLT pituitary neoplasms; or PT retinal detachment with Genvoya identified no additional adult or pediatric cases with uveitis, retinal detachment, or pituitary adenoma.

Attempted Suicide (n=2)
FAERS Case# 14043003, Great Britain, Expedited
PTs: *Intentional overdose; Suicide attempt*

- A nurse reported that a 12-year-old female attempted suicide by taking eight tablets of Genvoya. She was receiving Genvoya one tablet daily for HIV treatment. No other past medical history was reported. Concomitant medications were not reported. She was

admitted to the hospital and "had her stomach pumped." Genvoya was discontinued and outcome was not reported.

FAERS Case# 16327557, Turkey, Expedited

PTs: *Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood HIV RNA; Blood creatine phosphokinase increased; Blood lactate dehydrogenase increased; Drug ineffective; Hepatic enzyme increased; Overdose; Product dose omission; Product use issue; Rash; Renal failure; Renal impairment; Suicide attempt; Treatment noncompliance; Viral load increased; Vomiting*

- A physician reported that a 17-year-old male attempted suicide by taking 2 boxes (also reported as 3 or 4 tablets at the same time) of Genvoya. He was receiving Genvoya for HIV treatment. He did not have psychiatric history, but there was a family history of suicide attempt in his brother, with whom he lived. He reportedly experienced nausea, vomiting, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (values not reported), and abnormal renal function/renal failure (values not reported). He was admitted to the intensive care unit and discharged after two weeks when renal function normalized, and AST and ALT levels were improving. At the follow up appointment, the patient stated he attempted suicide because his HIV RNA level and viral load were not improving despite taking medication. He also stated he missed "some doses" and did not take Genvoya with food, as recommended. He was switched to Triumeq (abacavir, dolutegravir, lamivudine), but after experiencing an adverse event on Trumeq, he was switched back to Genvoya. He then experienced serious skin eruptions, and Genvoya therapy was stopped. The case did not provide additional information regarding the skin eruptions.

Reviewer's comments: *Both cases describe an adolescent attempting suicide with Genvoya. Depression and suicidality have been reported rarely with drugs in the INSTI class.[13] It is difficult to assess causality with Genvoya in these cases with limited information (i.e., past medical history, concomitant medications, current support system) especially in the setting of increased risk of mood disorders and suicide in people with HIV.[13] In addition, Section 6.1 of the Genvoya label describes the following in adults[1]:*

> *"The safety of GENVOYA in virologically-suppressed adults was based on Week 96 data from 959 subjects in a randomized, open-label, active-controlled trial (Study 109) in which virologically suppressed subjects were switched from a TDF-containing combination regimen to GENVOYA. Overall, the safety profile of GENVOYA in subjects in this study was similar to that of treatment-naïve subjects [see Clinical Studies (14.3)]. Additional adverse reactions observed with GENVOYA in Study 109 included suicidal ideation, suicidal behavior, and suicide attempt (<1% combined) all of these events were serious, and all occurred in subjects with a preexisting history of depression or psychiatric illness."*

Weight Gain (n=1)

FAERS Case# 14675420, USA, Non-Expedited

PTs: *Weight increased*

- A 14-year-old male experienced weight gain while on Genvoya for treatment of HIV infection. No other past medical history reported, concomitant medications were not reported, and patient was previously on Combivir (lamivudine/zidovudine) and Kaletra

(lopinavir/ritonavir). Over the course of 13 months, the patient gained 34.7 kg (76 lbs.). Genvoya was continued.

Reviewer's comments: *Despite a large weight gain over about 1 year, this case contains limited information which precludes a meaningful causality assessment, namely other growth parameters including height, BMI as well as information on patient's diet and exercise. Weight gain is known in the literature to be associated with the INSTI class, mainly dolutegravir.*[14-16] *Dolutegravir is the only INSTI labeled with "weight increased" in Section 6.2 Postmarketing Experience.*[10]

4 DISCUSSION

Of the four cases reviewed in pediatric patients, there were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with Genvoya. No specific pattern of adverse events was noted; single reports of uveitis and weight gain, and two cases of suicide attempt were reported. These reports of adverse events are consistent with known adverse reactions described in the Genvoya labeling (uveitis, suicide attempt) or the literature (weight gain) or had limited information which precluded a meaningful causality assessment.

5 CONCLUSION

DPV did not identify any new or unexpected pediatric safety concerns for Genvoya.

6 RECOMMENDATION

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

7 REFERENCES

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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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=4)

No.	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes *
1	10/4/2017	14043003	1	GB-GILEAD-2017-0296371	EXPEDITED (15-DAY)	12	FEMALE	GBR	HO,OT
2	2/6/2018	14496552; 14506647	1	US-GILEAD-2018-0319469	DIRECT; EXPEDITED (15-DAY)	14	FEMALE	USA	OT
3	3/23/2018	14675420	1	US-GILEAD-2018-0321334	NON-EXPEDITED	14	MALE	USA	
4	5/17/2019	16327557	4	TR-GILEAD-2019-0408124	EXPEDITED (15-DAY)	17	MALE	TUR	HO,LT,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. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: HO=Hospitalization, LT= Life-threatening, OT=Other Medically Significant

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