

**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 23, 2018

Safety Evaluator: Timothy Jancel, PharmD, MHSc, BCPS-AQ ID
Division of Pharmacovigilance II

Team Leader: Kelly Cao, PharmD
Division of Pharmacovigilance II

Deputy Division Director: Ida-Lina Diak, PharmD, MS
Division of Pharmacovigilance II

Product Name: Noxafil® (posaconazole)

**Pediatric Labeling
Approval Date:** September 9, 2016

Application Type/Number: NDA 022003, 022027 oral suspension, 40 mg per mL
NDA 205053 delayed-release tablets, 100 mg
NDA 205596 injection, 18 mg per mL

Applicant/Sponsor: Merck Sharp & Dohme Corp.

OSE RCM #: 2018-724

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Noxafil® (posaconazole) 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) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with posaconazole in pediatric patients.

Posaconazole is an azole antifungal initially approved by the FDA in 2006 as an oral suspension. The delayed-release tablets and injection were approved in November 2013 and March 2014, respectively. Posaconazole's approved dose, frequency, duration of therapy, and age range vary based on indication and formulation. The oral formulations are indicated in patients 13 years of age and older and are not interchangeable due to the differences in the dosing of each formulation; the injection is indicated in patients 18 years of age and older.

Of the pediatric 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 attributable to posaconazole. Of the four serious and unlabeled adverse event cases identified in this review, no specific pattern of adverse events was noted. One case described an overdose of posaconazole, another case was confounded by an underlying disorder, and two cases lacked sufficient information for a meaningful causality assessment.

DPV did not identify any pediatric safety concerns for posaconazole and recommends no regulatory action at this time.

DPV will continue to monitor all adverse events associated with the use of posaconazole.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Noxafil® (posaconazole) 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) Best Pharmaceuticals in Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with posaconazole in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Posaconazole is an azole antifungal initially approved in 2006 as an oral suspension; the delayed-release tablets and injection were approved in November 2013 and March 2014, respectively.¹⁻³

The Office of Surveillance and Epidemiology (OSE) previously evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for posaconazole in pediatric patients. OSE's evaluation⁴, dated March 3, 2016, was prompted by the pediatric labeling changes on November 25, 2013 after the approval of the posaconazole delayed-release tablets. FDA presented OSE's evaluation to the Pediatric Advisory Committee (PAC) on April 12, 2016. OSE's evaluation recommended continuing ongoing surveillance, and in addition, the further evaluation of serious vincristine-associated adverse events with the concomitant administration of posaconazole to determine if, and how, labeling may be modified.⁴ All eighteen PAC committee members voted and agreed with the FDA's plan to continue ongoing safety monitoring and to review and report back to the PAC regarding the drug-drug interaction between posaconazole and vincristine, and consider labeling change.⁵ After review, the posaconazole label was updated on September 9, 2016 with the addition of vincristine toxicity with the concomitant administration of posaconazole to the WARNINGS AND PRECAUTIONS section (5.6 *Vincristine Toxicity*); in addition, the DRUG INTERACTIONS section (7.10 *Vinca Alkaloids*) was updated.³

This current DPV review is prompted by the pediatric labeling change on September 9, 2016, which added a brief summary of pediatric clinical study report (P03579/P032) titled *Phase 1B study of the safety, tolerance, and pharmacokinetics of oral posaconazole in immunocompromised children with neutropenia*.^{6,7} The study was stopped early because it failed to meet its primary objective. In the study of 136 neutropenic pediatric patients 11 months to less than 18 years of age treated with posaconazole oral suspension, the exposure target of steady-state average concentration between 500 ng/mL and less than 2,500 ng/mL was attained in approximately 50% of patients instead of the pre-specified 90% of patients.⁷

Posaconazole's approved dose, frequency, duration of therapy, and age range varies based on indication and formulation. The oral formulations are indicated in patients 13 years of age and

older and are not interchangeable due to the differences in the dosing of each formulation; the injection is indicated in patients 18 years of age and older. The most recently approved DOSAGE AND ADMINISTRATION section of the posaconazole labeling is presented in Table 1.³

Table 1. Posaconazole Dosage and Administration	
Indication	Dose and Duration of Therapy
Prophylaxis of Invasive <i>Aspergillus</i> and <i>Candida</i> Infections	<p>Injection*: <u>Loading dose:</u> 300 mg intravenously twice a day on the first day. <u>Maintenance dose:</u> 300 mg intravenously once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.</p> <p>Delayed-Release Tablets[†]: <u>Loading dose:</u> 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. <u>Maintenance dose:</u> 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.</p> <p>Oral Suspension[‡]: 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression.</p>
Oropharyngeal Candidiasis	<p>Oral Suspension[‡]: <u>Loading dose:</u> 100 mg (2.5 mL) twice a day on the first day. <u>Maintenance dose:</u> 100 mg (2.5 mL) once a day for 13 days.</p>
Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole	<p>Oral Suspension[‡]: 400 mg (10 mL) twice a day. Duration of therapy is based on the severity of the patient's underlying disease and clinical response.</p>
<p>*Noxafil injection must be administered through an in-line filter. Administer by intravenous infusion over approximately 90 minutes via a central venous line. Never give Noxafil injection as an intravenous bolus injection. [†]Noxafil delayed-release tablets should be taken with food. [‡]Noxafil oral suspension should be taken with a full meal.</p>	

Additional information from the posaconazole label, section 8.4 *Pediatric Use*, is listed below. For more details, please refer to the full prescribing information.³

8.4 Pediatric Use

The safety and effectiveness of Noxafil injection in pediatric patients below the age of 18 years of age has not been established. Noxafil injection should not be used in pediatric patients because of nonclinical safety concerns.

The safety and effectiveness of posaconazole oral suspension and posaconazole delayed-release tablets have been established in the age groups 13 to 17 years of age. Use of posaconazole in these age groups is supported by evidence from adequate and well-controlled studies of posaconazole in adults. The safety and effectiveness of posaconazole in pediatric patients below the age of 13 years (birth to 12 years) have not been established.

A total of 12 patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) of posaconazole oral suspension for prophylaxis of invasive fungal infections. The safety

profile in these patients <18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these pediatric patients, the mean steady-state average posaconazole concentration (C_{avg}) was similar between these patients and adults (≥18 years of age). In a study of 136 neutropenic pediatric patients 11 months to less than 18 years treated with posaconazole oral suspension, the exposure target of steady-state posaconazole C_{avg} between 500 ng/mL and less than 2500 ng/mL was attained in approximately 50% of patients instead of the pre-specified 90% of patients.

1.2 RELEVANT LABELED SAFETY INFORMATION

The posaconazole labeling provides the following information excerpted from the pertinent sections.³

-----CONTRAINDICATIONS-----

- Do not administer to persons with known hypersensitivity to posaconazole or other azole antifungal agents.
- Do not coadminister Noxafil with the following drugs; Noxafil increases concentrations of:
 - Sirolimus: can result in sirolimus toxicity
 - CYP3A4 substrates (pimozide, quinidine): can result in QTc interval prolongation and cases of TdP
 - HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4: can lead to rhabdomyolysis
 - Ergot alkaloids: can result in ergotism

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

- Calcineurin Inhibitor Toxicity: Noxafil increases concentrations of cyclosporine or tacrolimus; reduce dose of cyclosporine and tacrolimus and monitor concentrations frequently.
- Arrhythmias and QTc Prolongation: Noxafil has been shown to prolong the QTc interval and cause cases of TdP. Administer with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs known to prolong QTc interval and metabolized through CYP3A4. Correct K⁺, Mg⁺⁺, and Ca⁺⁺ before starting Noxafil.
- Hepatic Toxicity: Elevations in LFTs may occur. Discontinuation should be considered in patients who develop abnormal LFTs or monitor LFTs during treatment.
- Noxafil injection should be avoided in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of Noxafil injection.
- Midazolam: Noxafil can prolong hypnotic/sedative effects. Monitor patients and benzodiazepine receptor antagonists should be available.
- Vincristine Toxicity: Concomitant administration of azole antifungals, including Noxafil, with vincristine has been associated with neurotoxicity and other serious adverse reactions; reserve azole antifungals, including Noxafil, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

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

- Common treatment-emergent adverse reactions in studies with posaconazole are diarrhea, nausea, fever, vomiting, headache, coughing, and hypokalemia.

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

Interaction Drug	Interaction
Rifabutin, phenytoin, efavirenz, cimetidine, esomeprazole*	<i>Avoid coadministration unless the benefit outweighs the risks</i>
Other drugs metabolized by CYP3A4	<i>Consider dosage adjustment and monitor for adverse effects and toxicity</i>
Digoxin	<i>Monitor digoxin plasma concentrations</i>
Fosamprenavir, metoclopramide*	<i>Monitor for breakthrough fungal infections</i>

*The drug interactions with esomeprazole and metoclopramide do not apply to posaconazole tablets.

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

- Pregnancy: Based on animal data, may cause fetal harm.
- Nursing Mothers: Discontinue drug or nursing, taking in to consideration the importance of drug to the mother.
- Severe renal impairment: Monitor closely for breakthrough fungal infections.

2 METHODS AND MATERIALS

2.1 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2. See Appendix A for a description of the FAERS database.

Date of Search	April 2, 2018
Time Period of Search	September 1, 2015* through March 31, 2018
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query Product-Manufacturer Reporting Summary
Product Name	Product Active Ingredient: Posaconazole
Search Parameters	All ages, all outcomes, worldwide

* End date of the last BPCA/PREA pediatric review (September 15, 2006 through August 31, 2015)

3 RESULTS

3.1 FAERS

3.1.1 Total number of FAERS reports by Age

Table 3. Total Adult and Pediatric FAERS Reports* from September 1, 2015 through March 31, 2018 with Posaconazole

	All reports (U.S.)	Serious [†] (U.S.)	Death (U.S.)
Adults (≥ 18 years)	670 (268)	603 (204)	218 (106)
Pediatrics (0 - <18 years)	79 (26)	76^{‡§} (19)	24 [§] (14)

* 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

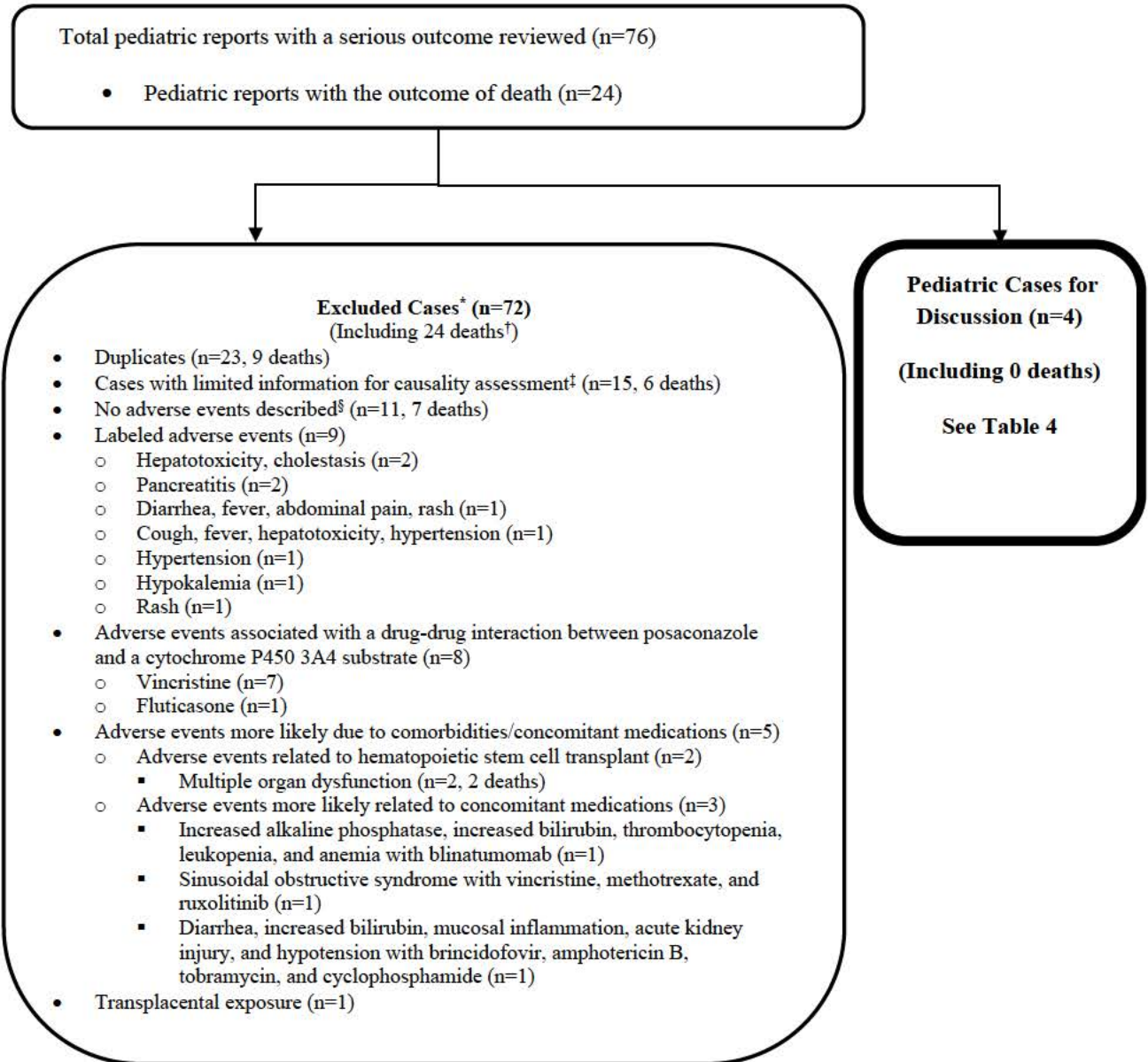
[‡] See Figure 1

[§] Five reports of pediatric deaths were identified among reports not reporting an age and were added to the pediatric serious and death report counts

3.1.2 Selection of Serious Pediatric Cases in FAERS

We identified 76 pediatric reports with a serious outcome (See Table 3). See **Figure 1** below for the specific selection of cases to be summarized in **Sections 3.2 and 3.3**.

Figure 1. Selection of Serious Pediatric Cases with Posaconazole



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

† The 24 reports resulting in death were excluded because they were duplicates (n=9), described treatment failure, development of resistance, and/or underlying disease progression (n=6; e.g., invasive fungal infections, multiple infections [bacterial, viral, or fungal], and tumor progression), contained limited case details for adequate assessment (n=6), or were associated with complications from hematopoietic stem cell transplant/chemotherapy (n=3; e.g., pulmonary hemorrhage after receiving defibrotide for sinusoidal obstruction syndrome [defibrotide labeled for pulmonary hemorrhage[§]], and multiorgan failure)

‡ Unknown time to event, concomitant medications and comorbidities, clinical course and outcome

§ Indication related, treatment failure, development of resistance, low posaconazole concentration

3.1.3 Characteristics of Pediatric Cases

Appendix B contains a line listing of the four pediatric cases.

Age	2 to < 6 years	1
	6 to <12 years	2
	12 to < 18 years	1
Sex	Male	1
	Female	3
Country	United States	1
	Foreign	3
Reported Reason for Use	Aspergillosis, treatment	1
	Mucormycosis, treatment	1
	Prophylaxis	1
	Unknown	1
Serious Outcome*	Hospitalization	2
	Other serious	3

* 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.

3.2 SUMMARY OF FATAL PEDIATRIC CASES (N=0)

We did not identify any fatal pediatric adverse event cases directly attributable to posaconazole.

3.3 SUMMARY OF PEDIATRIC SERIOUS ADVERSE EVENT CASES (N=4)

FAERS Case Number: 11768693 Country: France

Reported MedDRA Preferred Terms (PTs): *Dysphagia, Abdominal pain, Oesophagitis, Decreased appetite, Medication error*

An 11-year-old female with cystic fibrosis was erroneously prescribed posaconazole delayed-release tablets (200 mg twice daily) for an unreported indication; she previously received posaconazole oral suspension (200 mg twice daily). While receiving the posaconazole tablet formulation over the following 12 days, the patient experienced difficulty eating, pain in the right leg, abdominal pain, and esophageal pain. Twelve days after starting the tablet formulation, the patient was seen in an emergency unit because of persistent esophageal pain and right leg pain. On examination, “the patient’s abdomen was soft and painless. The mucous membranes were a bit dry, but the child ate poorly for few days with probable dehydration. The foot was cold with predominant pain under the right popliteal fossa, with cold and tightened calf. No wound, no thoracic pain, no dyspnea was found.” In addition, “the examination led to rule out vein or

arterial thrombosis and evidenced layer of fluid effusion between gastrocnemius muscle and soleus muscle aponeurosis, evoking strain muscle.” Following the diagnosis of esophagitis, omeprazole was started. The patient was then discharged from the emergency unit with crutches and unspecified analgesics; however, she was still receiving the posaconazole tablet formulation. Two days later, the patient was seen and was changed back to the posaconazole oral suspension (200 mg twice daily) and “the prescribing pediatrician was informed by the hospital pharmacy about the possible posaconazole overdose due to a tablet formulation bioavailability which is higher than the oral suspension one.” One month after restarting the posaconazole oral suspension, it was reported that the patient recovered from all of the events. The French Health Authority considered esophagitis as possibly related to the posaconazole delayed-release tablet formulation.

Reviewer’s Comments: Although the case lacked clinical information, such as medical history and concomitant medications required to assess causality, it demonstrated a temporal onset of symptoms after the patient was erroneously switched from the posaconazole oral suspension to the delayed-release tablet using the same dose and frequency (200 mg twice daily) and a positive dechallenge after switching from the delayed-release tablet back to the oral suspension.

Posaconazole is labeled for abdominal pain, upper abdominal pain, and decreased appetite³; the unlabeled events of dysphagia and esophagitis were possibly due to the delayed-release tablet formulation because the events resolved after switching back to the oral suspension.

Posaconazole oral suspension and tablet formulations are indicated in patients 13 years of age and the label states the following under the section OVERDOSAGE: there is no experience with overdosage of posaconazole injection and delayed-release tablets. As of November 2015, posaconazole is prominently labeled with the following: the delayed-release tablets and oral suspension are not to be used interchangeably due to differences in the dosing of each formulation.³

FAERS Case Number: 12949201 Country: France

Reported MedDRA PTs: *Aggression, Anxiety, Panic attack*

A 15-year-old male received posaconazole delayed-release tablets (“300 mg, BID”) after a computed tomography (CT) scan was suggestive of bronchopulmonary aspergillosis. The patient’s medical history included anxiety, bronchiolitis obliterans, agammaglobulinemia, allogeneic transplant, Epstein-Barr virus reactivation, and pulmonary graft-versus-host disease. Concomitant medications included esomeprazole, azithromycin, alizapride, ursodeoxycholic acid, furosemide, carvedilol, atorvastatin, teicoplanin, ruxolitinib, filgrastim, valacyclovir, imipenem/cilastatin, amikacin, and caspofungin. Eight days after starting posaconazole, the patient experienced severe anxiety, panic attacks, and impulsive aggressiveness. Posaconazole was discontinued and the patient was started on alprazolam and cyamemazine (an antipsychotic not approved in the U.S.). Five days after the event, psychiatric symptoms were still present and “the appearance of oral dryness and stiffness of the 4 limbs leading to the discontinuation of cyamemazine and systemic prescription alprazolam to treat the anxiety attacks.” No further

outcome was reported and the French Health Authority considered these events as questionably related to posaconazole.

Reviewer's Comments: This case demonstrated a temporal onset of symptoms and a likely negative dechallenge given posaconazole's long half-life (26 to 31 hours, delayed-release tablet³); in addition, the unlabeled psychiatric events (anxiety, panic attack, and aggression) were confounded by the patient's past medical history of anxiety. Posaconazole is not indicated for the treatment of aspergillosis in the U.S.³

FAERS Case Number: 14139490 Country: United States

Reported MedDRA PTs: *Adverse event, Overdose, Product use in unapproved indication, Chills, Tremor, Visual impairment*

A 10-year-old female received intravenous posaconazole for rhinocerebral mucormycosis. The patient's past medical history included an unspecified cancer and no history of drug reactions or allergies; the only reported concomitant medication was amphotericin B. The patient received one dose of intravenous posaconazole ("600 mg, once"), and then during the administration of the second dose of intravenous posaconazole ("600 mg once daily"), the patient developed "severe chills, tremors, and maybe visual disturbances." The patient had liver enzyme tests and an electrocardiogram performed; however, it was reported that the results were pending at the time of the submitted report. The outcome of the events was reported as "not recovered" and causality was not reported.

Reviewer's Comments: This case demonstrated a temporal onset of symptoms; however, the case contained insufficient information for a meaningful causality assessment of the unlabeled events (tremor and visual impairment). Posaconazole is labeled for chills and states the following under the section OVERDOSAGE: there is no experience with overdosage of posaconazole injection and delayed-release tablets. Posaconazole is not indicated for the treatment of mucormycosis in the U.S.; the intravenous formulation is indicated for prophylaxis in patients 18 years of age and older with dosing as 300 mg twice a day on the first day (loading dose), and then 300 mg once daily starting on the second day (maintenance dose).³

FAERS Case Number: 14147919 Country: China

Reported MedDRA PTs: *Anal fissure, Haemolysis, Interstitial lung disease, Off label use, Pyrexia, Upper respiratory tract congestion*

A 2-year-old female (weight: 14.9 kg) received posaconazole oral suspension (70 mg three times daily) for antifungal prophylaxis. The patient's past medical history included hemophagocytic syndrome and concomitant medications were not reported. Twenty days after starting posaconazole, the patient developed "mild fever with a body temperature of 38°C" which resolved 2 days later. Twenty-five days after starting posaconazole, the patient developed "mild congestion of throat" which resolved 4 days later. Forty-six days after starting posaconazole, the patient developed "mild anal fissure" which resolved 2 days later. Fifty-one days after starting posaconazole, the patient developed "mild interstitial pneumonia." Posaconazole was

discontinued 58 days after starting therapy. Seventeen days after discontinuing posaconazole, the patient developed “acute hemolysis” which resolved 4 days later. At the time of the report, the patient had “not recovered from interstitial lung disease.” The reporting physician considered the following events as not related to posaconazole: pyrexia, congestion, anal fissure, interstitial lung disease, and hemolysis.

Reviewer’s Comments: This case demonstrated a temporal onset for all events except for hemolysis; however, the case did not contain sufficient information for a meaningful causality assessment of the unlabeled events (anal fissure, interstitial lung disease, and throat congestion). Information regarding the patient’s past medical history, concomitant medications, and clinical details of the adverse events was not provided. Posaconazole oral suspension is indicated in patients 13 years of age and older and is labeled for fever/pyrexia.³

4 DISCUSSION

Of the 76 reports reviewed in pediatric patients less than 18 years of age, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly attributed to posaconazole. The majority of reports had limited information which precluded a meaningful causality assessment, described adverse events that were likely due to comorbidities or concomitant medications (e.g., hematopoietic stem cell transplant and/or chemotherapy), were consistent with the known adverse reactions described in labeling (e.g., hepatic reactions, pancreatitis, diarrhea, fever, abdominal pain, rash, hypertension, and hypokalemia), or did not describe an adverse event (e.g., indication related, treatment failure, and development of resistance).

Of the four serious and unlabeled adverse event cases in pediatric patients less than 18 years of age, no specific pattern of adverse events was noted. One case described an overdose of posaconazole, another case was confounded by an underlying disorder, and two cases lacked sufficient information for a meaningful causality assessment.

5 CONCLUSION

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

6 RECOMMENDATIONS

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

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 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 CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASES WITH POSACONAZOLE (N=4)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome*
1	November 23, 2015	11768693	5	FR-009507513-1511FRA011743	Expedited (15-DAY)	11	Female	France	HO, OT
2	November 16, 2016	12949201	1	FR-009507513-1611FRA005447	Expedited (15-DAY)	15	Male	France	OT
3	October 28, 2017	14139490	1	US-009507513-1710USA014384	Expedited (15-DAY)	10	Female	USA	HO
4	October 31, 2017	14147919	4	CN-009507513-1708CHN011432	Expedited (15-DAY)	2	Female	China	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, required intervention and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.

Abbreviations: HO, Hospitalization; OT, Other medically significant

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/s/

TIMOTHY J JANCEL
05/23/2018

KELLY Y CAO
05/23/2018

IDA-LINA DIAK
05/23/2018