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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pediatric Postmarketing Pharmacovigilance

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Product Name: Abacavir (Ziagen®) and Abacavir/Lamivudine (Epzicom®)

**Pediatric Labeling
Approval Date:** Ziagen: March 23, 2015/Epzicom: September 17, 2015

Application Type/Number: NDA 020977 (Ziagen)/ NDA 021652 (Epzicom)

Applicant/Sponsor: ViiV HealthCare/GlaxoSmithKline

OSE RCM #: 2018-589

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for abacavir and abacavir/lamivudine in pediatric patients ages 0 to <17. 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 focused on serious unlabeled adverse events associated with abacavir and abacavir/lamivudine in pediatric patients.

Ziagen® (abacavir) was first approved in 1998 and is indicated for the treatment of human immunodeficiency virus -1 (HIV-1) infection in adults and pediatric patients 3 months of age and older. In March 2015, abacavir was approved for once daily dosing (previously approved for twice a day dosing) in patients 3 months or older. Epzicom® (abacavir/lamivudine) was first approved in 2004 for the treatment of HIV-1 infection in adults only. In 2015, the indication expanded from adults to pediatrics weighing at least 25kg.

Of the pediatric reports reviewed, there were no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly attributable to abacavir and abacavir/lamivudine. Although we reviewed all serious FAERS reports in pediatric patients (ages 0 to <17 years) received from April 1, 2011 (end of the previous abacavir review data lock date) through August 31, 2017, only four non-fatal cases were included in our case series. Most excluded reports described transplacental exposure, adverse events attributable to concomitant medication or comorbidities (such as hypersensitivity with zidovudine or hypertension reported in a patient with a history of pulmonary hypertension), consistent with the known risks described in labeling (such as immune reconstitution inflammatory syndrome and hypersensitivity reactions), or contained insufficient information to determine causality.

The four cases included in our cases series described unlabeled adverse events (drug-induced hepatitis, HIV-associated nephropathy (HIVAN), hematuria/proteinuria, and lipoma). The cases either lacked sufficient details to determine causality or were known events associated with HIV disease (HIVAN) or prolonged antiretroviral therapy (lipomas).

DPV did not identify any new pediatric safety concerns with abacavir and abacavir/lamivudine and recommends no regulatory action at this time. We will continue to monitor all adverse events associated with the use of abacavir and abacavir/lamivudine.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for abacavir and abacavir/lamivudine in pediatric patients through 0 to <17 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 serious unlabeled adverse events associated with abacavir and abacavir/lamivudine in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Ziagen® (abacavir)

Abacavir tablets (300mg) and oral solution (20mg/ml) (NDA 020977/020978) were initially approved December 17, 1998, in combination with other antiretroviral agents for the treatment of human immunodeficiency virus -1 (HIV-1) infection. The initial pediatric dose (3 months – 16 years of age) of abacavir recommended in the labeling was 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents. Abacavir was approved for once-daily dosing in adults on August 2, 2004. On March 23, 2015, abacavir dosing was updated to 8mg per kg twice daily or 16mg per kg once-daily (up to a maximum of 600mg daily) in combination with other antiretroviral agents in patients 3 months or older.

The Office of Surveillance and Epidemiology previously evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Ziagen in pediatric patients on June 14, 2011.¹ This review did not identify any new safety concerns and recommended routine monitoring of adverse events for abacavir. FDA presented the June 2011 evaluation to the Pediatric Advisory Committee (PAC) on September 22, 2011.

Epzicom® (abacavir/lamivudine)

Abacavir/lamivudine (600mg/300mg) oral tablets (NDA 021652) was first approved on August 2, 2004, for the treatment of HIV-1 infection in adults. On September 17, 2015, the indication of Epzicom was expanded from adults to pediatric patients weighing at least 25kg; with a recommended dose of one tablet daily.² This is the first time Epzicom is being assessed under PREA.

1.2 Relevant Labeled Safety Information

The Ziagen³ and Epzicom⁴ USPIs includes the following information under HIGHLIGHTS:

1.2.1 Ziagen product labeling³

Highlights of Prescribing Information

Black Box Warning

WARNING: HYPERSENSITIVITY REACTIONS, and LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH

STEATOSIS

Hypersensitivity Reactions

- *Serious and sometimes fatal hypersensitivity reactions have occurred with ZIAGEN (abacavir).*
- *Hypersensitivity to ZIAGEN is a multi-organ clinical syndrome.*
- *Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir.*
- *ZIAGEN is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.*
- *Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible.*
- *Following a hypersensitivity reaction to ZIAGEN, NEVER restart ZIAGEN or any other abacavir-containing product.*

Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of nucleoside analogues.

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 300 mg scored

Oral Solution: 20 mg per mL

-----CONTRAINDICATIONS -----

Presence of HLA-B*5701 allele.

Prior hypersensitivity reaction to abacavir.

Moderate or severe hepatic impairment.

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

Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy.

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

The most commonly reported adverse reactions of at least moderate intensity (incidence greater than or equal to 10%) in adult HIV-1 clinical trials were nausea, headache, malaise and fatigue, nausea and vomiting, and dreams/sleep disorders.

The most commonly reported adverse reactions of at least moderate intensity (incidence greater than or equal to 5%) in pediatric HIV-1 clinical trials were fever and/or chills, nausea and vomiting, skin rashes, and ear/nose/throat infections.

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

Methadone: An increased methadone dose may be required in a small number of patients.

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

Lactation: Women infected with HIV should be instructed not to breastfeed due to potential for HIV transmission.

1.2.2 Epzicom product labeling ⁴

Highlights of Prescribing Information

Black Box Warning

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, and EXACERBATIONS OF HEPATITIS B

Hypersensitivity Reactions

- *Serious and sometimes fatal hypersensitivity reactions have occurred with abacavir-containing products.*
- *Hypersensitivity to abacavir is a multi-organ clinical syndrome.*
- *Patients who carry the HLA-B*5701 allele are at a higher risk of experiencing a hypersensitivity reaction to abacavir.*
- *EPZICOM is contraindicated in patients with a prior hypersensitivity reaction to abacavir and in HLA-B*5701-positive patients.*

- Discontinue EPZICOM as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible. Following a hypersensitivity reaction to EPZICOM, NEVER restart EPZICOM or any other abacavir-containing product.

Lactic Acidosis and Severe Hepatomegaly with Steatosis

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues.

Exacerbations of Hepatitis B

- Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of EPZICOM. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment.

-----**DOSAGE AND ADMINISTRATION**-----

Before initiating EPZICOM, screen for the HLA-B*5701 allele because EPZICOM contains abacavir.

- Adults: One tablet orally once daily.
- Pediatric patients weighing at least 25 kg: One tablet daily.

Because EPZICOM is a fixed-dose tablet and cannot be dose adjusted, EPZICOM is not recommended in patients requiring dosage adjustment or patients with hepatic impairment.

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

Presence of HLA-B*5701 allele.
Prior hypersensitivity reaction to abacavir or lamivudine.
Moderate or severe hepatic impairment.

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

Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with or without ribavirin. Discontinue EPZICOM as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both.

Immune reconstitution syndrome and redistribution/accumulation of body fat have been reported in patients treated with combination antiretroviral therapy.

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

The most commonly reported adverse reactions of at least moderate intensity (incidence greater than 5%) in an adult HIV-1 clinical trial were drug hypersensitivity, insomnia, depression/depressed mood, headache/migraine, fatigue/malaise, dizziness/vertigo, nausea, and diarrhea.

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	September 1, 2017
Time Period of Search	April 1, 2011 [†] - August 31, 2017
Search Type	FBIS Product Manufacturer Reporting Summary
Product Terms	Product Active Ingredient: abacavir, abacavir sulfate, abacavir/lamivudine, abacavir sulfate/lamivudine

MedDRA Search Terms (Version 20. 1)	All PT terms
Age	<16. 99 years
* See Appendix A for a description of the FAERS database.	
† This was the end of the June 11, 2011 review data lock date	

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 April 1, 2011 - August 31, 2017 with abacavir or abacavir/lamivudine.

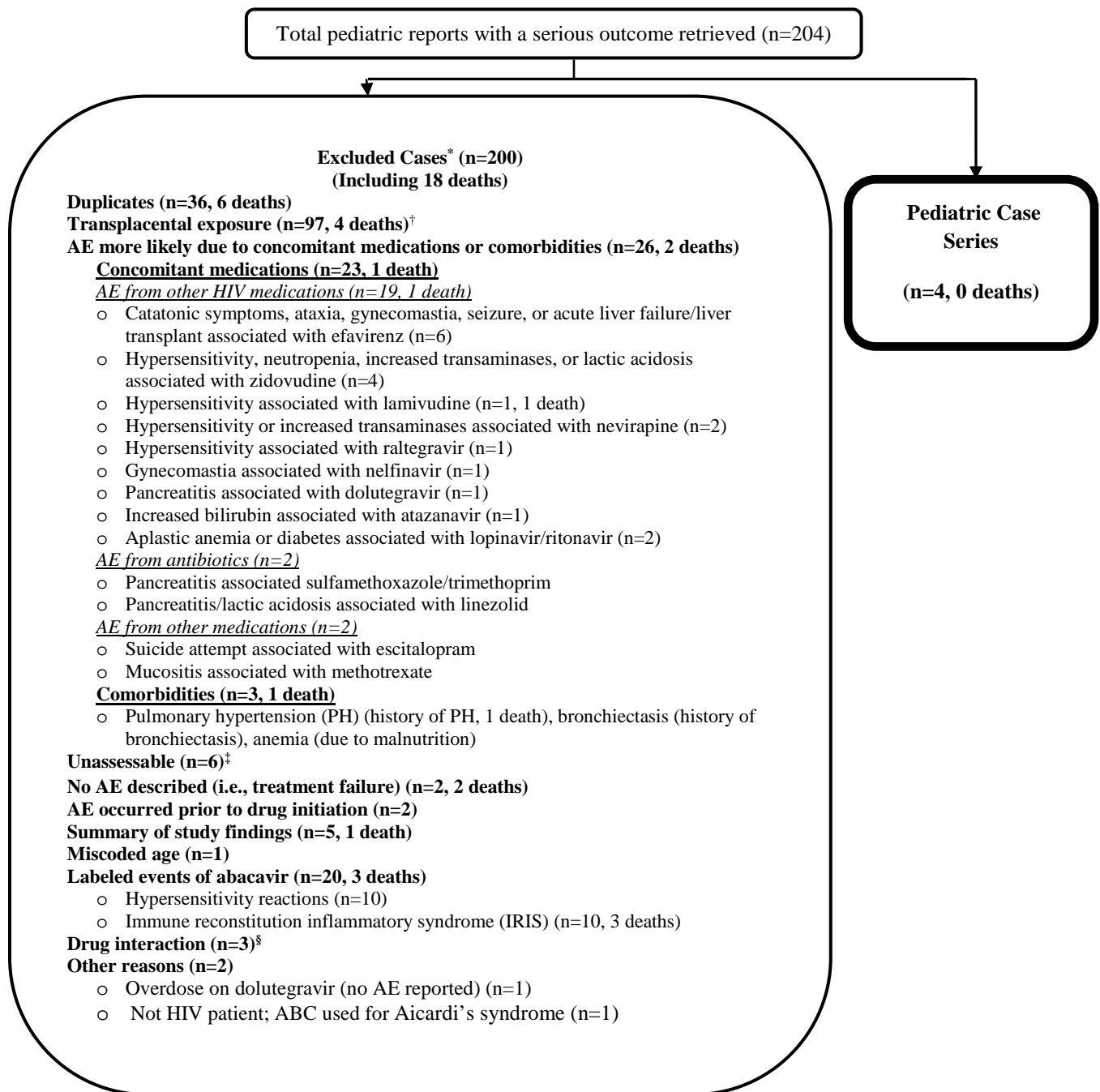
	All reports (U. S.)	Serious[†] (U. S.)	Death (U. S.)
Adults (\geq 17 years)	4614 (1030)	4213 (671)	410 (72)
Pediatrics (0 - <17 years)	211 (39)	204 (32)	18 (3)

* 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 Serious Pediatric Cases in FAERS

We retrieved 204 serious pediatric reports (See Table 2). See **Figure 1.** below for the selection of cases to be summarized in **Sections 3.2 and 3.3.**

Figure 1. Selection of Serious Pediatric Cases with abacavir and abacavir/lamivudine



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

[†]Transplacental deaths: Two cases were attributed to premature delivery and low birth weight. One case reported cardio-respiratory arrest with inconclusive autopsy results. One case reported spinal muscular atrophy likely to be a genetic defect.

[‡]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.

[§]There were three cases reporting concomitant use of Kaletra (lopinavir/ritonavir) and inhaled corticosteroids. This is a labeled event of Kaletra.⁵

3.2 SUMMARY OF FATAL PEDIATRIC CASES (N=0)

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

3.3 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS CASES (N=4)

Of the four non-fatal cases in pediatric patients included in our case series, there were no new safety signals identified. All four cases were of foreign origin.

FAERS Case #13787131 was of a 16-year-old female who experienced drug-induced hepatitis including increase in transaminases (more than 10x the upper limit of normal), jaundice, abdominal pain, nausea, vomiting 82 days after being switched from Kivexa[®] (lamivudine/abacavir) (brand) to generic lamivudine and abacavir for HIV management. The patient was on Kivexa for 35 days before being switched to the generic lamivudine and abacavir products. The report did not indicate if the patient experienced any adverse events on Kivexa. The patient was also taking darunavir and ritonavir concomitantly for an unknown duration. Abacavir and lamivudine were discontinued and liver function tests normalized. No further information was provided.

Reviewer comments: The case lacks additional clinical information to assess whether other exposures or disease-related factors contributed to the adverse events. The temporal association between abacavir initiation and the positive dechallenge upon its discontinuation support a causal association, however, the co-administration of lamivudine throughout abacavir therapy makes it impossible to discern if one or both medications contributed to the adverse events.

FAERS Case #8071716 was of a 13-year-old male patient from a literature article⁶ who developed HIV-associated nephropathy (HIVAN) while on efavirenz, nevirapine and abacavir sulfate) for HIV management and (rifampicin, pyrazinamide, ethambutol and isoniazid) for tuberculosis (TB) treatment. After four years of highly active antiretroviral therapy (HAART), the patient maintained undetectable viral load and CD4 counts; however, he developed nephrotic range proteinuria (protein: creatinine ratio 1300 mg/mmol; 7.5 gm protein in a 24-hour urine collection) and serum albumin was 31 gm/l; his urinalysis was otherwise normal. A kidney biopsy revealed sclerosed glomeruli and chronic interstitial infiltration, tubular dilatation and a non-collapsing focal segmental glomerular sclerosis (FSGS) was detected. The patient was diagnosed with HIVAN. The patient received prednisolone daily and enalapril over the course of eight weeks, continued his HAART therapy, and the proteinuria improved.

Reviewer comments: The clinical, microscopic, and laboratory findings are consistent with HIVAN. HIVAN typically occurs in patients with advanced HIV disease although cases like this have been reported in patients with asymptomatic HIV-infected children despite long-term maximal viral suppression from HAART.⁷ HIV infection is associated with chronic kidney disease (CKD) and acute kidney injury (AKI). The duration of TB therapy was not reported; rifampin is labeled for renal insufficiency and acute renal failure.⁸ The exact onset of the patient's renal disease is unclear as the patient did not have a urinalysis completed until after 2.5 years of HAART and TB therapy.

FAERS Case #9513629 was of an 11-year-old male who experienced hematuria and proteinuria while on abacavir therapy for HIV management. The patient was on abacavir, lamivudine and

nelfinavir for at least 3 years. A year after starting HIV therapy, the patient had a urinalysis completed as part of a work up for new nocturnal enuresis. The urinalysis revealed macrohematuria and proteinuria. The patient's medical history included infantile cerebral paralysis, mitral valve prolapse, and spastic hemiparesis. The patient was hospitalized and diagnosed with a urinary tract infection (UTI). An ultrasound of the bladder, kidney vessels and abdominal cavity did not show any pathological findings and a urine culture was positive for *Enterococcus faecalis*. The patient was discharged from the hospital with hematuria unresolved.

Reviewer comments: Lack of clinical information and confounding by underlying diseases complicate the assessment of this case. The patient is a quadriplegic and his condition poses an increased risk for bladder emptying complications and recurrent UTIs. Poor control of HIV infection could also contribute to recurrent UTIs. The hematuria is macroscopic, with normal cell morphology that suggests a lower urinary tract non-renal origin of the hematuria. Additional diagnostic tests would be required to determine the source of hematuria. Quantification of proteinuria was not done or reported; therefore, limiting the ability to determine its renal versus post-renal source. Dr. Paolo Fanti, a nephrologist in DPV, provided input for this case of hematuria and proteinuria.

FAERS Case #9164876, also reported in the literature⁹, was of a 10-year-old female patient who developed a lipoma while on HAART containing abacavir for HIV management. The patient was on abacavir, efavirenz and lopinavir therapy for three years until she was hospitalized with a palpable tumor in her left thigh. Magnetic resonance imaging (MRI) showed nonencapsulated, fatty tissue with a tumor measuring 40x32x9mm. The tumor was removed, and histological tests were consistent with a lipoma.

Reviewer comments: Lipomas may be present as part of a syndrome, such as lipodystrophy syndrome (LDS), which is a well-documented condition that occurs in adults and children on prolonged HAART. The clinical features in this case (rapidly progressing, singular, absence of other features suggestive of other syndromes) are consistent with LDS.

4 DISCUSSION

Of the pediatric reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths directly associated with abacavir or abacavir/lamivudine.

We reviewed all serious FAERS reports with abacavir and abacavir/lamivudine in the pediatric population (ages 0 to <17 years) during the period April 1, 2011 - August 31, 2017. We excluded duplicate reports, transplacental exposure reports, reports describing adverse events with strong alternative causes including comorbidities or concomitant medications (e. g. hypertension reported in a patient with a history of pulmonary hypertension, or hypersensitivity with zidovudine), reports of labeled adverse events, and reports with limited information which precluded a meaningful causality assessment.

Of the four serious and unlabeled adverse event cases included in this series, no specific pattern of adverse events was noted; single cases of drug-induced hepatitis, HIVAN, hematuria/proteinuria and lipoma were reported.

5 CONCLUSION

DPV did not identify pediatric safety concerns for abacavir or abacavir/lamivudine at this time.

6 RECOMMENDATIONS

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

7 REFERENCES

1. Boxwell, D. BPCA-PREA: Pediatric Postmarketing Adverse Event Review (NDA 20977, 20978). RCM #2011-1402. June 14, 2011.
2. Viswanathan, P. Combined Primary Clinical and Cross-Discipline Team Leader Review: Epzicom (abacavir/lamivudine) NDA 21652. July 31, 2015.
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9. Mazur-Melewska K. et al. Rapidly growing lipoma as the syndrome of lipodystrophy in HIV infected Child. *Central European Journal of Medicine*. 2012; 7(6): 753-755.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE FOUR (4) PEDIATRIC CASES FOR DISCUSSION

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	07/25/2017	13787131	1	GB-GLAXOSMITHKLINE-GB2017113566	Expedited (15-DAY)	16	FEMALE	GBR	LT,OT
2	08/05/2011	8071716	1	GB-BRISTOL-MYERS SQUIBB COMPANY-15924335	Expedited (15-DAY)	13	MALE	GBR	OT
3	09/10/2013	9513629	1	RU-VIIV HEALTHCARE LIMITED-B0915919A	Expedited (15-DAY)	11. 841	MALE	RUS	OT
4	02/23/2013	9164876	1	B0868762A	Expedited (15-DAY)	10	FEMALE	POL	HO,RI

*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: HO=Hospitalization, LT= Life-threatening, OT=Other medically significant, RI=Required intervention

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