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:	20-Dec-2018
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Product Name:	Selzentry (maraviroc)
Pediatric Labeling Approval Date:	04-Nov-2016
Application Type/Number:	NDA 208984 oral solution, NDA 22128 (S-17) oral tablets
Applicant/Sponsor:	ViiV Healthcare
OSE RCM #:	2018-1971

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for maraviroc in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with maraviroc in pediatric patients.

The FDA approved Selzentry (maraviroc), on August 6, 2007. Maraviroc a CCR5 co-receptor antagonist indicated in combination with other antiretroviral agents for the treatment of only CCR5-tropic HIV-1 infection. The approved pediatric labeling expanded the indication from adult patients to patients 2 years of age and older weighing at least 10 kg.

We reviewed all serious FAERS reports with maraviroc in the pediatric population through September 30, 2018. Of the reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly associated with maraviroc.

One case of Hodgkin's disease, an unlabeled event, was included in our case series. The potential risk of malignancy with maraviroc is discussed in the label under WARNINGS and PRECAUTIONS, but no increased risk of malignancy was identified in 5-year follow-up studies of clinical trial patients. This patient may have been at increased risk for the development of Hodgkin's disease due to underlying HIV infection. The incidence of Hodgkin's disease in HIV-infected individuals, including children, is increased compared to the general population.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for maraviroc in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with maraviroc in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Selzentry (maraviroc) is a selective, slowly reversible, small molecule antagonist of the interaction between human CCR5 and HIV-1 gp120. Blocking this interaction prevents CCR5-tropic HIV-1 entry into cells. Selzentry was initially approved in August 2007 and is indicated in combination with other antiretroviral agents for the treatment of only CCR5-tropic HIV-1 infection in patients 2 years of age and older weighing at least 10 kg. Selzentry is not recommended in patients with dual/mixed- or CXCR4-tropic HIV-1. Prior to initiation of Selzentry, all patients should be tested for CCR5 tropism using a highly sensitive tropism assay. Selzentry must be given in combination with other antiretroviral medications.

This review was prompted by pediatric labeling approved on November 4, 2016 that expanded the indication from adults to pediatric patients 2 years of age and older weighing at least 10 kg. In addition, a new oral solution and two lower dose strength tablets were approved.

Selzentry is supplied as oral film-coated tablets that contain 25, 75, 150, or 300 mg of maraviroc, and as an oral solution that contains 20mg per mL of maraviroc. Selzentry tablets and oral solution are taken twice daily by mouth and may be taken with or without food. Pediatric dosage should be based on body weight (kg) and concomitant medications and should not exceed the recommended adult dose. Dose adjustment may be necessary in patients with renal impairment.

The pediatric clinical trial used to gain the pediatric indication is described below:

Trial A4001031 (NCT00791700) in CCR5-Tropic, Treatment-Experienced Subjects
Safety, pharmacokinetic profile, and antiviral activity were evaluated in an open-label, multicenter trial in which 103 treatment-experienced, CCR5-tropic, HIV-1– infected pediatric subjects aged 2 to less than 18 years weighing at least 10 kg received maraviroc twice daily in combination with optimized background therapy (OBT).

Subjects were required to have HIV-1 RNA greater than 1,000 copies per mL at screening. Dosing of maraviroc was based on body surface area (BSA) and doses were adjusted based on whether the subject was receiving potent cytochrome P450 (CYP) 3A inhibitors and/or inducers. The population was 52% female and 69% black, with mean age of 10 years (range: 2 to 17

years). At baseline, mean plasma HIV-1 RNA was 4.4 log10 copies per mL (range: 2.4 to 6.2 log10 copies per mL), mean CD4+ cell count was 551 cells per mm3 (range: 1 to 1,654 cells per mm3), and mean CD4+ percent was 21% (range: 0% to 42%). The median duration of therapy with maraviroc was 131 weeks with 72% of subjects receiving study treatment for greater than 48 weeks and 62% of subjects receiving study treatment for 96 weeks. At 48 weeks, 48% of subjects treated with maraviroc and OBT achieved plasma HIV-1 RNA less than 48 copies per mL and 65% of subjects achieved plasma HIV-1 RNA less than 400 copies per mL. The mean CD4+ cell count (percent) increase from baseline to Week 48 was 247 cells per mm3 (5%).

In these 103 children and adolescents, the safety profile through 96 weeks was similar to that for adults. Most of the adverse reactions reported were mild to moderate; severe (Grade 3 and 4) adverse reactions occurred in 2% of subjects. The most common adverse reactions (all grades reported with twice-daily therapy with maraviroc were vomiting (12%), abdominal pain (4%), diarrhea (4%), nausea (4%), and dizziness (3%). Three subjects (3%) discontinued due to adverse events. Maraviroc-related gastrointestinal adverse events through 48 weeks (nausea, vomiting, diarrhea, constipation, and abdominal pain/cramps) were observed more commonly in subjects who received the maraviroc oral solution (21%) compared with those who received maraviroc tablets (16%). Subjects were permitted to change formulations after Week 48.

No new safety concerns were identified in the Division of Antiviral Products (DAVP) clinical review other than the increased rate of gastrointestinal adverse events in subjects who were administered the oral solution compared to those who were administered tablets. This information is included in the label under ADVERSE REACTIONS - Clinical Trials Experience in Pediatric Subjects. [1]

Maraviroc has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Selzentry labeling [2] includes the following information under Highlights of Prescribing Information:

BOXED WARNING:

WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning

- **Hepatotoxicity has been reported which may be preceded by severe rash or other features of a systemic allergic reaction (e.g., fever, eosinophilia, or elevated IgE).**
- **Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction.**

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

- SELZENTRY is contraindicated in patients with severe renal impairment or end-stage renal disease (ESRD) (CrCl less than 30 mL per minute) who are concomitantly taking potent CYP3A inhibitors or inducers.

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

- Hepatotoxicity accompanied by severe rash or systemic allergic reaction, including potentially life-threatening events, has been reported. Hepatic laboratory parameters including ALT, AST, and bilirubin should be obtained prior to starting SELZENTRY and at other time points during treatment as clinically indicated. If rash or symptoms or signs of hepatitis or allergic reaction develop, hepatic laboratory parameters should be monitored, and discontinuation of treatment should be considered. When administering SELZENTRY to patients with pre-existing liver dysfunction or who are co-infected with hepatitis B and/or C virus, additional monitoring may be warranted.
- Severe and potentially life-threatening skin and hypersensitivity reactions have been reported in patients taking SELZENTRY. This includes cases of Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis. Immediately discontinue SELZENTRY and other suspected agents if signs or symptoms of severe skin or hypersensitivity reactions develop and monitor clinical status, including liver aminotransferases, closely.
- More cardiovascular events, including myocardial ischemia and/or infarction, were observed in treatment-experienced subjects who received SELZENTRY. Additional monitoring may be warranted.
- If patients with severe renal impairment or ESRD receiving SELZENTRY (without concomitant CYP3A inducers or inhibitors) experience postural hypotension, the dose of SELZENTRY should be reduced from 300 mg twice daily to 150 mg twice daily.

The Selzentry labeling also includes the following under WARNINGS AND PRECAUTIONS about the potential risk of malignancy that is not included in the Highlights of Prescribing Information:

- Potential Risk of Malignancy:
  While no increase in malignancy has been observed with SELZENTRY, due to this drug's mechanism of action, it could affect immune surveillance and lead to an increased risk of malignancy.

  The exposure-adjusted rate for malignancies per 100 patient-years of exposure in adult treatment experienced trials was 4.6 for SELZENTRY compared with 9.3 on placebo. In treatment-naïve adult subjects, the rates were 1.0 and 2.4 per 100 patient-years of exposure for SELZENTRY and efavirenz, respectively.

  Long-term follow-up is needed to more fully assess this risk.

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

- The most common adverse reactions in treatment-experienced pediatric subjects (greater than or equal to 3% incidence) are vomiting, abdominal pain, diarrhea, nausea, and dizziness.

The Selzentry labeling also includes the following information under USE IN SPECIFIC POPULATIONS about pediatric use that is not included in the Highlights of Prescribing Information:

- *Pediatric Use:*
  The pharmacokinetics, safety, and efficacy of maraviroc in patients younger than 2 years have not been established. Therefore, SELZENTRY is not recommended in this patient population. Additionally, there are insufficient data to make dosing recommendations for use of SELZENTRY in pediatric patients concomitantly receiving noninteracting medications and

weighing less than 30 kg or in pediatric patients concomitantly receiving potent CYP3A inducers without a potent CYP3A inhibitor.

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	01-Oct-2018
Time Period of Search	All reports from 06-Aug-2007† through 30-Sep-2018
Search Type	Product-Manufacturer Reporting Summary, FBIS Quick Query
Product Terms	Selzentry, maraviroc
MedDRA Search Terms (Version 20.1)	All PT terms
* See Appendix A for a description of the FAERS database. † U.S. approval date.	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports through 30-Sep-2018 with maraviroc.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from 06-Aug-2007 through 30-Sep-2018 with Maraviroc			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	1132 (394)	1073 (342)	178 (54)
Pediatrics (0 - <18 years)	18 (9)	**17‡ (8)**	0 (0)
* 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 1.			

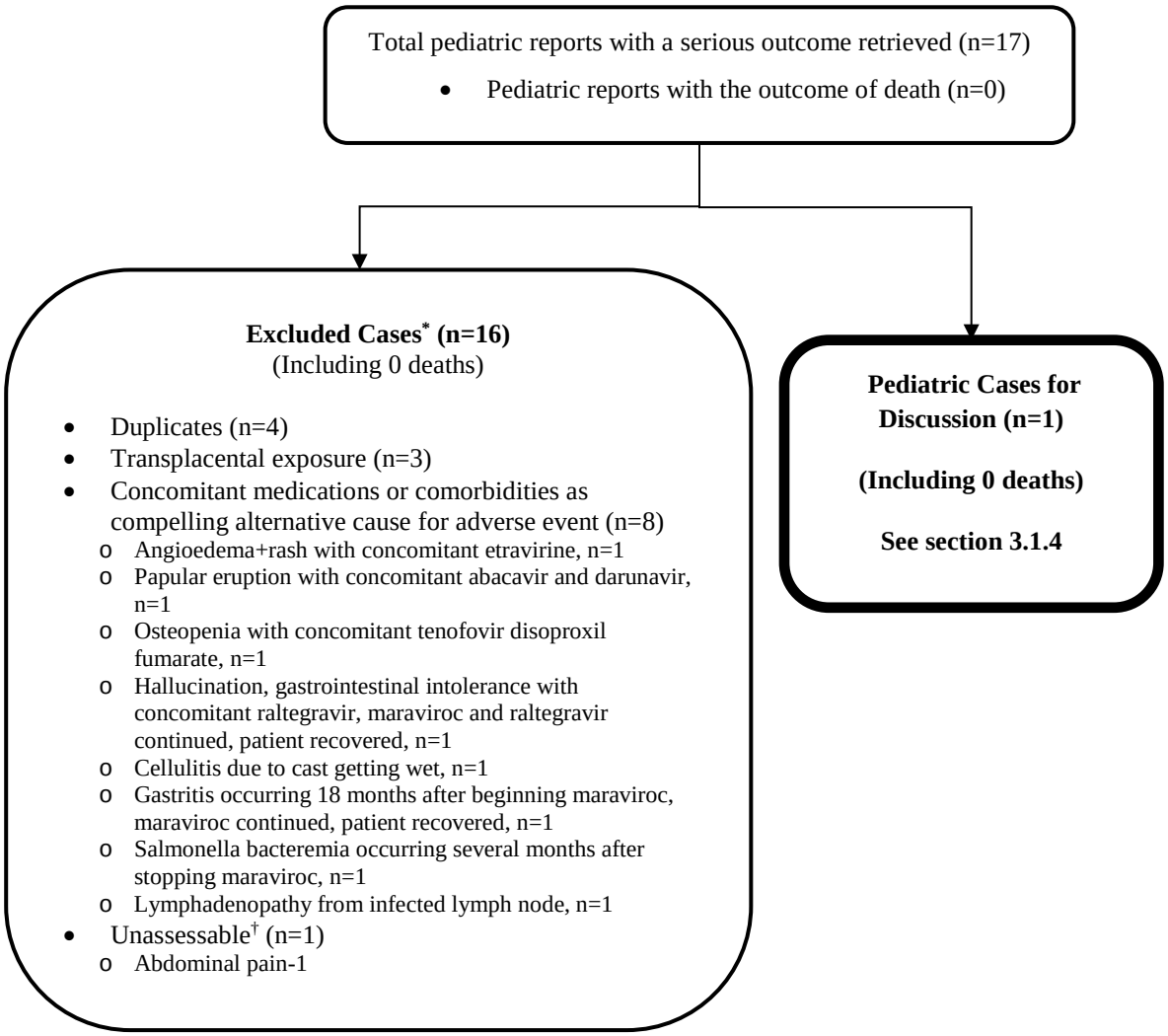
3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 17 pediatric reports with a serious outcome through 30-Sep-2018.

We reviewed all FAERS pediatric reports with a serious outcome. We excluded 16 reports from the case series for various reasons, most of which described compelling alternative causes for the adverse event (e.g., co-morbid diseases or concomitant medications). We summarize the remaining case in section 3.1.4 below.

Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Maraviroc



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

† 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)

We did not identify any fatal pediatric adverse event cases.

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

We identified one serious FAERS case with maraviroc in the pediatric population reporting a non-fatal serious outcome. Appendix B contains a line listing of the one pediatric case. This case is summarized below:

FAERS Case Number 10457855 (duplicate report: 10559809)
Initial FDA Received Date: 16-Sep-2014
Country: Brazil
Unlabeled event: Hodgkin's disease:
A 13-year-old Caucasian female subject with HIV-1 infection was enrolled in pediatric clinical trial NCT00791700 (Trial A4001031 - the same pivotal trial in treatment-experienced patients used to gain the pediatric indication for maraviroc). Her weight was 43 kg. She began maraviroc therapy at 100mg twice daily. Concomitant therapy was reported as abacavir, tenofovir disoproxil fumarate, and atazanavir+ritonavir. Maraviroc therapy was discontinued after 18 months. Four months after maraviroc was discontinued, her CD4 lymphocytes count was 507 cells/mm3 and her plasma HIV RNA viral load was 2,832 copies/mL. Six months after maraviroc was discontinued the subject was hospitalized for cervical adenomegaly preceded by fever and sore throat. A lymph node biopsy revealed Hodgkin's lymphoma. The subject had no history of previous malignancies and no family history of malignancies. There was no suspicion or evidence of immune reconstitution inflammatory syndrome. Antiretroviral therapy at this time was abacavir, tenofovir disoproxil fumarate, and atazanavir+ritonavir. Approximately two months later, the subject began treatment for Hodgkin's disease which included four cycles of chemotherapy with dexamethasone, vincristine, and cyclophosphamide, followed by six cycles of doxorubicin, bleomycin, vinblastine and dacarbazine, and several weeks of radiotherapy. Her treatment was completed after seven months and follow-up phase was initiated.

Reviewers' comments: Maraviroc is not specifically labeled for Hodgkin's lymphoma (also known as Hodgkin's disease), but the potential risk of malignancy with maraviroc is discussed in the label under WARNINGS AND PRECAUTIONS. The labeling states that due to this drug's mechanism of action, it could affect immune surveillance and lead to increased risk of malignancy. Further study is needed, but no increased risk of malignancy was identified in 5-year follow-up studies of pivotal clinical trial patients.[3,4] This patient may have been at increased risk for the development of Hodgkin's disease due to underlying HIV infection. Hodgkin's disease is not an AIDS-defining malignancy, but the incidence in HIV-infected individuals, including children, is increased compared to the general population.[5] The incidence of Hodgkin's disease in HIV-infected patients has increased during the highly active

antiretroviral therapy (HAART) era, and HIV-infected patients with moderate immunosuppression appear to be at highest risk. [6]

4 DISCUSSION

We reviewed all serious FAERS reports with maraviroc in the pediatric population (ages 0 - < 18 years) through September 30, 2018. Of the reports reviewed, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths reported with maraviroc.

One case of Hodgkin's disease, an unlabeled event, was included in our case series. The potential risk of malignancy with maraviroc is discussed in the label under WARNINGS and PRECAUTIONS. The labeling states that due to this drug's mechanism of action, it could affect immune surveillance and lead to increased risk of malignancy. Further study is needed, but no increased risk of malignancy was identified in 5-year follow-up studies of pivotal clinical trial patients. [3 4]

5 CONCLUSION

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

7 REFERENCES

1. Baylor M. DAVP Clinical Review - NDA 208984 and NDA 22128 (S-17). 07 Oct 2016.
2. Selzentry [package insert]. Research Triangle Park, NC: ViiV Healthcare, revised July 2018.
3. Cooper AC, Heera J, Ive P, et al. Efficacy and safety of maraviroc vs. efavirenz in treatment-naïve patients with HIV-1: 5-year findings. AIDS 2014; 28: 717-25.
4. Gulick RM, Fatkenheuer G, Burnside R, et al. Five-Year Safety Evaluation of Maraviroc in HIV-1 Infected Treatment-Experienced Patients. J Acquir Immune Defic Syndr 2016; 65:78-81.
5. Biggar RJ, Frisch MF, Goedert JJ, et al. Risk of Cancer in Children With AIDS. JAMA 2000; 284:205-209.
6. Grogg KL, Miller RF, Dogan A. HIV infection and lymphoma. J Clin Pathol 2007; 60:1365-1372.

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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	16-Sep-2014	10457855 10559809 (dup)	4 5 (dup)	BR-VIIV HEALTHCARE LIMITED-B1031536A B1031536A (dup)	Expedited (15-day)	13	Female	BRA	HO, RI, 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: Dup=Duplicate report for same patient, BRA=Brazil, HO=Hospitalization, RI=Required intervention, OT=Other medically significant

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