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 Review

Date:	May 11, 2021
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Product Name:	Intelence® (etravirine)
Pediatric Labeling Approval Date:	March 26, 2012
Application Type/Number:	NDA 022187
Applicant:	Janssen Products, L.P.
OSE RCM #:	2021-241
Acknowledgement:	We acknowledge Charlotte Moureaud, PharmD, a regulatory pharmaceutical fellow in medication safety, for her work reviewing case reports, evaluating potential safety signals, and co-authoring this review.

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EXECUTIVE SUMMARY

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

We reviewed all FAERS reports with etravirine in the pediatric population (ages 0 to <18 years) during the period from March 1, 2015 through February 4, 2021. We identified two FAERS cases with etravirine in the pediatric population for further discussion. Both cases reported a serious outcome. No cases resulted in death. The two reported adverse events were consistent with the known adverse events described in the labeling for etravirine. These adverse events are adequately described in the labeling: Stevens-Johnson Syndrome (SJS) in Warnings and Precautions and hematemesis in Adverse Reactions. We identified no new safety signals and no new aspects of known adverse events, such as increased severity or frequency, from the two cases.

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

1 INTRODUCTION

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

1.1 PEDIATRIC REGULATORY HISTORY

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) in antiretroviral treatment-experienced patients 2 years of age and older.[1] Etravirine was first approved for adult use on January 18, 2008.

On March 26, 2012, the first pediatric approval was granted for patients 6 years of age and older.[2] This approval was supported by two clinical trials: TMC125-C126, a phase 1, open-label, dose-finding study, and TMC125-C213, a phase 2, open-label, efficacy, safety, tolerability, and pharmacokinetic study. This study satisfied the PREA requirement for ages 6 to <18 years. The clinical review evaluated safety data from 101 subjects from these trials aged 6 to <18 years. No deaths were observed. Nonfatal serious adverse events were observed in 6% of subjects, all of whom were adolescents (≥12 years old). Upper respiratory tract infection and rash were the most frequently observed adverse events, with overall adverse event profiles in pediatric patients similar to adults. The reviewers evaluated rash and hypersensitivity reactions as specific safety concerns, finding that 25% of subjects experienced any treatment-emergent skin events of interest, and female subjects were more likely to experience these events than males. The majority of these events were Grade 1 or 2 in severity, with no Grade 4 events, however, all Grade 3 events occurred in female subjects. The review concluded that etravirine was safe and tolerable in patients of this age group. It was noted that serious cutaneous adverse events were more common in female pediatric patients than males.[3]

On June 19, 2015, the Applicant was released from the postmarketing requirement to study etravirine in patients aged 2 months to <2 years based on lack of a meaningful therapeutic benefit over existing therapies and unlikely use in a substantial number of patients in that age group. A new postmarketing requirement was issued to study efficacy for pediatric patients aged 2 to <6 years of age.

On July 16, 2018, a supplemental new drug application (sNDA) was approved to expand the patient population to include pediatric patients 2 years to <6 years weighing at least 10 kg.[4] The sNDA contained results from a single study which fulfilled the remaining PREA postmarketing requirement. The study, TMC125-C234, was an open-label, efficacy, safety, tolerability, and pharmacokinetic study in 25 treatment-experienced HIV-1 infected children ≥1 year to <6 years of age. The clinical review considered adverse events (AEs) of interest to be skin adverse events, hepatic adverse events, pancreatic adverse events, and lipid-related adverse events. Safety data from 20 subjects from 2 to <6 years of age who received at least one dose of etravirine was reviewed. Additional safety data was also submitted for 5 subjects aged 1 year to < 2 years of

age. There were no deaths. Non-fatal serious adverse events (SAEs) were reported in 5 of 20 subjects (25%) from 2 to <6 years of age and in 2 of 5 subjects from 1 to <2 years of age (40%). There was one discontinuation due to a Grade 4 increase in lipase. The clinical review concluded that the types of adverse events experienced by patients in this age group were consistent with previously described adverse events, with the exception that the etravirine tablet dispersed in liquid was difficult to tolerate with some patients refusing or spitting out the dose.[5]

OSE Pediatric Postmarketing Pharmacovigilance Reviews

The Office of Surveillance and Epidemiology (OSE) previously evaluated postmarketing adverse event reports and drug utilization data for etravirine in pediatric patients less than 18 years of age on two occasions. The first review, dated November 18, 2013, was prompted by the pediatric labeling changes on March 26, 2012, which expanded the indication to pediatric patients 6 years of age and older.[6] FDA presented OSE's evaluation to the Pediatric Advisory Committee (PAC) on April 21, 2014. OSE's evaluation did not identify any new safety concerns, and recommended return to routine pharmacovigilance monitoring for adverse events with etravirine. The second review, dated August 7, 2015, was conducted in response to revised pediatric labeling that included postmarketing information on 48-week safety.[7] Zero pediatric cases of etravirine associated adverse events were identified in the FAERS database and OSE recommended routine pharmacovigilance monitoring.

1.2 RELEVANT LABELED SAFETY INFORMATION

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

5 WARNINGS AND PRECAUTIONS

5.1 Severe Skin and Hypersensitivity Reactions

Severe, potentially life-threatening and fatal skin reactions have been reported. In clinical trials, these include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. In Phase 3 clinical trials, Grade 3 and 4 rashes were reported in 1.3% of subjects receiving INTELENCE compared to 0.2% of placebo subjects. A total of 2.2% of HIV-1-infected subjects receiving INTELENCE discontinued from Phase 3 trials due to rash *[see Adverse Reactions (6.1)]*. Rash occurred most commonly during the first 6 weeks of therapy. The incidence of rash was higher in females *[see Adverse Reactions (6.1)]*. Stevens-Johnson syndrome was reported in 1.1% (2/177) of pediatric patients less than 18 years of age receiving INTELENCE in combination with other HIV-1 antiretroviral agents in an observational study.

Discontinue INTELENCE immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping INTELENCE treatment after the onset of severe rash may result in a life-threatening reaction.

5.2 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of INTELENCE and other drugs may result in potentially significant drug interactions, some of which may lead to *[see Drug Interactions (7.3)]*:

- Loss of therapeutic effect of concomitant drug or INTELENCE and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of INTELENCE or other concomitant drugs.

See Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during INTELENCE therapy and review concomitant medications during INTELENCE therapy.

5.3 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including INTELENCE. 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 jiroveci* pneumonia (PCP) or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) 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.

5.4 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.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Severe skin and hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.
- Immune reconstitution syndrome *[see Warnings and Precautions (5.3)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience in Pediatric Subjects (2 Years to Less Than 18 years of age)

The safety assessment in pediatric subjects is based on two single-arm trials. TMC125-C213 is a Phase 2 trial in which 101 antiretroviral treatment-experienced HIV-1 infected pediatric subjects 6 years to less than 18 years of age received INTELENCE in combination with other antiretroviral agents (Week 24 analysis). TMC125-C234/IMPAACT P1090 is a Phase 1/2 trial in which 20 antiretroviral treatment-experienced HIV-1 infected pediatric subjects 2 years to less than 6 years of age received INTELENCE in combination with other antiretroviral agents (Week 24 analysis) *[see Clinical Studies (14.2)]*.

In TMC125-C213, the frequency, type and severity of adverse drug reactions in pediatric subjects 6 years to less than 18 years of age were comparable to those observed in adult subjects, except for rash which was observed more frequently in pediatric subjects. The most common adverse drug reactions in at least 2% of pediatric subjects were rash and diarrhea. Rash was reported more frequently in female subjects than in male subjects (rash ≥ Grade 2 was reported in 13/64 [20.3%] females versus 2/37 [5.4%] males; discontinuations due to rash were reported in 4/64 [6.3%] females versus 0/37 [0%] males). Rash (greater than or equal to Grade 2) occurred in 15% of pediatric subjects from 6 years to less than 18 years of age. In the majority of cases, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy. Rash was self-limiting and generally resolved within 1 week on continued therapy. The safety profile for subjects

who completed 48 weeks of treatment was similar to the safety profile for subjects who completed 24 weeks of treatment.

In TMC125-C234/IMPAACT P1090, the frequency, type and severity of adverse drug reactions in pediatric subjects 2 years to less than 6 years of age through Week 24 were comparable to those observed in adults. The most common adverse drug reactions (any grade) of pediatric subjects were rash (50% [10/20]) and diarrhea (25% [5/20]). In this age group, no subjects had Grade 3 or Grade 4 rash and no subjects discontinued prematurely due to rash. One subject discontinued etravirine due to asymptomatic lipase elevation.

6.2 Postmarketing Experience

The following events have been identified during postmarketing use of INTELENCE. Because these events are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Severe hypersensitivity reactions including DRESS and cases of hepatic failure have been reported *[see Warnings and Precautions (5.1)]*.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis

Skin and Subcutaneous Tissue Disorders: Fatal cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to INTELENCE during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Prospective pregnancy data from clinical trials and the APR are not sufficient to adequately assess the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Etravirine use during pregnancy has been evaluated in a limited number of individuals as reported by the APR, and available data show 1 birth defect in 66 first trimester exposures to etravirine-containing regimens *(see Data)*.

The estimated background rate for major birth defects is 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of major birth defects and miscarriage for the indicated population is unknown.

In animal reproduction studies, no adverse developmental effects were observed with orally administered etravirine at exposures equivalent to those at the maximum recommended human dose (MRHD) of 400 mg daily *(see Data)*.

8.4 Pediatric Use

The safety and effectiveness of INTELENCE have been established for the treatment of HIV-infected pediatric patients from 2 years of age to less than 18 years *[see Indications and Usage (1) and Dosage and Administration (2.3)]*. Use of INTELENCE in pediatric patients 2 years to less than 18 years of age is supported by evidence from adequate and well-controlled studies of INTELENCE in adults with additional data from two Phase 2 trials in treatment-experienced pediatric subjects, TMC125-C213, 6 years to less than 18 years of age (N=101) and TMC125-C234/IMPAACT P1090, 2 years to less than 6 years of age (N=20).

Both studies were open-label, single arm trials of etravirine plus an optimized background regimen. In clinical trials, the safety, pharmacokinetics, and efficacy were comparable to that observed in adults except for rash (greater than or equal to Grade 2) which was observed more frequently in pediatric subjects *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*. Postmarketing reports of Stevens-Johnson syndrome in pediatric patients receiving INTELENCE have been reported [*see Warnings and Precautions (5.1), and Adverse Reactions (6.2)*].

Treatment with INTELENCE is not recommended in pediatric patients less than 2 years of age *[see Clinical Pharmacology (12.3)]*. Five HIV-infected subjects from 1 year to < 2 years of age were enrolled in TMC125-C234/IMPAACT P1090. Etravirine exposure was lower than reported in HIV-infected adults (AUC12h geometric mean ratio [90% CI] was 0.59 [0.34, 1.01] for pediatric subjects from 1 year to < 2 years of age compared to adults). Virologic failure at Week 24 (confirmed HIV-RNA greater than or equal to 400 copies/mL) occurred in 3 of 4 evaluable subjects who discontinued before or had reached Week 24. Genotypic and phenotypic resistance to etravirine developed in 1 of the 3 subjects who experienced virologic failure.

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	February 5, 2021
Time period of search	March 1, 2015† - February 4, 2021
Search type	FAERS Business Intelligence Solution (FBIS) Quick Query
Product terms	Product Name: Intelence Product Active Ingredient: etravirine
Search parameters	Age: 0 – 17.99 years‡
MedDRA search terms (Version 23.1)	All MedDRA Preferred Terms (PTs)

* See Appendix A for a description of the FAERS database.

† FAERS cutoff date for the last pediatric review completed in 2015.

‡ The upper age limit was chosen to be consistent with the highest age cutoff of <18 years used in pediatric clinical trials of etravirine.

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 with etravirine received by FDA from March 1, 2015 to February 4, 2021.

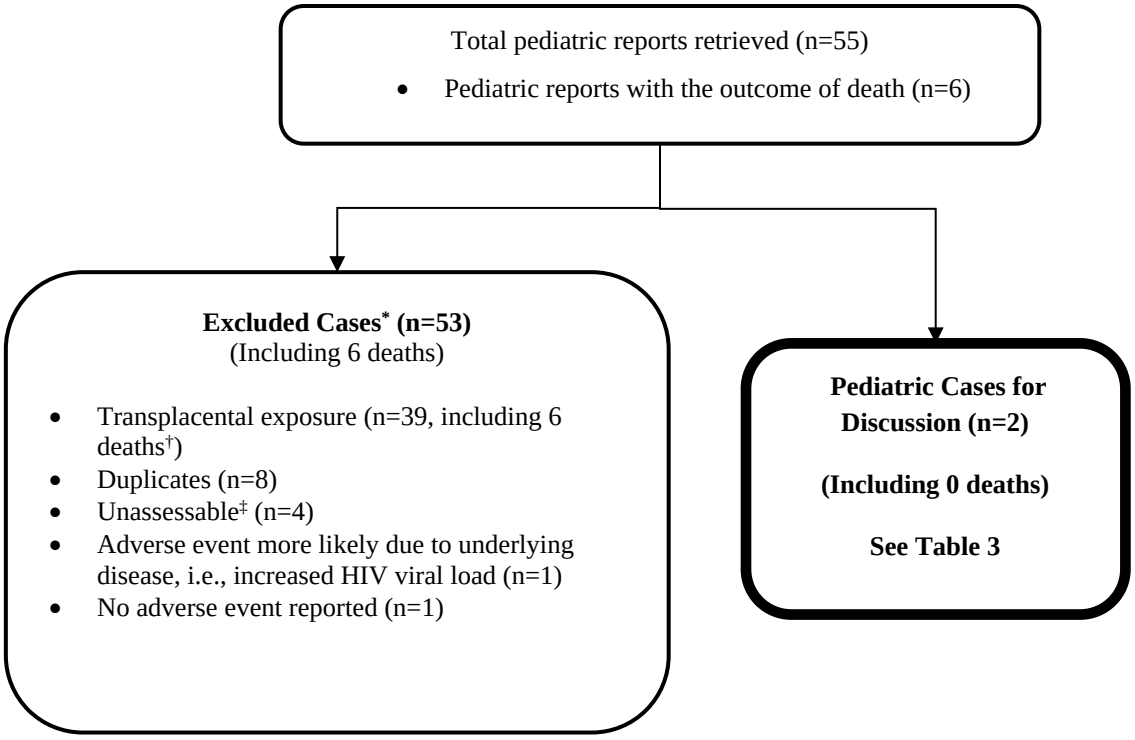
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from March 1, 2015 to February 4, 2021 with etravirine			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	533 (151)	440 (59)	35 (5)
Pediatrics (0 - <18 years)	55 (17)	**48 (10)**	6 (6)

* 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, or other serious important medical events.

3.1.2 Selection of Pediatric Cases in FAERS

The FAERS search retrieved 55 pediatric reports with etravirine, received by FDA from March 1, 2015 to February 4, 2021. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Pediatric Cases with Etravirine



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

† All reports with fatal outcomes were duplicates of one case. The case reported the death of a premature and small-for-dates neonate with transplacental exposure of multiple concomitant antiretroviral therapies. The narrative contained no additional clinical information.

‡ Unassessable: Case cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), or the information is contradictory, or information provided in the case cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There were no fatal pediatric adverse event cases for further discussion.

3.1.4 Summary of Non-Fatal Pediatric Cases (N=2)

We identified two FAERS cases with etravirine in the pediatric population reporting a non-fatal outcome. Appendix B contains a line listing of the two pediatric cases. The cases are summarized below.

FAERS #12283156; Italy; 2016; 5-year-old Female; Serious outcome: hospitalization

A 5-year old female was hospitalized due to intense upper abdominal pain and two episodes of emesis occurring 3 hours after taking darunavir 600 mg and ritonavir 100 mg (coded as hematemesis, although the narrative makes no mention of bleeding). The patient also had two episodes of emesis after taking etravirine 200 mg (unknown time to onset). No additional information was reported.

Reviewer Comments: This report contained limited information for evaluation. The fact that emesis occurred after administration of other oral medications suggests alternative causality. The potential contribution of etravirine to the patient's emesis also cannot be ruled out. However, hematemesis, retching, and abdominal distension are labeled under Clinical Trials Experience in Adults in Section 6 Adverse Reactions for etravirine. This section also states that the frequency, type, and severity of adverse drug reactions in pediatric clinical trial subjects 2 years to <6 years of age through week 24 were comparable to those observed in adults. This report does not suggest increased severity or new aspects of these adverse reactions.

FAERS #15017665; United Kingdom; 2018; 15-year-old Male; Serious outcomes: hospitalization, life-threatening, and other medically significant

A 15-year old male experienced Stevens-Johnson Syndrome (SJS) while taking etravirine, raltegravir, darunavir, and ritonavir for HIV infection for approximately 1 month and trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* pneumonia prophylaxis for approximately 6 weeks prior to symptom onset. Initially, the patient had symptoms described as "facial oedema, rash, pruritus, dysuria, painful lips, ulcers on foreskin and mouth, fine papules right cheek, was spreading to right forearm (3 days later), bullous dermatitis, photoallergic reaction, erythroderma." The patient stopped etravirine and trimethoprim-sulfamethoxazole, and the rash was noted to improve. On an unknown date, the patient restarted etravirine and, within 6-7 hours, experienced recurring symptoms including "localized maculopapular reaction on face and on both arms" and "ulcer under tongue, lip and foreskin." Less than 10% body surface area was involved and there was no skin necrosis, eye involvement, or a generalized reaction. The patient was hospitalized for SJS and seen by a dermatologist who performed a skin biopsy (results not reported). The patient was treated with oral antihistamines and menthol cream and was discharged 5 days later.

Reviewer Comments: This report contained a dermatologist-documented case of SJS that suggests a possible causal relationship between etravirine and SJS, although the

patient's other medications may also be culpable, particularly trimethoprim-sulfamethoxazole. Severe skin and hypersensitivity reactions including SJS are labeled in Section 5 Warnings and Precautions for etravirine. This report does not describe increased severity or a new aspect of the adverse event.

4 DISCUSSION

We reviewed all FAERS reports with etravirine in the pediatric population (ages 0 to <18 years) during the period from March 1, 2015 through February 4, 2021. We identified two FAERS cases with etravirine in the pediatric population for further discussion. Both cases reported a serious outcome. No cases resulted in death. The two reported adverse events were consistent with the known adverse events described in the labeling for etravirine. These adverse events are adequately described in the labeling: SJS in Warnings and Precautions and hematemesis in Adverse Reactions. We identified no new safety signals and no new aspects of known adverse events, such as increased severity or frequency, from the two cases.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for etravirine 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 etravirine.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=2)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	4/19/2016	12283156	1	IT-ABBVIE-16P-083-1606208-00	Expedited (15-Day)	5	Female	Italy	HO
2	6/15/2018	15017665	2	GB-JNJFOC-20111001501	Expedited (15-Day)	15	Male	United Kingdom	HO, LT, OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. A case may have more than one serious outcome.
Abbreviations: HO=hospitalization, LT=life-threatening, OT=other medically significant

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JAMES M KIDD
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