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Pediatric Postmarketing Pharmacovigilance Review

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Product Name: Kaletra (lopinavir/ritonavir)

**Pediatric Labeling
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Application Type/Number: NDA 21251, NDA 21226, NDA 21906

Applicant/Sponsor: AbbVie

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for Kaletra in pediatric patients. Kaletra, an HIV-1 protease inhibitor, is a combination of lopinavir and ritonavir and was first approved in 2000. Kaletra is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older).

Of the seven serious pediatric cases assessed in the FDA Adverse Event Reporting System (FAERS), we found no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Kaletra. There is no evidence from these data that there are new pediatric safety concerns with Kaletra at this time.

DPV-II will continue routine pharmacovigilance monitoring associated with the use of Kaletra in pediatric patients.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Kaletra (lopinavir/ritonavir) is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients (14 days and older). Table 1.1.1 shows the various formulations and application numbers for Kaletra.

Application Number	Date of Approval	Formulation Type	Strength
NDA 21251	9/15/2000	Oral Solution	80 mg lopinavir and 20 mg ritonavir per milliliter
NDA 21226	9/15/2000	Oral Capsule*	133.3 mg lopinavir and 33.3 mg ritonavir
NDA 21906	10/28/2005	Oral Tablet	1. 100 mg lopinavir and 25 mg ritonavir 2. 200 mg lopinavir and 50 mg ritonavir

*This formulation of Kaletra has been discontinued from the market. Commercialization of the capsule formulation has been discontinued in those countries, including the United States, where the tablet formulation (NDA 21906) is approved and available.

Table 1.1.2 Pediatric labeling regulatory history.

Pediatric Labeling Date	Indications Studied	Label Changes Summary	Therapeutic Category
06/26/2015 (PREA)	Treatment of HIV-1 infection	<p>Kaletra should not be administered once daily in pediatric patients.</p> <p>* A multicenter, open-label study evaluated the efficacy and safety of twice-daily versus once-daily dosing of Kaletra tablets dosed by weight in 173 virologically suppressed HIV-1 infected children.</p> <p>* New dosing regimen, postmarketing study.</p>	Antiviral
06/20/2008 (PREA and BPCA)	Use in combination with other antiretroviral agents for HIV-1 infection	<p>Extended indication down to age 14 days from 6 months and up to 18 years from 12 years. The safety, efficacy, and pharmacokinetic profiles in pediatric patients < 14 days have not been established. Dose should be calculated based on body weight or body surface area not to exceed adult dose. Because no data exists for dosage when administered with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir, it is recommended that lopinavir/ ritonavir not be administered in combination with these drugs in patients < 6 months of age. Infants <6 months of age generally had lower lopinavir AUC₁₂ than children 6 months to 12 years of age. Information on dose, PK parameters, clinical studies, and AEs.</p>	Antiviral
11/09/2007 (PREA)	HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV - 1 infection.	<p>Dosing and administration information provided for children. Use of a lower strength tablet in a twice daily dosing regimen for pediatric patients weighing greater than 15 kg. New dosing regimen.</p>	Antiviral

Past PAC presentations for Kaletra

June 20, 2008 (BCPA & PREA) Kaletra Oral Solution, 80 mg/20 mg and Kaletra (lopinavir/ritonavir) Tablets, 200 mg/50 mg were approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. Kaletra's pediatric safety review was presented to the PAC on December 8, 2009 and the committee voted to return to standard, ongoing monitoring for adverse events.

At the PAC meeting on September 22, 2011 there was an informational update to the PAC about the safety signal identified in neonates receiving Kaletra formulation containing polyethylene glycol and ethanol.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

Kaletra¹ (lopinavir/ritonavir) package insert revised October 18, 2017.

The following have been observed in patients receiving KALETRA:

- The concomitant use of KALETRA and certain other drugs may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions.
- Toxicity in preterm neonates: KALETRA oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of KALETRA oral solution in this patient population has not been established.
- Pancreatitis: Fatalities have occurred; suspend therapy as clinically appropriate.
- Hepatotoxicity: Fatalities have occurred. Monitor liver function before and during therapy, especially in patients with underlying hepatic disease, including hepatitis B and hepatitis C, or marked transaminase elevations.
- QT interval prolongation and isolated cases of torsade de pointes have been reported although causality could not be established. Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval.
- PR interval prolongation may occur in some patients. Cases of second and third degree heart block have been reported. Use with caution in patients with pre-existing conduction system disease, ischemic heart disease, cardiomyopathy, underlying structural heart disease or when administering with other drugs that may prolong the PR interval.
- Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia, immune reconstitution syndrome, redistribution/accumulation of body fat.
- Total cholesterol and triglycerides elevations. Monitor prior to therapy and periodically thereafter.
- Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required.

Selected Warnings and Precautions in full text are noted below:

WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Adverse Reactions Due to Drug Interactions

Initiation of KALETRA, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving KALETRA, may increase plasma concentrations of medications metabolized by CYP3A. Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of KALETRA, respectively. These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of KALETRA.
- Loss of therapeutic effect of KALETRA and possible development of resistance.

5.2 Toxicity in Preterm Neonates

KALETRA oral solution contains the excipients ethanol, approximately 42% (v/v) and propylene glycol, approximately 15% (w/v). When administered concomitantly with propylene glycol, ethanol competitively inhibits the metabolism of propylene glycol, which may lead to elevated concentrations. Preterm neonates may be at increased risk of propylene glycol-associated adverse events due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. Postmarketing life-threatening cases of cardiac toxicity (including complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death have been reported, predominantly in preterm neonates receiving KALETRA oral solution.

KALETRA oral solution should not be used in preterm neonates in the immediate postnatal period because of possible toxicities. A safe and effective dose of KALETRA oral solution in this patient population has not been established. However, if the benefit of using KALETRA oral solution to treat HIV infection in infants immediately after birth outweighs the potential risks, infants should be monitored closely for increases in serum osmolality and serum creatinine, and for toxicity related to KALETRA oral solution including: hyperosmolality, with or without lactic acidosis, renal toxicity, CNS depression (including stupor, coma, and apnea), seizures, hypotonia, cardiac arrhythmias and ECG changes, and hemolysis. Total amounts of ethanol and propylene glycol from all medicines that are to be given to infants should be taken into account in order to avoid toxicity from these excipients.

5.5 QT Interval Prolongation

Postmarketing cases of QT interval prolongation and torsade de pointes have been reported although causality of KALETRA could not be established. Avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval.

5.8 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including KALETRA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis) which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.10 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Current *pediatric* specific labeling includes weight-based dosing down to 14 days of age, adverse reactions from clinical trial experience, pharmacokinetic data, clinical study data, and the following limitations of use:

- Kaletra should not be administered once daily in pediatric patients < 18 years of age
- Healthcare professionals should pay special attention to accurate calculation of the dose of Kaletra for each individual child based on body weight (kg) or body surface area (BSA) and should not exceed the recommended adult dose

ADVERSE REACTIONS

6.1 Clinical Trials Experience

Adverse Reactions in Pediatric Patients

KALETRA oral solution dosed up to 300/75 mg/m² has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse reaction profile seen during Study 940 was similar to that for adult patients.

Dysgeusia (22%), vomiting (21%), and diarrhea (12%) were the most common adverse reactions of any severity reported in pediatric patients treated with combination therapy for up to 48 weeks in Study 940. A total of 8 patients experienced adverse reactions of moderate to severe intensity. The adverse reactions meeting these criteria and reported for the 8 subjects include: hypersensitivity (characterized by fever, rash and jaundice), pyrexia, viral infection, constipation, hepatomegaly, pancreatitis, vomiting, alanine aminotransferase increased, dry skin, rash, and dysgeusia. Rash was the only event of those listed that occurred in 2 or more subjects (N = 3).

KALETRA oral solution dosed at 300/75 mg/m² has been studied in 31 pediatric patients 14 days to 6 months of age. The adverse reaction profile in Study 1030 was similar to that observed in older children and adults. No adverse reaction was reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included decreased neutrophil count (N=3), anemia (N=2), high potassium (N=2), and low sodium (N=2).

KALETRA oral solution and soft gelatin capsules dosed at higher than recommended doses including 400/100 mg/m² (without concomitant NNRTI) and 480/120 mg/m² (with concomitant NNRTI) have been studied in 26 pediatric patients 7 to 18 years of age in Study 1038. Patients also had saquinavir mesylate added to their regimen at Week 4. Rash (12%), blood cholesterol abnormal (12%) and blood triglycerides abnormal (12%) were the only adverse reactions reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included rash (N=3), blood triglycerides abnormal (N=3), and electrocardiogram QT prolonged (N=2). Both subjects with QT prolongation had additional predisposing conditions such as electrolyte abnormalities, concomitant medications, or pre-existing cardiac abnormalities.

The Office of Pediatric Therapeutics (OPT) noted and informed DPV-II of some potential safety concerns with lopinavir/ritonavir identified from the literature. The potential signals identified included bone growth, cardiovascular disease, and gastric mucormycosis. Specifically, two foreign articles^{2,3} highlighted that bone resorption marker levels are higher with the use of lopinavir/ritonavir which might manifest with effects on bone or growth. OPT also noted there are currently no published pediatric case reports of fractures after lopinavir/ritonavir exposure. Another foreign article⁴ included pediatric patients in which the authors concluded that efavirenz along with lopinavir/ritonavir may mediate cardiovascular disease in HIV patients on highly-active antiretroviral therapy. Furthermore, one additional article⁵ involved a pediatric case of gastric mucormycosis.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV-II 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 21, 2017
Time Period of Search	July 1, 2009* - October 31, 2017
Search Type	Quick Query
Product Name	Product Name: Kaletra Product Active Ingredient: Lopinavir/Ritonavir
Search Parameters	All ages, all outcomes, worldwide

* Date based on the last pediatric FAERS review for Kaletra.

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS Reports* from July 1, 2009 to October 31, 2017 with Kaletra

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 17 years)	2988 (722)	2743 (491)	313 (33)
Pediatrics (0 - 16.99 years)	424 (121)	408 (106) [‡]	61 (10)

* May include duplicates and transplacental exposures, and have not been assessed for causality

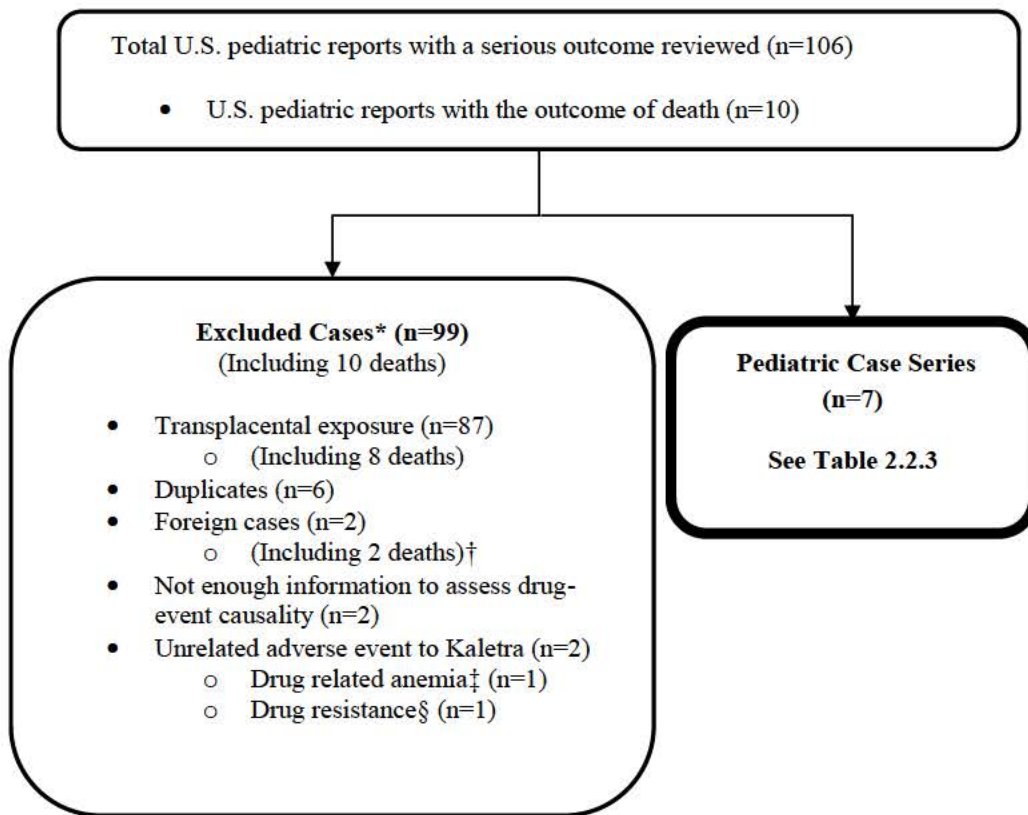
[†] For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

[‡] See Figure 2.2.1

2.2.2 Selection of Serious U.S. Pediatric Cases in FAERS

We identified 106 U.S. pediatric reports with a serious outcome (See Table 2.2.1). See **Figure 2.2.1** below for the specific selection of cases to be summarized in **Sections 2.3 and 2.4**.

Figure 2.2.1 Selection of Serious U.S. Pediatric Cases with Kaletra.



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

† Both cases were reviewed and one reported gastroenteritis and the other reported headache. There was insufficient clinical information for assessment reported

‡ The drug related anemia report described treatment with zidovudine and the patient experienced a decrease in hematocrit. The patient was also on maintenance therapy of lamivudine, nevirapine, and lopinavir/ritonavir. The anemia occurred with the patient's dose of zidovudine and lamivudine was increased

§ The drug resistance report described treatment with indinavir without any other additional clinical information for assessment reported

2.2.3 Characteristics of Pediatric Case Series

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 2.2.3 Characteristics of U.S. Serious Pediatric Case Series with Kaletra (N=7)

Age (n=7)	0 - < 1 month	1
	6- <12 years	2
	12- < 17 years	4
Sex	Male	2
	Female	5
Reported Reason for Use	HIV Infection	7
Serious Outcome*	Life-threatening	1
	Hospitalization	2
	Other serious	6

* 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. Reports may have more than one outcome.

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

There were no pediatric deaths in the case series. We excluded all 10 reports with a reported outcome of death for the following reasons: transplacental exposure (n=8) and originated from foreign clinical studies cases that were coded as U.S. (n=2).

2.4 SUMMARY OF NON-FATAL U.S. PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=7)

2.4.1 Cushing's Syndrome (n=5)

DPV-II identified five cases with lopinavir/ritonavir and subsequent development of Cushing's syndrome. All five patients were concomitantly taking other antiviral medications such as stavudine, lamivudine, and/or abacavir along with inhaled corticosteroids (i.e., fluticasone propionate). The reporters of these five cases noted symptoms of Cushing's syndrome including weight gain, hirsutism, and central adiposity. In all five cases, the outcomes resolved with dechallenge. Cushing's syndrome is a well-known complication of Kaletra due to a drug-drug interaction between the ritonavir component of the antiretroviral and inhaled corticosteroids. Ritonavir is a strong inhibitor of CYP3A system and is known to increase corticosteroid levels. Cushing's syndrome is labeled under the Drug Interactions sections of the Kaletra label. These events are consistent with the known risks already described in the labeling and no increased severity was observed in these reports.

2.4.2 Immune Reconstitution Syndrome (n=1)

DPV-II identified one FAERS case which was also published in the literature⁶ regarding a 14-year-old male Hispanic patient, perinatally infected with HIV and hepatitis C who has been on long-term highly active antiretroviral therapy (HAART). This patient has maintained a high CD4+ T-lymphocyte count for most of his life. Due to an unstable social situation, the patient had a history of poor adherence to HAART. This patient has been followed since birth and starting at six years of age was diagnosed with one to three episodes of symptomatic streptococcal pharyngitis per year. At 14 years of age, he was noted to have an increased HIV RNA viral load (>100,000) and CD4+ T-lymphocyte count of 721 cells/mm. At that time, he was changed to a new HAART regimen (zidovudine, didanosine, and lopinavir/ritonavir). Three months later, he was diagnosed with culture-positive streptococcal pharyngitis, which was treated with antibiotics. Within the same year, he was also diagnosed with bilateral herpes zoster infection, which was treated for seven days with acyclovir. The patient subsequently developed gross hematuria

and elevated creatinine. Kidney biopsy revealed postinfectious glomerulonephritis without evidence of membranoproliferative disease. The patient continued on his HAART therapy and his gross hematuria resolved and creatinine normalized within six months. Repeat throat cultures done three months and two years after onset of hematuria were both negative. Despite this patient's normal CD4+ T-lymphocyte count and prior HAART therapy, the authors concluded the patient's clinical course suggested immune reconstitution inflammatory syndrome (IRIS). The authors note that while this was not a typical case of IRIS due to baseline high CD4+ count, there were several features that made this patient's clinical course unusual: "HIV-infected patient, receipt of effective HAART as shown by a decrease in HIV RNA concentration from baseline, clinical symptoms consistent with an inflammatory process, short interval between initiation of symptoms and change of HAART therapy, clinical course not consistent with expected course, and spontaneous resolution of disease with continuation of HAART."

Reviewer's Comments: We recognize the patient lacked typical risk factors associated with IRIS. Specifically, the patient was not naïve to HAART, he did not have any baseline opportunistic infections, and did not appear to have a very low CD4+ T-lymphocyte count during the initiation of the new HAART regimen. It is important to note post-streptococcal glomerulonephritis may occur in individuals without HIV and therefore, in the setting of high CD4+ T-lymphocyte count, we cannot conclude that post-streptococcal glomerulonephritis is indeed IRIS. However, immune reconstitution syndrome (whether arising from post-streptococcal glomerulonephritis, or herpes zoster) is already labeled in the Warning and Precautions and Drug Interactions sections of the Kaletra labeling and therefore no new safety concerns arise from this case report.

2.4.1 Medication Error / Accidental Overdose (n=1)

DPV-II identified one FAERS case which involved a female patient who was born at 29-weeks gestation to a 29-year-old HIV positive mother with no prenatal care. The mother did not know she was HIV positive prior to delivery. The baby was born at approximately 1.4 kilograms (kgs) and was ordered Kaletra oral solution 12 mg/kg per dose every 12 hours for HIV infection. One day after birth, the patient experienced elevated alcohol level, lactic acidosis, pericardial effusion, QT prolongation, and hyperbilirubinemia. The patient was given 16.5 mL of Kaletra oral solution in one dose on the day of birth. The baby developed a blood alcohol level of 285 (units not specified), which decreased to less than 10 the next day. Health care providers monitored the patient and noted no changes in her hemodynamics one day after receiving an overdose of Kaletra solution.

Reviewer's Comments: This is a case of accidental overdose as the patient received a much greater amount of Kaletra oral solution than prescribed. Kaletra oral solution contains ethanol and propylene glycol which contributed to the patient's elevated blood alcohol level. Lactic acidosis is a known adverse event that can be caused by elevated propylene glycol in preterm neonates. QT prolongation is currently labeled in the Warning and Precautions section of the Kaletra labeling. Both pericardial effusion and hyperbilirubinemia are unlabeled events and are not clearly described in this case. These events could be the result of the overdose or the excipients used in the oral solution for Kaletra. Additionally, the approved pediatric indication for Kaletra is in patients from 14 days old to 18 years of age. In this case, the patient was one day old and received Kaletra. However, if the benefit of using Kaletra oral solution to treat HIV infection in infants immediately after birth outweighs the potential risks, infants should be closely monitored for toxicity related to hyperosmolality, with or without lactic acidosis, renal toxicity, central nervous system depression, seizures, hypotonia, cardiac arrhythmias, and hemolysis, if the benefit of using Kaletra oral solution in infants immediately after birth outweighs the potential risks. It is well established and labeled in the Kaletra labeling to monitor for ethanol and propylene glycol toxicity in preterm neonates born with HIV infection and therefore no new safety concerns arise from this case report.

3 DISCUSSION

Of the seven serious pediatric cases assessed in FAERS, we found no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Kaletra.

The adverse events of Cushing's syndrome (n=5) and immune reconstitution syndrome (n=1) are both labeled with antiretroviral therapy, including Kaletra. The case involving the adverse event due to medication error / accidental overdose (n=1) required monitoring for ethanol and propylene glycol toxicity in the neonate patient which is also labeled for Kaletra.

As per the literature search conducted by the Office of Pediatric Therapeutics, potential signals identified included bone growth, cardiovascular disease, and gastric mucormycosis. However, we did not identify any cases in FAERS reporting these events. We will continue to monitor these events during routine pharmacovigilance activities.

4 CONCLUSION

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

5 RECOMMENDATIONS

DPV-II will continue routine pharmacovigilance monitoring associated with the use of Kaletra in pediatric patients.

6 REFERENCES

¹ Kaletra [package insert]. North Chicago, IL: AbbVie, Inc; Revised 10/2017.

² Nagot, N, et al. Lopinavir/ritonavir initiated at 7 days of life impairs infant growth. *Topics in Antiviral Medicine*. 2017;25(1):332s-333s.

³ Hsieh E, et al. Increased bone resorption during tenofovir plus lopinavir/ritonavir therapy in Chinese individuals with HIV. *Osteoporos Int*. 2015;26(3):1035-44.

⁴ Gleason, RL, et al. Efavirenz and ritonavir-boosted lopinavir use exhibited elevated markers of atherosclerosis across age groups in people living with HIV in Ethiopia. *Journal of Biomechanics*. 2016;49(13):2584-2592.

⁵ Makongwana, BS, et al. Gastric mucormycosis in an HIV infected child: Rare and unexpected. *Southern African Journal of Epidemiology and Infection*. 2015;30(3):173.

⁶ Martin, et al. Acute poststreptococcal glomerulonephritis: a manifestation of immune reconstitution inflammatory syndrome. *Pediatrics*. 2012;130:e710-e713.

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 CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE U.S. SERIOUS PEDIATRIC CASE SERIES WITH KALETRA (N=7)

FAERS Case #	Version Number	Manufacturer Control #	Report Type	Initial FDA received Date	Age in Years	Sex	Adverse Event	All Outcomes
10479608	1	2014HINLIT0827	Expedited (15-Day)	9/25/2014	11	FEMALE	Cushing's syndrome; drug-drug interaction	OT
10479916	1	2014HINLIT0834	Expedited (15-Day)	9/25/2014	16	MALE	Cushing's syndrome; drug-drug interaction	OT
10480518	1	2014HINLIT0831	Expedited (15-Day)	9/25/2014	15	FEMALE	Cushing's syndrome; drug-drug interaction	OT
10480720	1	2014HINLIT0828	Expedited (15-Day)	9/25/2014	12	FEMALE	Cushing's syndrome; drug-drug interaction	HO
10480727	1	2014HINLIT0826	Expedited (15-Day)	9/25/2014	10	FEMALE	Cushing's syndrome; drug-drug interaction	OT
8900122	1	US-TEVA-369039USA	Expedited (15-Day)	11/9/2012	14	MALE	Immune Reconstitution Syndrome	OT
7819542	1	US-ABBOTT-11P-163-0705769-00	Expedited (15-Day)	2/18/2011	0	FEMALE	Medication error; accidental overdose	HO,LT,OT

HO: hospitalization (initial or prolonged)

LT: life-threatening

OT: other serious important medical events

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/s/

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