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

Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name:	Isentress® (raltegravir)
Pediatric Labeling Approval Date:	20-Dec-2013
Application Type/Number:	NDA 022145 (tablet), NDA 203045 (chewable), NDA 205786 (powder for oral suspension)
Applicant/Sponsor:	Merck Sharp & Dohme
OSE RCM #:	2016-350

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

In accordance with the Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for raltegravir in pediatric patients.

Raltegravir (Isentress®) was first approved in 2007 and is a selective inhibitor of human immunodeficiency virus (HIV-1) integrase catalyzed strand transfer. Raltegravir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 4 weeks of age and older, weighing at least 3 kg.

In order to capture pediatric use of raltegravir and to provide context for the adverse event reports submitted to the FDA Adverse Event Reporting System (FAERS) database for raltegravir, drug utilization patterns were assessed. From March 2013 through February 2016, a nationally estimated number of 133,730 patients received a dispensed prescription for raltegravir from U.S. outpatient retail pharmacies, of which the pediatric population aged 0-16 years accounted for 1% (1,958 patients).

Six adverse event cases in pediatric patients received from 28-Feb-2013 (FAERS cutoff date of last pediatric review) to 29-Feb-2016 were evaluated. The small number of reports is consistent with low domestic use in pediatric patients.

No new safety signals were identified. No known risks were reported in unusual numbers in pediatric patients. Two deaths were reported due to immune reconstitution inflammatory syndrome (IRIS) which is labeled for all antiretrovirals under **Warnings and Precautions**.

There is no evidence from these data that there are new pediatric safety concerns with this drug at this time. We recommend routine pharmacovigilance monitoring.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

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. Raltegravir was presented at the Pediatric Advisory Committee (PAC) meeting in September 2013.

This updated review was prompted by revised pediatric labeling on 20-Dec-2013 that expanded the indication to infants and toddlers aged 4 weeks and older, weighing at least 3 kg.

- Formulations:

Raltegravir is administered orally and is supplied as film-coated tablets 400mg, as chewable tablets 100mg scored and 25mg, and as 100mg granular powder for suspension in 5 mL of water to give a final concentration of 20mg/mL. Because the formulations are not bioequivalent, raltegravir chewable tablets or raltegravir granular powder for suspension cannot be substituted for the raltegravir 400mg film-coated tablet. Specific dosing guidance for chewable tablets and granular powder for oral suspension are provided in the United States Package Insert (USPI).

- Approved Indications for Use:

Raltegravir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 4 weeks of age and older.

- Pivotal Clinical Trials in Pediatric Patients:

The safety, tolerability, pharmacokinetic profile, and efficacy of raltegravir were evaluated in HIV-1 infected infants, children and adolescents 4 weeks to 18 years of age in an open-label, multicenter clinical trial, IMPAACT P1066.

Safety and dosing information have not been established in infants less than 4 weeks of age.

IMPAACT P1066:

2 to 18 Years of Age:

Raltegravir has been studied in 126 antiretroviral treatment-experienced HIV-1 infected children and adolescents 2 to 18 years of age, in combination with other antiretroviral agents in IMPAACT P1066.

Of the 126 subjects, 96 received the recommended dose of raltegravir. In these 96 children and adolescents, frequency, type, and severity of drug related adverse reactions through Week 24 were comparable to those observed in adults.

One patient experienced drug related clinical adverse reactions of Grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia; one patient experienced a Grade 2 serious drug related allergic rash. One patient experienced drug related laboratory abnormalities, Grade 4 AST and Grade 3 ALT, which were considered serious.

4 Weeks to Less Than 2 Years of Age:

IMPAACT P1066 also studied raltegravir in combination with other antiretroviral agents in 26 HIV-1 infected infants and toddlers 4 weeks to less than 2 years of age.

In these 26 infants and toddlers, the frequency, type, and severity of drug-related adverse reactions through Week 48 were comparable to those observed in adults.

One patient experienced a Grade 3 serious drug-related allergic rash that resulted in treatment discontinuation.

1.2 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS

DPV completed one previous pediatric review:

- September 2013 PAC meeting:
  Revised pediatric labeling on 21-Dec-2011 expanded the indication to patients 2 years of age and older. DPV completed a review of 17 raltegravir pediatric reports received from 12-Oct-2007 (initial approval) to 28-Feb-2013. No new pediatric safety concerns were identified.

No recent DPV reviews have been completed that included pediatric cases and are currently pending regulatory action.

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

The USPI [1] 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 raltegravir 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 100mg and 25mg 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 raltegravir. 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**----------

- Co-administration of raltegravir with drugs that are strong inducers of UGT1A1 may result in reduced plasma concentrations of raltegravir.

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

- Pregnancy: Raltegravir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Nursing Mothers: Breastfeeding is not recommended while taking raltegravir.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to the FDA to conduct this analysis. ***Appendix A*** includes detailed descriptions of the databases.

2.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the various settings of care where raltegravir (Isentress®) is distributed by the manufacturer. Sales data from March 2013 through February 2016 showed that approximately 55% of raltegravir bottles were sold to U.S. outpatient retail pharmacies, followed by 21% to mail order/specialty pharmacy settings, and 24% to non-retail settings.[2] As a result, outpatient retail pharmacy utilization patterns were examined. Based on these results, we examined the drug utilization data for only the U.S. outpatient retail settings.

2.1.2 Data Sources Used

The IMS Health, Total Patient Tracker™ database was used to obtain the nationally estimated number of unique patients who received dispensed prescriptions for raltegravir from U.S. outpatient retail pharmacies, stratified by patient age groups (0-1, 2-16, and 17 years and older) from March 1, 2013 through February 29, 2016, aggregated.

2.2 DRUG UTILIZATION DATA RESULTS

Table 2.2. Nationally estimated number of unique patients with dispensed prescriptions for raltegravir (Isentress®), stratified by patient age*, from U.S. outpatient retail pharmacies, March 2013 through February 2016, aggregated.

	March 1, 2013 - February 29, 2016	
	Patient Count†	*Share*
	N	*%*
Total Patients	**133,730**	***100%***
0-16 years	1,958	*1%*
0-1 year	26	*1%*
2-16 years	1,933	*99%*
17+ years	131,464	*98%*
Unknown age	944	*1%*

Source: IMS Health, Total Patient Tracker. Mar 2013 – Feb 2016. Extracted Apr 2016. File: TPT 2016-350 raltegravir Isentress by age Mar2013-Feb2016.xlsx.

* Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years of age (16 years and 11 months old).

† Unique patient counts may not be added due to the possibility of double counting those patients aging during the study, and may be counted more than once in the individual categories.

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See ***Appendix B*** for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	29-Feb-2016
Time Period of Search	28-Feb-2013* - 29-Feb-2016
Search Type	Quick Query and Product-Manufacturer Reporting Summary
Product Name(s)	Raltegravir, raltegravir sodium
Search Parameters	All ages, all outcomes, worldwide

** FAERS cutoff date from last pediatric review completed in 2013.*

3.2 RESULTS

3.2.1 Total Number of FAERS Reports by Age

Table 3.2.1 below includes the number of adult and pediatric FAERS reports received since the last pediatric review completed in 2013. We identified 83 pediatric reports with a serious outcome including seventeen with an outcome of death. These numbers include duplicate reports and transplacental exposures, and have not been assessed for causality.

Table 3.2.1 Total Adult and Pediatric FAERS reports* 28-Feb-2013 to 29-Feb-2016 with Raltegravir

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 years)	1379 (421)	1138 (185)	228 (34)
Pediatrics (0 - <17 years)	88(37)	**83‡ (32)**	17(10)

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

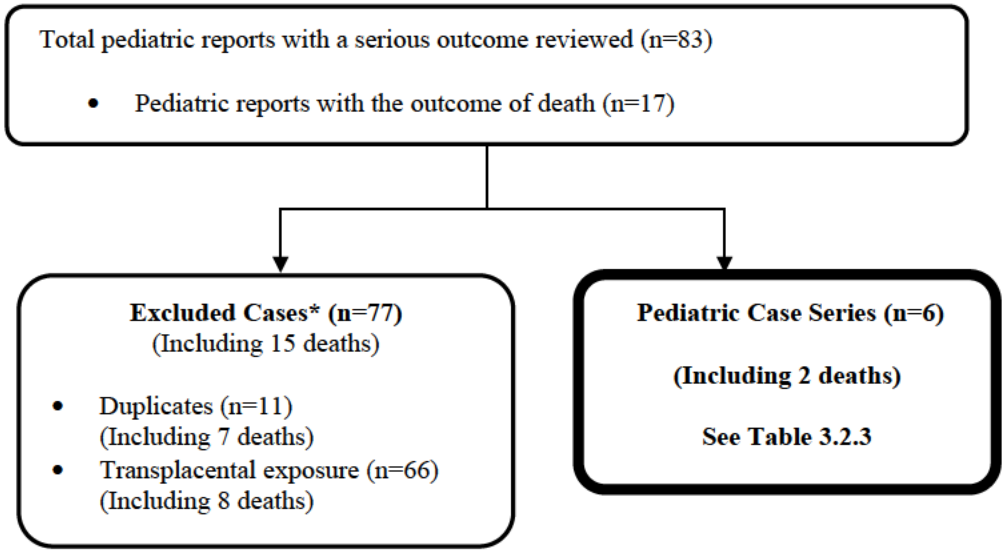
† *For the purposes of this review, the following outcomes qualify as serious:* ***death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.***

‡ ***See Figure 3.2.2***

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 83 pediatric reports with a serious outcome (See Table 3.2.1). After excluding transplacental exposure cases and combining duplicate reports, six cases of direct exposure remained, including two deaths. See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

Figure 3.2.2 Selection of Serious Pediatric Cases with Raltegravir



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

3.2.3 Characteristics of Pediatric Case Series

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

Table 3.2.3 Characteristics of Pediatric Case Series with Raltegravir (N=6)

Age (n=6)	0 - < 1 month	1
	1 month - <2 years	0
	2- < 6 years	0
	6- <12 years	2
	12- < 17 years	3
Sex	Male	2
	Female	4
Country	United States	2
	Foreign	4
Reported Reason for Use	HIV Infection	4
	Prophylaxis against HIV	1
	Antiretroviral therapy	1
Serious Outcome*	Death	2
	Life-threatening	1
	Hospitalized	2
	Disability	0
	Congenital anomaly	0
	Required Intervention	0
	Other serious	1

* 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.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=2)

Two cases reported death as an outcome. Both deaths were due to immune reconstitution inflammatory syndrome (IRIS), which is labeled for all antiretrovirals under **Warnings and Precautions**. IRIS is an inflammatory response to indolent opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jiroveci pneumonia, tuberculosis), which may necessitate further evaluation and treatment. Both cases are described below.

- FAERS case #10169889-1 (duplicate case #s: 10185195-1,10187187-1,10195849-2, 10200376-1, 10210926-1, and 10196482-2), USA.

  Literature case report: Schwenk H, Ramirez-Avila L, Sheu SH, et al. Progressive multifocal leukoencephalopathy in pediatric patients: case report and literature review. Pediatr Infect Dis J 2014; 33: e99-e105.

  A 15-year-old female patient, whose biological mother was HIV-positive, was diagnosed with AIDS and progressive multifocal leukoencephalopathy (PML). She began receiving combination antiretroviral therapy with nevirapine, raltegravir and emtricitabine+tenofovir disoproxil fumarate (routes, dosages and duration of treatment to reaction onset not stated). She soon developed worsening dysarthria, dysphagia and aspiration of liquids. An MRI showed new and increased bilateral medullary lesions suggestive of immune reconstitution inflammatory syndrome (IRIS). The girl was treated with methylprednisolone and prednisone, and was discharged following improvement of her neurologic status. One week later, she was readmitted with worsening dysarthria, urinary incontinence, inability to ambulate and new left hemiplegia. A repeat MRI demonstrated interval increase in T2-signal abnormalities of the cerebellum and brainstem, and she received further treatment with methylprednisolone. However, she experienced progressive weakness, generalised tonic-clonic seizures and inability to clear secretions. New diffuse supratentorial lesions were seen on an MRI. Her condition deteriorated and she died 8 weeks after her initial presentation.

- FAERS case #10305812-1, Malawi.

  Patient enrolled in study CO-US-164-0423, entitled: "REduction of Early MortALITY in HIV-infected Adults and Children Starting Antiretroviral Therapy: a Randomised Controlled Trial (REALITY)."

  A 16-year-old female subject (race unspecified), with a history of HIV infection, was hospitalized pending exploratory laparotomy for left adnexal/ ovarian mass that was seen on a pelvic scan that was thought to possibly be lymphadenopathy or a tumor. Her baseline CD4 cell count was 4 cells/uL. A pregnancy test was negative. While hospitalized study treatment with emtricitabine+tenofovir disoproxil fumarate, efavirenz and raltegravir was commenced. Eighteen days later the patient developed vomiting, shortness of breath and hypotension with a blood pressure of 84/39, heart rate of 116 and oxygen saturation of 95%. She had normocytic anemia and ascites. The patient scored a 14/15 on the coma scale and was noted as having a tender epigastrium and bilateral pleural effusion. The patient was diagnosed with disseminated tuberculosis and abdominal sepsis. The patient received treatment with unspecified tuberculosis medications, ceftriaxone, metronidazole, and fluids. Nineteen days after starting study treatment, the patient died due to presumptive disseminated tuberculosis and abdominal sepsis.

3.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=4)

Four non-fatal adverse event cases in pediatric patients received since the last pediatric review were evaluated. DPV did not identify potential new risks, or known/labeled risks reported in unusual numbers in pediatric patients. Two cases reported unlabeled events (medication error, off-label use-1, gastroenteritis-1) and two cases reported labeled events (hypersensitivity with liver involvement-1, drug reaction with eosinophilia and systemic symptoms or DRESS-1).

Unlabeled Event: Medication error, off-label use (n=1)– One case reported a 10-fold over-dosing error in a 4-day old infant receiving raltegravir for HIV prophylaxis through a special access program. Raltegravir is not approved for use in pediatric patients less than 4 weeks of age. No adverse event was reported in association with the events. The case is described below.

- FAERS case #10915176-1, Canada.

  A 4-day-old male patient (weight 3.6kg) via a special access program was taking 0.27ml twice daily raltegravir potassium granules for suspension (strength 10 mg/mL or 100 mg/sachet, daily dose 1.5mg/kg or 5.4 mg, frequency twice daily/every 12 hours) as prophylaxis of HIV. The concomitant drugs reported were zidovudine, lamivudine, lopinavir, and ritonavir. On day 4 of baby's life the patient received 2.7ml (15mg/kg which is 10 times the recommended dose) of raltegravir potassium instead of 0.27ml (equivalent to 1.5 mg/kg) for the morning dose. The stomach contents were aspirated 25 minutes after drug administration. All parameters of complete blood count (CBC), biochemistry, blood gases and lactate were found to be normal. The drug was held for 48 hours and then restarted. The baby was monitored in the hospital for about one week following the drug dosing error. No adverse clinical events were noted.

Unlabeled Event: Gastroenteritis (n=1) – One case reported gastroenteritis. Causality to raltegravir cannot be established due to underlying immunosuppression and lymph node tuberculosis. Raltegravir was continued and the subject recovered from the events. The case is described below.

- FAERS case #10978477-2 (duplicate case #11055572-1), Kenya.

  Patient enrolled in a study entitled "Reduction of Early mortALITY in HIV-infected African Adults and Children Starting Antiretroviral Therapy: a Randomised Controlled Trial (REALITY)".

  A 12-year-old male subject with a history of HIV infection and lymph node tuberculosis started tuberculosis (TB) medications. Concomitant medications included trimethoprim+sulfamethoxazole initiated on an unknown date. Baseline CD4 cell count was 34 cells/ul (WHO stage IV). On an unknown date, the subject started antiretroviral (ARV) therapy with efavirenz and raltegravir. The subject presented within 1 month of

starting ARV therapy and within 2 months of starting TB medications with a two-day history of abdominal pain, diarrhea and vomiting and was hospitalized for gastroenteritis (grade III). On examination, the subject was looking sick, febrile and temperature was 38.8 degree C. The investigation for malarial parasite was negative and lab reports revealed alanine aminotransferase (ALT) at 141 units/litre (U/L), bilirubin at 77.3 micromol/L and aspartate aminotransferase (AST) at 228 U/L. The subject developed hepatitis induced by TB adenitis. He responded well to gastroenteritis treatment and was discharged home. ARV, trimethoprim+sulfamethoxazole, and TB adenitis therapy were ongoing.

Labeled Events: Hypersensitivity (n=2) – Two cases reported hypersensitivity reactions that were consistent with the known risk in the labeling and no increased severity was observed in these reports. The labeling includes, under **Warnings and Precautions**, severe rash, or rash with systemic symptoms, eosinophilia or organ dysfunction, including hepatic failure. Both cases are described below:

- FAERS case #10861281-2 (duplicate case #10873994-1), South Africa.

  Hypersensitivity with liver involvement:

  Patient enrolled in study entitled "Phase I/II dose-finding, safety and tolerance study of a RALTEGRAVIR-containing antiretroviral therapy (ART) regimen in ART-naive HIV-Infected and HIV/TB Co-Infected Children >3 years TO < 12 years of Age (IMPAACT P1101)".

  A 9-year-old black female subject with HIV infection and disseminated tuberculosis was treated with rimactazid, pyrazinamide, ethambutol, trimethoprim+sulfamethoxazole, multivitamin and pyridoxine. One month later she started raltegravir; concomitant medications included abacavir, efavirenz, and lamivudine. At this time, her HIV viral load was 618578 copies/ml and CD4 cell count was 75 cells/mm3. Fifteen days after beginning raltegravir, the patient had vomiting and loose stools, followed by fixed drug reaction (grade 3), increased levels of ALT (grade 2) and AST (grade 4). Annular skin lesions were noted on the trunk, abdomen, arms and face. No mucosal involvement and no pruritis. ALT worsened to grade 4. Peak reported values: total bilirubin 92 umol/L (normal range: 5-21), conjugated bilirubin 76 umol/L (normal range: 0-5), ALT 230 U/L , AST 366 U/L, GGT 170 U/L, LDH 538 U/L, CRP 54 mg/L (normal range:<10). Raltegravir, abacavir, efavirenz, lamivudine and trimethoprim+sulfamethoxazole were held. Fluconazole for oral candidiasis and cefotaxime for fever were started. PCR HLA-B5 and blood cultures including TB showed negative results. Her CD4 count improved to 106. Following discontinuation of antiretrovirals and trimethoprim+sulfamethoxazole, improvement in fixed drug reaction, AST, ALT, fever, vomiting and loose stools occurred over 14 days. Therapy with efavirenz and lamivudine were restarted and patient was discharged. Raltegravir, abacavir and trimethoprim+sulfamethoxazole were not restarted.

- FAERS case #11853779-1, (duplicate case #11865118-1), USA.

  Drug reaction with eosinophilia and systemic symptoms (DRESS):

  Literature case report: Palmisano EL, et al. DRESS syndrome in an HIV positive child after initiation of raltegravir and abacavir with negative HLA B*5701 testing. Ann Allergy Asthma Immunol 2015;115 (Suppl):A77 abstr. P132.

  A 10-year-old female patient's HIV regimen was changed from zidovudine, lamivudine and lopinavir+ritonavir to abacavir, emtricitabine and raltegravir. The patient had negative HLA-B*5701 screening. One month later, she presented with 1-2 weeks of erythematous pruritic rash, tactile temperatures and 2 days of scleral icterus. Physical exam demonstrated lymphadenopathy, and an erythematous, morbilliform generalized rash. Initial laboratory evaluation revealed AST 3918 U/L, ALT 2809 U/L, total bilirubin 11.5 mg/dL (conjugated 8.27 mg/dL), INR 2.71, WBC 9.58 x 10^3 and eosinophil count of 1.74 x 10^3. She was diagnosed with drug reaction with eosinophilia and systemic symptoms (DRESS). Antiretroviral therapy was held and intravenous (IV) steroids were started. After 3 doses of methylprednisolone administered in 6 hour intervals the patient's eosinophils dropped to 0.02 x 10^3 and liver function tests began to trend down. The patient was continued on IV steroids for six days followed by an eight-week taper of oral steroids. Antiretroviral therapy was resumed 10 weeks later with lamivudine, etravirine and ritonavir boosted darunavir with no reaction. The authors believed the most likely culprit for DRESS in this case was raltegravir. According to the authors, emtricitabine is similar to lamivudine which the patient had previously tolerated long term. Abacavir was more commonly implicated with DRESS but this was almost exclusively seen with HLA B*5701, which was not the case in this patient. Furthermore, the patient had negative patch testing to abacavir.

4 DISCUSSION

Analysis of drug utilization data showed that pediatric patients aged 0-16 years old accounted for 1% (1,958 patients) of total patients who received a dispensed prescription for raltegravir from U.S. outpatient retail pharmacies from March 2013 through February 2016. Of the raltegravir use among patients 16 years or younger, the vast majority of use was seen among children 2 to 16 years old. However, a small fraction of use was seen among children younger than two years old. Of note, we focused our analyses on the outpatient retail pharmacy setting only where the largest proportion of raltegravir sales was distributed. However, because HIV medications may be dispensed from HIV clinics and other settings not captured in this analysis, it is important to note that these estimates may not be representative of all treatment for HIV in the U.S. and should be interpreted with caution.

Six reports were received in pediatric patients since the last review in 2013, and this small number is consistent with low domestic use. Low use may decrease the voluntary reporting of any adverse event.

Of the 6 reports reviewed in pediatric patients, 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 raltegravir.

5 CONCLUSION

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

6 RECOMMENDATIONS

Return to routine pharmacovigilance monitoring.

7 REFERENCES

1. Isentress® [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; revised February 2015.

2. IMS Health, IMS National Sales Perspectives™. Mar 2013 – Feb 2016. Extracted Mar 2016. File:NSP 2016-350 raltegravir Isentress eaches by channel Mar2013-Feb2016.xlsx.

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Findings from the drug utilization analysis should be interpreted in the context of the known limitations of the databases used. Based on sales data from March 2013 through February 2016, raltegravir was primarily distributed to U.S. outpatient retail pharmacies. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

IMS, Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

8.2 APPENDIX B 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.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH RALTEGRAVIR (N=6)

FAERS case-version numbers and manufacturer control numbers included in pediatric case series (n=6)		
Ref #	**FAERS case-version #**	**Mfr#**
1	10169889-1 duplicate10185195-1 duplicate10187187-1 duplicate10195849-2 duplicate10200376-1 duplicate10210926-1 duplicate10196482-2	US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2014-BI-20890GD duplicateUS-MYLANLABS-2014S1010796 duplicate2014AP002970 duplicateAUR-APL-2014-05930 duplicateUS-MICRO LABS LIMITED-ML2014-00383 duplicate2014HINLIT0444 duplicateAUR-APL-2014-05906
2	10305812-1	MW-GILEAD-2014-0108679
3	10861281-2 duplicate10873994-1	US-BRISTOL-MYERS SQUIBB COMPANY-BMS-2014-002624 duplicateZA-009507513-1412ZAF004514
4	10915176-1	CA-MERCK-1502CAN010944
5	10978477-2 duplicate11055572-1	KE-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-019001 duplicateUS-009507513-1503GBR013971
6	11853779-1 duplicate11865118-1	US-009507513-1512USA008213 duplicateUS-VIIV HEALTHCARE LIMITED-US2015GSK180959

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