Department of Health and Human Services
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

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Product Name:	Isentress and Isentress HD (raltegravir)
Pediatric Labeling Approval Date:	Isentress: November 22, 2017 Isentress HD: May 26, 2017
Application Type/Number:	NDAs 022145, 203045, 205786
Sponsor:	Merck
OSE RCM #:	2019-1130

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for raltegravir in pediatric patients through 16 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with raltegravir in pediatric patients.

The Office of Surveillance and Epidemiology (OSE) conducted two previous raltegravir reviews, dated June 17, 2014 and July 11, 2016, that did not identify any new safety concerns in pediatric patients. Raltegravir was presented at the Pediatric Advisory Committee (PAC) meeting in September 2013 after raltegravir first received a pediatric indication in 2011.

This review was triggered by the approval of the use of raltegravir 600 mg tablets (Isentress HD) in pediatric patients weighing at least 40 kg on May 26, 2017, and approval of the use of raltegravir oral suspension (Isentress) in neonates ages 0-4 weeks and weighing at least 2 kg on November 22, 2017.

Our FAERS search identified one serious case in the U.S. pediatric population reporting a non-fatal serious outcome between February 29, 2016 and May 29, 2019. The case reported adverse events of hallucinations and panic attack but lacked sufficient information to determine the extent to which raltegravir, concomitant medications, or comorbid conditions contributed to the event.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for raltegravir in pediatric patients through 16 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious, unlabeled adverse events associated with raltegravir in pediatric patients. The approval for use of raltegravir 600 mg tablets (Isentress HD) in pediatric patients weighing at least 40 kg, and approval of the use of raltegravir oral suspension (Isentress) in neonates ages 0-4 weeks and weighing at least 2 kg triggered this review.

1.1 PEDIATRIC REGULATORY HISTORY

1.1.1 Formulations and Approvals

Raltegravir, a human immunodeficiency virus integrase strand transfer inhibitor (INSTI) first FDA approved on October 12, 2007, is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in both adults and children. Table 1 displays the approval dates of the different raltegravir dosage forms, and dates of new pediatric labeling changes.

Table 1: Raltegravir Approval Dates, Dosage Forms, and New Indication Population

Date	New Dosage Form	New Indication Population
October 12, 2007	400 mg film-coated tablets	Adults
December 21, 2011	25 mg and 100 mg chewable tablets	Children and adolescents 2 years of age and older and weighing at least 10 kg
December 20, 2013	100 mg single-use oral suspension packet	Pediatric patients 4 weeks of age and older, weighing at least 3 kg to less than 20 kg
May 26, 2017	600 mg film-coated tablets	Pediatric patients weighing at least 40 kg*
November 22, 2017		Oral suspension: neonates ages 0-4 weeks and weighing at least 2 kg*
* Indications that triggered the PAC current review		

1.1.2 Pivotal Clinical Trials in Pediatric Patients

Pediatric patients weighing at least 40 kg:

Raltegravir 600 mg film-coated tablets have not been studied in pediatric patients. However, population pharmacokinetic modeling and simulation in pediatric subjects weighing at least 40 kg administered 1200 mg of raltegravir (2 x 600 mg) once daily were predicted to be comparable to adult exposures observed from Phase III in the ONCEMRK trial (ClinicalTrials.gov Identifier:

NCT02131233). ONCEMRK was a randomized, double-blind, active-control trial, that evaluated 1200 mg of raltegravir once daily in treatment-naïve adult subjects for 96 weeks.

Neonates ages 0-4 weeks and weighing at least 2 kg:

The safety and pharmacokinetics of raltegravir for oral suspension were evaluated in 42 full-term HIV-1 exposed neonates at high risk of acquiring HIV-1 infection in a Phase 1, open-label, multicenter clinical study, IMPAACT P1110 (ClinicalTrials.gov Identifier: NCT01828073). Cohort 1 neonates received two single doses of raltegravir for oral suspension: the first within 48 hours of birth and the second at 7 to 10 days of age. This limiting dosing regimen was employed for Cohort 1 because both raltegravir and bilirubin are metabolized by uridine diphosphate glucuronosyltransferase 1A1, which is maturing during the first weeks of life. Pharmacokinetic data from Cohort 1 were used to devise the dosing schema used in Cohort 2, which accounts for progressive enzyme maturation. Cohort 2 neonates received daily dosing of raltegravir for oral suspension for 6 weeks, with dose escalations occurring at Week 1 and Week 5.

Sixteen neonates were enrolled in Cohort 1 (10 were exposed and 6 were unexposed to raltegravir in utero) and 26 neonates were enrolled in Cohort 2 (all unexposed to raltegravir in utero). Raltegravir was administered in addition to the local standard-of-care neonatal antiretroviral drug regimen, which was nevirapine + zidovudine in the majority of cases. Although raltegravir was only administered for a maximum of 6 weeks, all subjects were followed for safety for a duration of 24 weeks. The overall safety profile was found to be comparable to that observed in adults and no increased risk was detected for safety issues unique to this age group, including neonatal jaundice.

1.1.3 Previous OSE Reviews

The Office of Surveillance and Epidemiology (OSE) previously evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for raltegravir in pediatric patients. Raltegravir was presented at the Pediatric Advisory Committee (PAC) meeting in September 2013 after raltegravir first received a pediatric indication in 2011 for the treatment of HIV-1 infection in children and adolescents 2 years of age and older. DPV completed a review of 17 raltegravir pediatric reports received from October 12, 2007 (initial approval) to February 28, 2013. This review did not identify any pediatric safety concerns and recommended routine pharmacovigilance monitoring.[1]

A second pediatric review, dated July 11, 2016, was prompted after pediatric labeling was revised on December 20, 2013 expanding the indication to infants and toddlers aged 4 weeks and older, and weighing at least 3 kg. Six adverse event cases in pediatric patients received from February 28, 2013 (FAERS cutoff date for the last pediatric review) to February 29, 2016 were evaluated. This review also did not identify any new safety concerns, and recommended return to routine monitoring for adverse events with raltegravir.[2]

1.2 RELEVANT LABELED SAFETY INFORMATION

The raltegravir labeling includes the following information under Highlights:

----------CONTRAINDICATIONS----------

- None

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

- Severe, potentially life-threatening and fatal skin reactions have been reported. This includes cases of Stevens-Johnson syndrome, hypersensitivity reaction and toxic epidermal necrolysis. Immediately discontinue treatment with ISENTRESS or ISENTRESS HD and other suspect agents if severe hypersensitivity, severe rash, or rash with systemic symptoms or liver aminotransferase elevations develops and monitor clinical status, including liver aminotransferases closely.
- Monitor for Immune Reconstitution Syndrome.
- Inform patients with phenylketonuria that the 100 mg and 25 mg chewable tablets contain phenylalanine.

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

- The most common adverse reactions of moderate to severe intensity (≥2%) are insomnia, headache, dizziness, nausea and fatigue.
- Creatine kinase elevations were observed in subjects who received ISENTRESS or ISENTRESS HD. Myopathy and rhabdomyolysis have been reported. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions and patients with a history of rhabdomyolysis, myopathy or increased serum creatine kinase.

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

- Coadministration of ISENTRESS or ISENTRESS HD and other drugs may alter the plasma concentration of raltegravir. The potential for drug-drug interactions must be considered prior to and during therapy.
- Coadministration of ISENTRESS or ISENTRESS HD with drugs that are strong inducers of UGT1A1, such as rifampin, may result in reduced plasma concentrations of raltegravir.

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

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

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of Search	May 30, 2019
Time Period of Search	February 29, 2016† - May 29, 2019
Search Type	Quick Query
Product Terms	Raltegravir; raltegravir potassium; Isentress
MedDRA Search Terms (Version 22.0)	All Preferred Terms (PT)
* See Appendix A for a description of the FAERS database. † FAERS cutoff date for the last pediatric review completed in 2016	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

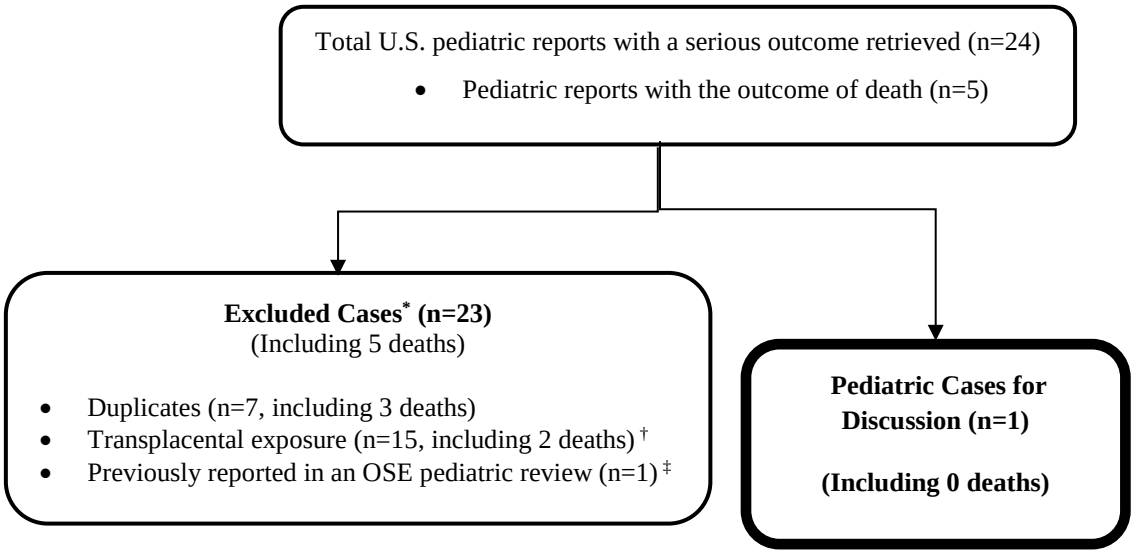
Table 3 presents the number of adult and pediatric FAERS reports from February 29, 2016 to May 29, 2019 with raltegravir.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from February 29, 2016 - May 29, 2019 with Raltegravir			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	1622 (534)	1242 (163)	106 (19)
Pediatrics (0 - <17 years)	195 (60)	**159 (24)**	19 (5)
* 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 U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 24 U.S. serious pediatric reports from February 29, 2016 to May 29, 2019. We reviewed all U.S. FAERS pediatric reports with a serious outcome. Figure A presents the selection of cases for the pediatric case series.

Figure A. Selection of Serious U.S. Pediatric Cases with Raltegravir



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

† FDA is currently evaluating the potential signal of neural tube defects (NTD) following transplacental exposure to the INSTI dolutegravir (tracked safety issue #1898) that was identified in a birth outcomes surveillance study in Botswana (Tsepamo study). The FDA evaluation is ongoing and includes a broad review of all INSTIs including raltegravir. There were no cases of NTD retrieved in our search.

‡This case described a 10-year-old patient who developed drug reaction with eosinophilia and systemic symptoms (DRESS) while on multiple antiretroviral medication for perinatally transmitted HIV. The case was included in the 2016 raltegravir pediatric review. The case was described in two published articles that were published after the review's data lock date and captured during the current FAERS review.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

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

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=1)

We identified one FAERS cases with raltegravir in the U.S. pediatric population reporting a non-fatal serious outcome.

FAERS #13405338; 2017; 8-year-old male:
The patient is an 8-year-old boy with human immunodeficiency virus (HIV), insomnia, and attention deficit/hyperactivity disorder (ADHD). His medications included lamivudine/ zidovudine, nevirapine, melatonin, and dextroamphetamine saccharate/amphetamine aspartate/dextroamphetamine sulfate/amphetamine sulfate (Adderall XR). It was reported that

the patient took nevirapine and lamivudine/zidovudine in the morning of Day 1, but started a new regimen of raltegravir potassium, lamivudine, and abacavir in the afternoon.
On Day 2, the patient had his first hallucination about a lamp before school and another one at school during lunch. On Day 6, he had another hallucination about a ceiling fan and doorknobs in the morning and another one at Children's Hospital in the afternoon. On Day 7, the patient had a significant episode at dinner, and so raltegravir was discontinued and he was given nevirapine and lamivudine/abacavir combination at bedtime. On Day 8, the patient had a mild panic attack. He has had no hallucinations or panic attacks since that time. The physician reported that the patient's adverse events stopped after discontinuing raltegravir.

Reviewer comment: Although the raltegravir label does not explicitly list hallucinations and panic attack as adverse events, it does broadly describe psychiatric adverse events in the Adverse Reactions section of the product label. Hallucination and other psychotic experiences are associated with insomnia and hallucinations is a labeled event for dextroamphetamine.[3] The panic attack reportedly occurred after raltegravir discontinuation and it is not clear whether the patient experienced panic attacks during raltegravir exposure. The narrative does not include sufficient information about the patient's baseline psychosocial status, insomnia symptoms, or details about concomitant medication to determine the extent to which these factors contributed to the adverse events.

4 DISCUSSION

We reviewed all U.S. serious, unlabeled FAERS reports with raltegravir in the pediatric population through 16 years of age during the period February 29, 2016 to May 29, 2019, and we identified one case for discussion. The case reported adverse events of hallucinations and panic attack but lacked sufficient information to determine the extent to which raltegravir, concomitant medications, or comorbid conditions contributed to the event.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for raltegravir at this time.

6 RECOMMENDATION

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

7 REFERENCES

1. Gish P. Isentress® (raltegravir) pediatric review. 2013-335, June 17, 2013.
2. Gish P. Isentress® (raltegravir) pediatric review. 2016-350. July 11, 2016.
3. Freeman D et al. The effects of improving sleep on mental health (OASIS): a randomized controlled trial with mediation analysis. Lancet Psychiatry. 2017;4(10):749.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

Data Mining of FAERS Using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=3)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	19-May-2017	13405338	3	US-009507513-1704USA000965	Exp	8 years	M	USA	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, OT=Other medically significant

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