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

Date:	March 3, 2016
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Product Name:	Noxafil® (posaconazole)
Pediatric Labeling Approval Date:	November 25, 2013
Application Type/Number:	NDA 022003, 022027 oral suspension, 40 mg/mL NDA 205053 delayed-release tablets, 100 mg NDA 205596 injection, 18 mg/mL
Applicant/Sponsor:	Merck Sharp & Dohme Corp.
OSE RCM #:	2015-1946

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and 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 Noxafil® (posaconazole) in pediatric patients.

Posaconazole is an azole antifungal initially approved on 15-Sep-2006 as an oral suspension. The oral delayed-release tablets and injection were approved on 25-Nov-2013 and 13-Mar-2014, respectively. The approved pediatric indication for posaconazole oral suspension and delayed-release tablets is for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 13 to 17 years of age at high risk for developing these infections due to being severely immunocompromised. In addition, the oral suspension is approved for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole in patients 13 to 17 years of age.

The vast majority of patients who had a hospital billing for posaconazole were adults 18 years and older who accounted for 90% or more of total patients during the examined time period. Pediatric patients aged 0-17 years accounted for 10% or less of total patients. Among the pediatric patients, the majority of patients were between 13-17 years.

The Food and Drug Administration Adverse Event Reporting System (FAERS) database was searched for serious adverse event reports associated with posaconazole from 15-Sep-2006 through 31-Aug-2015. The FAERS review identified a case series of 34 pediatric cases (fatal outcomes [n=13] and those with serious, and unlabeled adverse events [n=21]). Six of the 34 pediatric cases (18%) were domestic, which is consistent with the low domestic use in pediatric patients.

A signal of vincristine-induced neurotoxicity (e.g., paralytic ileus, inappropriate antidiuretic hormone secretion, peripheral neuropathy, seizure, etc.) was noted in 10 cases with the concomitant administration of posaconazole with vincristine. These serious and potentially life-threatening neurologic adverse events are unlabeled with respect to posaconazole. There is mechanistic plausibility (i.e., inhibitor of CYP3A4 and P-glycoprotein) by which posaconazole can increase plasma concentrations of vincristine when administered concomitantly; therefore, it is reasonable to suspect that posaconazole may have played a role in these adverse events.

Other than the cases of posaconazole and vincristine drug interaction, no other safety signals were identified in pediatric patients (0 to 17 years of age) exposed to posaconazole. None of the fatal cases (n=13) were directly associated with posaconazole. The fatal cases all identified adverse events currently in the posaconazole product labeling or lacked significant clinical details needed to assess causality.

The Division of Pharmacovigilance II (DPV II) recommends further evaluation of the safety signal (i.e., serious outcomes associated with posaconazole and vincristine drug interaction) through consultation with the FDA/Center for Drug Evaluation and Research (CDER) Office of Clinical Pharmacology and the Division of Hematology and Oncology Products, to inform FDA of the next steps (e.g., labeling revision). Revisions to the label(s) and other regulatory actions will be considered, pending the additional information.

1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

This PREA and BPCA review was triggered as a result of Noxafil® (posaconazole) delayed-release tablets receiving FDA approval and subsequent labeling changes on 25-Nov-2013.[1]

Posaconazole is an azole antifungal initially approved on 15-Sep-2006 as an oral suspension. The oral delayed-release tablets and injection were approved on 25-Nov-2013 and 13-Mar-2014, respectively.[1] Posaconazole's approved dose, frequency, duration of therapy, and age range varies based on indication and formulation. The oral formulations are the only products 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 product labeling is presented in Table 1.1 (updated 16-Nov-2015).[2]

Table 1.1 Noxafil® (posaconazole) DOSAGE AND ADMINISTRATION

Indication	Dose and Duration of Therapy
Prophylaxis of Invasive *Aspergillus* and *Candida* Infections	**Oral Suspension:** 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression. **Delayed-Release Tablets:** Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. Maintenance dose: 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. **Injection:** Loading dose: 300 mg intravenously twice a day on the first day. Maintenance dose: 300 mg intravenously once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression.
Oropharyngeal Candidiasis	**Oral Suspension:** Loading dose: 100 mg (2.5 mL) twice a day on the first day. Maintenance dose: 100 mg (2.5 mL) once a day for 13 days.
Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole	**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.

Additional information from section 8.4 *Pediatric Use* of the posaconazole product labeling is listed below. For full details, please refer to the full prescribing information.[2]

> *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 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 (Cavg) was similar between these patients and adults (≥18 years of age).

1.2 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS

There are no previous or current DPV reviews that are pending regulatory action for posaconazole.

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

The current Noxafil® (posaconazole) product labeling provides the following information excerpted from the pertinent sections (updated 16-Nov-2015).[2]

----------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.

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

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

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

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

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

7.10 Vinca Alkaloids

Most of the vinca alkaloids are substrates of CYP3A4. Posaconazole may increase the plasma concentrations of vinca alkaloids (e.g., vincristine and vinblastine) which may lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered.

----------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 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

2.1.1 Determining Settings of Care

Proprietary drug utilization databases were used to conduct this analysis.

The IMS Health, IMS National Sales Perspectives™ database (see Appendix A for full database descriptions) was used to determine various settings of care, to which oral posaconazole was sold. During year 2014, the sale of posaconazole by number of bottles sold from the manufacturer indicated that approximately 53% was distributed to the non-retail pharmacy settings, 37% to the retail pharmacy setting, and 10% to the mail-order/specialty pharmacies.[3] As a result, non-retail pharmacy utilization patterns were examined. Retail pharmacies and mail-order/specialty settings data were not included in this analysis.

2.1.2 Data Sources Used

The IMS Health, Inpatient HealthCare Utilization System (ICHarUS) database was used to obtain the nationally estimated number of patients who had a hospital billing for oral and injectable posaconazole in the U.S. inpatient and outpatient ER setting, stratified by patient age (0-17 years old and 18 years and older), from September 2010 through August 2015.

2.2 RESULTS

2.2.1 Number of Patients With a Hospital Billing for Posaconazole

Table 2.2.1 provides the nationally estimated number of patients with an inpatient and outpatient ER hospital billing for posaconazole, stratified by formulation and patient age, from September 2010 through August 2015, annually. Approximately 5,300 patients had a hospital billing for oral

posaconazole in 12-month period ending in August 2011 and increased to approximately 11,200 in 12-month period ending in August 2015. The vast majority of patients were adults aged 18 years and older who accounted for nearly 98% (11,000 patients), while patients aged 0-17 years accounted for approximately 2% (255 patients) of total patients in 12-month period ending in August 2015. Among the pediatric patients, approximately 67% (170 patients) were aged 13-17 years while 33% (85 patients) were aged 0-12 years.

The injectable formulation of posaconazole was approved on March 13, 2014, and accounted for approximately 11% (1,300 patients) of total patients. The majority of patients with a hospital billing for injectable posaconazole were adults 18 years and older (98%) while pediatric patients accounted for 1.6% (21 patients).

Table 2.2.1

Nationally Estimated Number Of Patients With Inpatient and Outpatient ER Hospital Billing for Posaconazole, from U.S. Non –Federal Hospital Settings, Stratified by Formulation and Patient Age, September 2010 - August 2015, Annually

	Sept. 2010 - Aug. 2011		Sept. 2011 - Aug. 2012		Sept. 2012 - Aug. 2013		Sept. 2013 - Aug. 2014		Sept. 2014 - Aug. 2015	
	Patient (n)	% Share	Patient (n)	% Share	Patient (n)	% Share	Patient (n)	% Share	Patient (n)	% Share
Total	**5,318**	**100.0%**	**6,049**	**100.0%**	**7,853**	**100.0%**	**9,166**	**100.0%**	**11,980**	**100.0%**
Posaconazole (Oral)	5,318	100.0%	6,049	100.0%	7,853	100.0%	9,166	100.0%	11,183	93.3%
0 - 17 years	85	1.6%	184	3.0%	860	10.9%	278	3.0%	255	2.3%
0 -12 years	28	32.9%	122	65.9%	700	81.5%	192	69.0%	84	33.0%
13 - 17 years	57	67.1%	63	34.1%	160	18.6%	86	31.0%	171	67.0%
18+ years	5,233	98.4%	5,865	97.0%	6,993	89.0%	8,888	97.0%	10,928	97.7%
Posaconazole (Injectable)	--	--	--	--	--	--	56	0.6%	1,344	11.2%
0 - 17 years	--	--	--	--	--	--	7	11.9%	21	1.6%
0 -12 years	--	--	--	--	--	--	7	100.0%	--	--
13 - 17 years	--	--	--	--	--	--	--	--	21	100.0%
18+ years	--	--	--	--	--	--	50	88.1%	1,322	98.4%

*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)

**Patient age subtotals may not sum exactly due to patients aging during the study, and may be counted more than once in the individual age categories For this reason, summing across patient age bands is not advisable and will result in overestimates of patient counts

IMS Health, ICHarUS. July 2014 through June 2015. Extracted December 2015. File: 2015-1946 Posaconazole BPCA.xlsx

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	5-Jan-2016
Time Period of Search	15-Sep-2006* through 31-Aug-2015
Search Type	FAERS Business Intelligence Solution (FBIS) Profile Query (Product-Manufacturer Reporting Summary)
Product Names	Noxafil, Posaconazole
Search Parameters	All ages, all outcomes, worldwide

** Initial US approval date*

3.1.2 Inclusion Criteria for Pediatric Case Series

For the purposes of this review, DPV included pediatric cases that reported:

- Fatal outcomes, OR
- Serious, unlabeled adverse events

AND

- Did not meet exclusion criteria (see Figure 3.2.2)

All FAERS reports retrieved were analyzed and reviewed. The reports that met the inclusion criteria were included in the case series.

3.2 RESULTS

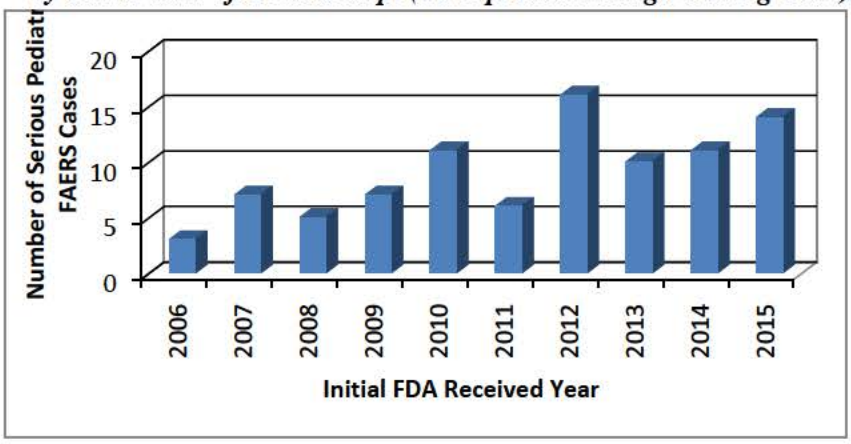
3.2.1 Total Number of FAERS Cases by Age

Table 3.2.1 Total Adult and Pediatric FAERS Reports from 15-Sep-2006 through 31-Aug-2015 with Posaconazole*

	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 18 years)	763 (222)	714 (178)	245 (94)
Pediatrics (0 - <18 years)	105 (42)	**90‡ (27)**	18 (5)

*** May include duplicates and transplacental exposures, and have not been assessed for causality**
† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
‡ See Figure 3.2.2

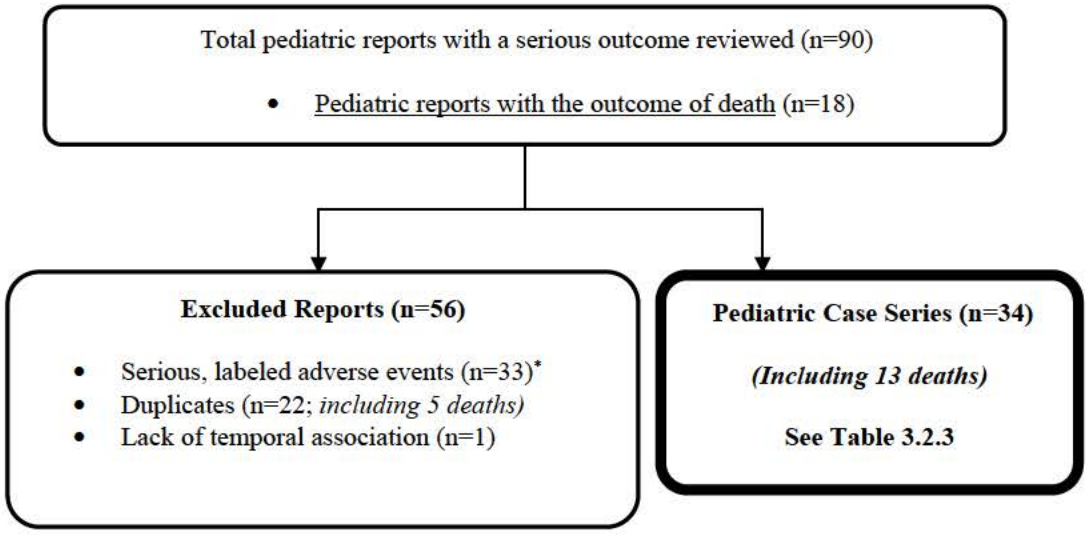
Figure 3.2.1 Serious Pediatric Reports for Posaconazole (N=90)
-- by Initial Year of FDA Receipt (15-Sep-2006 through 31-Aug-2015)



3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 90 pediatric reports with posaconazole and a serious outcome (See Table 3.2.1). See Figure 3.2.2 below for the specific selection of cases to be summarized in Section 3.3.

Figure 3.2.2 Selection of Serious Pediatric Cases with Posaconazole



* DPV reviewed 33 cases associated with non-fatal, labeled adverse events. These cases did not meet the inclusion criteria and were not included in the primary case series.

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. The Pediatric Case Series in Appendix C is divided into three tables: posaconazole and vincristine adverse event cases (Table C1), fatal cases (Table C2), and unlabeled adverse event cases (Table C3).

Table 3.2.3 summarizes the 34 FAERS cases of serious pediatric adverse events reported with posaconazole for the Pediatric Case Series.

Table 3.2.3	***Characteristics of Pediatric Case Series with Posaconazole (N=34)***	
Age	0 - < 2 years	1
	2 - < 13 years	21
	13 - 17 years	12
Sex	Male	19
	Female	14
	Not Reported	1
Country	United States	6
	Foreign	28
Underlying Diagnosis (n=31)	Leukemia	22
	Aplastic Anemia	2
	Cystic Fibrosis	1
	Diamond-Blackfan Anemia	1
	Diabetes Mellitus	1
	Hematologic Disease	1
	Lymphoma	1
	Medulloblastoma	1
	Solid Organ Transplant	1
Formulation (n=31)	Oral Suspension*	27
	Oral Suspension, presumed*	17
	Oral Suspension	10
	Delayed-Release Tablet	2
	Injection	1
	Oral Suspension and Injection	1
Reported Indication† (n=32)	Treatment	21
	Prophylaxis	10
	Prophylaxis and Treatment	1
Reported Fungal Disease, treatment (n=22)	Mucormycosis	10
	Aspergillosis	5
	Mold, not otherwise specified	3
	Candidiasis	1
	Not Reported	3
Serious Outcome‡	Other	22
	Hospitalized	13
	Death	13
	Life-threatening	3
	Disability	1

***** Specific formulation not reported; selection based on date of administration and description of reported dose, route, or frequency.

† Reported indication: the information provided in the indication field of the MedWatch report or from the case narratives.

‡ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.

3.3 SUMMARY OF PEDIATRIC ADVERSE EVENT CASES (N=34)

3.3.1 Summary of Serious Adverse Event Cases with Posaconazole and Vincristine (n=10)

During the course of our review, a pattern of cases emerged that primarily described unlabeled adverse events with the concomitant administration of posaconazole with vincristine. Ultimately, we identified 10 cases in the FAERS database from 15-Sep-2006 through 31-Aug-2015. One of the cases (FAERS Case# 6975058) also reported an outcome of death that was not directly related to the reported adverse events associated with the concomitant administration of posaconazole with vincristine. This case is also discussed in the fatal pediatric case series (Section 3.3.2).

Appendix C (Table C1) lists all the FAERS case numbers, FAERS version numbers, manufacturer control numbers, and summary case narratives of posaconazole with vincristine; one representative case is included after Table 3.3.1.

Table 3.3.1 summarizes the 10 pediatric FAERS cases reported with adverse events associated with the concomitant administration of posaconazole with vincristine.

Table 3.3.1	***Characteristics of Pediatric (0 to 17 years) Case Series with Posaconazole and Vincristine (N=10)***	
Age (years)	Median:	7
	Range:	3 – 12
Sex	Male	6
	Female	4
Country	Foreign	9
	United States	1
Product	Oral Suspension*	10
	Oral Suspension	5
	Oral Suspension, presumed*	5
Initial Posaconazole Dose and Frequency (n=8)	200 mg QID (21 mg/kg/day)	1
	200 mg TID	1
	220 mg BID	1
	200 mg BID (16 mg/kg/day)	1
	160 mg BID (18 mg/kg/day)	1
	100 mg BID (17 mg/kg/day)	1
	50 mg TID	1
	7 mg/kg/day	1
Underlying Diagnosis	Leukemia	10
Reported Indication† (n=9)	Prophylaxis	5
	Treatment	4
Reported Fungal Disease, treatment (n=4)	Mucormycosis	2
	Aspergillosis	1
	Fungal Infection, not otherwise specified	1
Number of Vincristine Doses Administered with Concomitant Posaconazole (n=7)	One	2
	Two	5
Vincristine Dose Adjustment Prior to Reported Event(s) (n=2)	Vincristine Dose Reduction (25%)	1
	Indeterminate	1
Reported MedDRA Preferred Terms Associated with Concomitant Administration of Posaconazole and Vincristine‡	Drug interaction	5
	Ileus paralytic	3
	Inappropriate antidiuretic hormone secretion	3
	Brain oedema	2
	Constipation	2
	Neuropathy peripheral	2
	MedDRA Preferred Terms Reported Once	
	Abdominal pain, Hallucination, Hallucination visual, Hyponatraemia, Ileus, Mental disorder,	

	Metabolic encephalopathy, Neurotoxicity, Pain in jaw, Paraesthesia, Partial seizures, Polyuria, Seizure	
Resolution of Reported Adverse Event(s) Associated with Concomitant Administration (n=9)	Recovered/Resolved	8
	Partial Recovery	1
Serious Outcome**	Other Serious	8
	Hospitalization	5
	Life-Threatening	3
	Death	1
	Disability	1

* Specific formulation not reported; selection based on date of administration and description of reported dose, route, or frequency
† Reported indication: the information that was provided in the indication field of the MedWatch report or from the case narratives.
‡ Reports may have more than one MedDRA preferred term
**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may have more than one outcome.
Abbreviations: BID, twice daily; QID, four times daily; TID, three times daily

Representative Case: Posaconazole with Vincristine

FAERS Case #7399499, India, Literature Report[5] Initial FDA Received Date: 26-May-2010

Title: *Severe life threatening neurotoxicity in a child with acute lymphoblastic leukemia receiving posaconazole and vincristine.*

Case Narrative: A 4-year-old male with acute lymphoblastic leukemia (ALL) received induction therapy with Berlin-Frankfurt-Münster 95 protocol. On day 19 of this protocol, disseminated mucormycosis was detected that responded to amphotericin B. He underwent wedge resection of the pulmonary lesions and surgical debridement of the cutaneous lesions. Induction was completed with prednisolone, vincristine, and L-asparaginase. He achieved complete remission and subsequent chemotherapy per protocol. Posaconazole (7 mg/kg/day) was initiated for secondary prophylaxis during re-induction (route, frequency, and formulation were not reported). On day 20 of re-induction, he presented with repeated episodes of seizures. He had no past or family history of seizure disorder. He had been lethargic the past few days, but had no history of fever, constipation, diarrhea, or vomiting. Persistent seizures led to respiratory compromise requiring mechanical ventilation. Laboratory values revealed the following: sodium 99 mEq/L (normal range not reported), potassium 2.8 mEq/L (normal range not reported), and normal renal function. Serum osmolality was low (243 Osm/kg H_2O, normal range not reported), urinary osmolality was high (415 Osm/kg H_2O, normal range not reported), and urinary sodium was high (125 mEq/L, normal range not reported), thus confirming a diagnosis of syndrome of inappropriate antidiuretic hormone secretion. Baseline serum electrolytes prior to events were reported as normal. A magnetic resonance imaging (MRI) scan of the brain was performed the same day and found to be normal. Posaconazole was discontinued and seizures were treated with phenytoin, fluid restriction, and sodium and potassium supplementation. His biochemical parameters and mental status normalized and no other apparent cause of seizure was identified. He did not have further episodes of seizure or neurotoxicity when vincristine was subsequently administered alone without posaconazole.

Reviewer Comments: *Based on the temporal association, a causal relationship between posaconazole and the events of inappropriate antidiuretic hormone secretion and seizure cannot be excluded. The adverse events of seizure and neurotoxicity only occurred when vincristine was administered with concomitant posaconazole. The patient received vincristine before and after concomitant posaconazole administration without experiencing any episodes of seizure or neurotoxicity. It was not reported if vincristine was dose-reduced during concomitant administration with posaconazole. Vincristine sulfate is labeled for neurotoxicity, convulsions, and inappropriate antidiuretic hormone secretion.[6] Posaconazole is labeled as a drug interaction with vincristine due to posaconazole's ability to increase vincristine plasma concentrations which may lead to neurotoxicity.[2]*

3.3.2 Summary of Fatal Pediatric Cases (n=13)

We identified 13 fatal pediatric cases with posaconazole in the FAERS database from 15-Sep-2006 through 31-Aug-2015. Although most of the cases lacked clinical details and autopsy findings, none of the fatal cases appeared to be directly associated with posaconazole. The majority of cases described the clinical course of immunocompromised patients and deaths were associated with underlying disease progression or various infectious diseases. Appendix C (Table C2) lists all the FAERS case numbers, FAERS version numbers, and manufacturer control numbers. Summary narratives of these fatal cases are listed after Table 3.3.2.

Table 3.3.2 summarizes the 13 fatal pediatric FAERS cases reported with posaconazole.

Table 3.2.3 Characteristics of Fatal Pediatric (0 to 17 years) Case Series with Posaconazole (N=13)

Age (years)	Median:	13
	Range:	1.5 – 17
Sex	Male	6
	Female	6
	Unknown	1
Weight (kg) (n=4)	Median:	27.5
	Range:	11.6 – 38
Country	Foreign	9
	United States	4
Formulation	Oral Suspension*	10
	Oral Suspension, presumed*	7
	Oral Suspension	3
	Injection	1
	Oral Suspension and Injection	1
	Not Reported	1
Primary Underlying Disease (n=12)	Leukemia	8
	Aplastic Anemia	2
	Diamond-Blackfan Anemia	1
	Diabetes Mellitus	1
Reported Indication† (n=12)	Treatment	10
	Prophylaxis	1
	Prophylaxis and Treatment	1
Reported Pathogen Causing Disease, treatment (n=11)	Single Pathogen Reported	6
	Mucormycete, not otherwise specified	2
	Aspergillus spp	1
	Pythium insidiosum	1
	Rhizopus oryzae	1
	Rhizopus spp	1
	Multiple Pathogens Reported	4
	Absidia corymbifera, Alternaria alternata	1
	Aspergillus spp , *Mucor* spp	1
	Rhizomucor spp , *Scedosporium apiospermum*	1
	Rhizomucor variabilis, Hormographiella aspergillata	1
	Invasive Fungal Infection, not otherwise specified	1

* Specific formulation not reported; selection based on date of administration and description of reported dose, route, or frequency

† Reported posaconazole indication - provided in the indication field of the MedWatch report or from the case narratives

FAERS Case # 6161759, Germany, Literature Report[7] Initial FDA Received Date: 20-Oct-2006

Title: *Rhinocerebral zygomycosis in a young girl undergoing allogeneic stem cell transplantation for severe aplastic anaemia.*

Case Narrative: A 10-year-old female with aplastic anemia received immunosuppressive therapy in May-2004 consisting of methylprednisolone, cyclosporine, and anti-thymocyte globulin (ATG). In Jul-2004, she developed febrile neutropenia and eventually rhinocerebral mucormycosis caused by *Absidia corymbifera* and possible co-infection with *Alternaria alternata*. The treatment of her invasive fungal disease consisted of liposomal amphotericin B, caspofungin, voriconazole, granulocyte transfusions, discontinuation of immunosuppressive therapy, and surgical debridement of the right maxillary sinus. Two weeks after the start of antifungal treatment, imaging studies revealed significant progression of the infection. Based on the lack of *in vitro* activity against the mucormycetes, caspofungin and voriconazole were discontinued and replaced by posaconazole oral suspension 200 mg by mouth (PO) four times daily (QID). Despite remaining neutropenic, her clinical condition improved while on posaconazole and liposomal amphotericin B. Hematopoietic stem cell transplantation (HSCT) was performed in Aug-2004 with a conditioning regimen consisting of total body irradiation (TBI), fludarabine, cyclophosphamide, and ATG. Unfortunately, the graft rejected and she was re-transplanted with another matched unrelated donor six weeks later using an identical conditioning regimen except for reduced TBI. The post-HSCT period was uneventful; however, six weeks after the second transplant, she developed a disseminated adenovirus infection. Despite treatment with acyclovir, ganciclovir, foscarnet, and ribavirin, she died five months after the first HSCT. Death was attributable to the disseminated adenovirus infection and multiorgan failure. At the time of death, there were no signs of uncontrollable fungal infection and no severe side effects of the antifungal drugs were reported. It was not reported if an autopsy was performed.

Reviewer Comments: *This literature report describes an immunocompromised patient with a complicated clinical course after two HSCTs. This case lacks clinical details and autopsy findings, which limits our causality assessment. Death was reportedly associated with an infection (disseminated adenovirus) and multiorgan failure.*

FAERS Case # 6800724, Slovenia Initial FDA Received Date: 21-Oct-2008

Case Narrative: A 13-year-old patient received oral posaconazole for the treatment of an unspecified invasive fungal infection and died on an unspecified date. The posaconazole dose, frequency, product, and duration of therapy were not reported (oral suspension presumed). The reporting physician considered the patient's death unrelated to posaconazole. It was not reported if an autopsy was performed.

Reviewer Comments: *This case lacks clinical details and autopsy findings, which limits our causality assessment.*

FAERS Case # 6975058, Chile Initial FDA Received Date: 13-Apr-2009

Case Narrative: A 12-year-old male was diagnosed with ALL in March 2008 and received chemotherapy from 17-Mar-2008 to 31-Mar-2008. On 2-Apr-2008, he developed febrile neutropenia thought to be associated with a break of urinary or oral mucosa (hard palate injury) and was started on amikacin, cloxacillin, and ceftazidime. On 7-Apr-2008, a necrotic lesion of the palate was noted and he was started on amphotericin B. Otorhinolaryngology showed zygomycetes fungal infection of the oral mucosa and endoscopic surgery was performed on (b) (6). The pathology report confirmed it was consistent with mucormycosis. After surgery, he was transferred to the intensive care unit (ICU), the amphotericin B dose was increased, and he was started on posaconazole 200 mg PO QID (oral suspension presumed) on 24-Apr-2008. After starting posaconazole, he experienced nausea and vomiting, and chemotherapy was adjusted to weekly on 28-Apr-2008. On 5-May-2008, he presented with intense intestinal ileus and it was decided to discontinue vincristine because of a possible drug interaction with posaconazole. On 8-May-2008, posaconazole was temporarily discontinued because of lack of drug in the country. Posaconazole was restarted on 16-May-2008 using 400 mg PO twice daily (BID). On 2-Jun-2008, alkaline phosphatase was elevated to 320 U/L (normal range: 10-49 U/L). Posaconazole was discontinued on 4-Jul-2008 when it was found the mucormycosis infection had worsened. The clinical team determined the patient should be admitted for treatment of pain management and given amphotericin B to improve quality of life. The

patient died in (b) (6) secondary to leukemia disease progression. It was not reported if an autopsy was performed.

Reviewer Comments: *Posaconazole was discontinued secondary to lack of effect approximately six months prior to the patient's death. Death was reportedly associated with an underlying disease process (leukemia).*

FAERS # 7022019, Chile Initial FDA Received Date: 06-Mar-2009

Case Narrative: A 13-year-old male with recurrent acute myeloid leukemia (AML) and prolonged febrile neutropenia developed pansinusitis and osteomyelitis with *Aspergillus* and probable *Mucor*. It was reported the *Aspergillus* isolate was resistant to amphotericin B and voriconazole. The patient received posaconazole 200 mg PO three times daily (TID; oral suspension presumed) for the treatment of the invasive fungal disease from 12-Dec-2008 to 20-Mar-2009. On an unknown date, the patient developed a *Pseudomonas* infection after an unspecified transplant and died as a result of this infection. It was not reported if an autopsy was performed.

Reviewer Comments: *This case lacks clinical details and autopsy findings, which limits our causality assessment. Death was reportedly associated with an infection (Pseudomonas).*

FAERS # 7252749, USA, Literature Report[8] Initial FDA Received Date: 22-Jan-2010

Title: *Rhizomucor variabilis var. regularior and Hormographiella aspergillata infections in a leukemic bone marrow transplant recipient with refractory neutropenia.*

Case Narrative: A 14-year-old female with AML underwent an allogeneic bone marrow transplant (BMT) in December 2007. She experienced a relapse in April 2008 and later failed re-induction chemotherapy. In September 2008, a computed tomography (CT) scan revealed patchy ground-glass opacities with tiny peripheral nodular densities in both lung fields and a 1.2 cm nodule in the right upper lobe. Her condition was deemed too fragile to tolerate a diagnostic lung biopsy and she was empirically treated with antibacterials and voriconazole. Shortly afterward, she presented with a two-week history of odynophagia and persistent febrile neutropenia. An examination revealed white plaques involving the soft palate and pharynx. A smear from a throat culture showed hyphal elements and conidiophores. A biopsy of the palate lesion showed submucosa and mucosa infiltrated with hyphal forms with sparse septation, rare branching, and chlamydoconidia. She was started empirically on posaconazole 800 mg PO BID (oral suspension presumed). A CT scan of the head and sinuses was negative and a CT scan of the lungs confirmed pulmonary nodules that had been previously visualized. Serial galactomannan assay results were negative. The fungus in the culture from the palate biopsy was identified as *Rhizomucor variabilis* var. *regularior*. The option of surgical debridement was declined by the family because of potentially severe morbidity. At week two of therapy, caspofungin was added as an adjunct therapy. By week two, the lesion decreased and at week three of therapy, the patient was placed on therapy with a new regimen of chemotherapy along with granulocyte transfusion. By week four, the patient's symptoms had resolved and by week five, the palate lesion was no longer visualized even though the patient had persistent severe refractory pancytopenia. One and one-half months after initiation of therapy, she developed altered mental status and had a generalized seizure. A CT scan of the brain showed multiple hypodense lesions of the cerebral hemispheres and cerebellum. Serum and cerebrospinal fluid (CSF) toxoplasma and cryptococcal studies were negative. A repeat CT scan of the lungs showed cavitating lesion in the right upper lobe/right middle lobe. At that time, posaconazole was discontinued, and she was switched to liposomal amphotericin B while caspofungin was maintained. At this time, she developed high fevers and a new small erythematous skin papule developed on the right knee and the skin was biopsied. Ten days later, a new skin lesion appeared on the left arm. The patient's respiratory status progressively deteriorated and she died from respiratory failure two weeks after the appearance of the initial skin lesion. The mold from the skin biopsy was identified postmortem as *Hormographiella aspergillata*. No autopsy was performed.

Reviewer Comments: *This literature report describes an immunocompromised patient with a complicated clinical course. Posaconazole was discontinued at least two weeks prior to the patient's death secondary to the addition of liposomal amphotericin B for better central nervous system penetration. Death was reportedly associated with infection (disseminated fungal disease) after BMT.*

FAERS # 7959150, Portugal, Literature Report[9] Initial FDA Received Date: 25-May-2011

Title: *Rhizomucor and Scedosporium infection post hematopoietic stem-cell transplant.*

Case Narrative: A 17-year-old male was diagnosed with severe idiopathic acquired aplastic anemia in Jan-2007. He did not have a matched donor for HSCT, so he underwent a five-month course of therapy with cyclosporine and ATG without response. In Feb-2008 he received an allogeneic HSCT from a matched unrelated donor. The preparative regimen consisted of alemtuzumab, fludarabine, and cyclophosphamide. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and methotrexate starting on day one. Evidence of hematopoietic engraftment occurred on day 17. On day 25, biopsy proven gastrointestinal GVHD developed and was treated with corticosteroids and tacrolimus with gradual resolution. The evaluation on day 33 showed complete chimerism and normal bone marrow and he was discharged on day 41 with tacrolimus, oral prednisone, and fluconazole for prophylaxis. On day 115, he was admitted with neutropenia and odynophagia and received piperacillin/tazobactam and amikacin. He recovered and was discharged on day 125 and did well until day 165 when he was admitted with acute tonsillitis and febrile neutropenia. A CT scan showed an abscess in the peritonsillar space and a tonsillar biopsy was made which revealed an eosinophil-rich polymorphic infiltrate and no other findings. He received piperacillin/tazobactam, posaconazole (dose and frequency not reported) and eventually clindamycin. The febrile episode resolved and he was discharged on day 179 with GVHD therapy (steroids and tacrolimus) and antifungal prophylaxis with posaconazole 200 mg PO TID (oral suspension presumed). Although improved, he had persistent complaints of cough and serous sputum. A thoracic x-ray then revealed a small pulmonary node that gradually enlarged and a thoracic CT scan revealed a cavitated lesion on the right superior pulmonary lobe. Thoracic surgery was proposed but the patient was not considered a candidate for such an intervention. At this time, voriconazole was started. The patient's clinical condition began to deteriorate and he developed persistent cough, dyspnea, headaches, otalgia, fever, and neutropenia. On day 211 he was admitted to the hospital and developed hemoptysis, acute respiratory failure, and renal failure necessitating ICU admission. The fungal culture result of the bronchoalveolar lavage revealed *Rhizomucor* spp. infection on day 215 and he was started on liposomal amphotericin B and caspofungin combination therapy. He started to improve and was discharged from the ICU on day 223. He maintained a persistent fever and the cavitated pulmonary nodule continued to get worse on thoracic x-ray. On day 237, he started to complain of right periorbital edema and gradually developed sinusitits, exoftalmia, and amaurosis of the right eye. A CT scan of the perinasal sinuses revealed an infiltrative lesion of the perinasal sinuses with ethmoiditis and compression of the right optic nerve. Ethmoidectomy was performed on day 264 and pathology analysis showed signs of ethmoiditis and numerous fungal hyphae. Microbiological analysis revealed fungal infection caused by *Scedosporium apiospermum*. His clinical condition continued to deteriorate, and antifungal combination therapy was changed to posaconazole along with liposomal amphotericin B but no response was obtained. On day 310, he started to complain of persistent headache, and on day 322, he developed left hemiparesis and dysarthria probably associated with rhinoencephalitis. His consciousness became gradually depressed and he died on day 324. It was not reported if an autopsy was performed.

Reviewer Comments: *This literature report describes an immunocompromised patient with a complicated clinical course. Death was reportedly associated with pulmonary mucormycosis and rhinocerebral scedosporiosis after HSCT.*

FAERS # 8886217, USA, Literature Report[10] Initial FDA Received Date: 05-Nov-2012

Title: *Poor absorption of high-dose posaconazole in pediatric bone marrow transplant patients.*

Case Narrative: A 19-month-old male with a history of seizures, infant B-cell ALL, and recent central nervous system relapse, received a matched allogeneic sibling cord blood transplant. The preparative regimen consisted of TBI, melphalan, and cyclophosphamide. Approximately two weeks later, he developed a facial lesion on the right cheek that was debrided on day 21. On day 43, the site was debrided again and examination of the tissue revealed

abundant fungal hyphal elements identified from the tissue culture. On day 52, *Rhizopus* spp. was identified from the tissue culture. In addition, a thoracic CT scan revealed increased consolidations with air bronchograms and adjacent ground glass opacity in the right lower lobe. Amphotericin B lipid complex was administered starting on day 43. Continuous venovenous hemodiafiltration was used on days 32-54 and 147-156. Posaconazole was initiated due to the patient's continued graft failures and inconsistent administration of amphotericin B lipid complex therapy and associated adverse effects. Given the use of famotidine, pantoprazole, sucralfate, and the patient's inability to tolerate oral feeding along with the use of parenteral nutrition, posaconazole oral suspension was initiated per jejunostomy tube at 200 mg every four hours (1200 mg/day; 120 mg/kg/day). Posaconazole concentrations remained under 200 ng/mL during the first 2 weeks of therapy despite doses ranging from 120-300 mg/kg/day, discontinuation of pantoprazole and sucralfate, and initiation of low-rate tube feeds. On day 60, posaconazole was changed to 3000 mg/day (300 mg/kg/day) continuous oral infusion via jejunostomy tube. Posaconazole serum concentrations ranged from 360-850 ng/mL over the next 40 days. Posaconazole was discontinued on day 135 as the skin lesion healed and lung abnormalities resolved without any other signs of fungal infection. No adverse drug events were associated with posaconazole and serum concentrations never exceeded 1000 ng/mL. On day 135, he received a matched unrelated donor transplant for recurrent disease. He died 21 days following this transplant from overwhelming vancomycin-resistant enterococcus sepsis. At necropsy, centrilobar hepatic congestion with necrosis and fibrosis, multiorgan failure with acute respiratory distress syndrome, and congestive heart failure were reported. No evidence of fungal infection was noted.

Reviewer Comments: *This literature report describes an immunocompromised patient with a complicated clinical course. Death was reportedly associated with infection (vancomycin-resistant enterococcal sepsis) after matched unrelated donor transplant for recurrent disease.*

FAERS # 9720098, Spain Initial FDA Received Date: 28-Nov-2013

Case Narrative: A 7-year-old male with diabetes mellitus type 1 and pulmonary and mediastinal mucormycosis (*Rhizopus oryzae*) received caspofungin, liposomal amphotericin B, and posaconazole 200 mg PO QID (oral suspension presumed) from 28-Feb-2013 to 14-Mar-2013. From (b) (6) to (b) (6), he was admitted to the ICU for the management of hypokalemia, hypomagnesemia, and nephropathy. On (b) (6) he experienced a massive lung hemorrhage and died. Other concomitant medications included insulin detemir, clarithromycin, meropenem, and omeprazole. It was not reported if an autopsy was performed.

Reviewer Comments: *This case lacks clinical details, and autopsy findings that limit our causality assessment. Posaconazole was discontinued for unspecified reasons five weeks prior to the patient's death. Death was reportedly associated with infection (disseminated mucormycosis).*

FAERS # 9776700, USA, Literature Report[11] Initial FDA Received Date: 20-Dec-2013

Title: *Fatal disseminated Pythium insidiosum infection in a child with Diamond-Blackfan anemia.*

Case Narrative: 14-year-old female with a transfusion-dependent congenital red cell aplasia (Diamond-Blackfan anemia) was admitted with a one-week history of progressive vaginal and left inguinal pain, dysuria, periurethral bruising, intermittent fevers, and elevated inflammatory markers. She had a lifelong transfusion requirement, and poor adherence with chelation therapy led to severe hemosiderosis. Although prescribed subcutaneous deferoxamine, she had not received it in the two weeks prior to admission. A pelvic magnetic resonance imaging demonstrated myositis of her perineum and left hip that progressed despite treatment with broad-spectrum antimicrobials. Imaging over the next two weeks demonstrated pelvic abscess formation. Fluid collected by CT-guided drainage of the abscesses and four surgical incisions over the ensuing two weeks demonstrated occasional hyphal elements with negative bacterial cultures. Bone and muscle biopsies yielded a poorly growing mold with concern for mucormycosis and her antifungal therapy was expanded to include combinations of amphotericin B, micafungin, posaconazole, voriconazole, and terbinafine (dosing and dates of administration not reported; oral suspension presumed). She developed continued reaccumulation of pelvic abscesses, development of new inflammatory sites by MRI scan in a clavicle and chest wall, and worsening clinical status necessitated transfer to the ICU. Secondary to her leukopenia, granulocyte colony-stimulating factor was started, and later, granulocyte-

macrophage colony-stimulating factor was added. During the fourth week of hospitalization, she was noted to have lower extremities that were cool to the touch and without pulses. A CT angiogram demonstrated occlusion of the bilateral iliac and femoral arteries. The fungal organism that had grown from samples of pelvic bone, muscle and pelvic fluid was tentatively identified as *Pythium insidiosum*. Azithromycin and minocycline were added based on reports of *in vitro* activity. Surgical eradication by hemicorpectomy/total pelvectomy above the sites of lower extremity occlusion was not possible; therefore, bilateral embolectomies of the iliac and femoral arteries were performed which demonstrated invasive hyphal elements. Unfortunately occlusions rapidly occurred and repeat embolectomies rapidly reoccluded. Five weeks after the onset of symptoms, *P. insidiosum* was identified by DNA sequencing. Susceptibility testing showed high-level resistance with the following minimum inhibitory concentrations: amphotericin B ≥16 mcg/mL, caspofungin ≥8 mcg/mL, fluconazole ≥64 mcg/mL, itraconazole ≥16 mcg/mL, posaconazole ≥16 mcg/mL, voriconazole ≥16 mcg/mL, and terbinafine ≥2 mcg/mL. Two doses of emergency compassionate-use *Pythium* allergen extract vaccination were administered, but neither dose was noted to cause the desired immune reaction at the site of infection. The patient then experienced a continued decline in renal function and required continuous venovenous hemodialysis. Over the next two days, the patient's cardiac output and respiratory function continued to decline and she required escalation of ventilation and vasopressor support. She died approximately six weeks after initial presentation. It was not reported if an autopsy was performed.

Reviewer Comments: *This literature report describes an immunocompromised patient with a complicated clinical course. Death was reportedly associated with infection (disseminated P. insidiosum) leading to cardiac and respiratory decline.*

FAERS Case # 10030949, Hungary Initial FDA Received Date: 23-Mar-2014

Case Narrative: A 15-year-old female with AML and history of BMT received posaconazole oral suspension 200 mg PO TID as prophylaxis for 29 days. Follow-up information reported the patient died after three months. It was not reported if an autopsy was performed.

Reviewer Comments: *This case lacks clinical details and autopsy findings, which limits our causality assessment. The reporter did not provide an assessment of causal relationship between the use of posaconazole and death.*

FAERS Case # 10792393, USA Initial FDA Received Date: 13-Feb-2015

Case Narrative: A 6-year-old female with leukemia received posaconazole injection on an unknown date for an unspecified condition. The posaconazole dose and frequency were not reported. In Oct-2014, the reporting pharmacist stated the patient died secondary to leukemia, and posaconazole was not the cause of the patient's death. It was not reported if an autopsy was performed.

Reviewer Comments: *This case lacks clinical details and autopsy findings, which limits our causality assessment. Death was reportedly associated with an underlying disease process (leukemia).*

FAERS Case # 10899669, Australia Initial FDA Received Date: 09-Mar-2015

Case Narrative: A 13-year-old male with a history of relapsed biphenotypic ALL, BMT, previous *Aspergillus* infection of the chest, anaphylactic reaction to liposomal amphotericin B, and peripheral neuropathy associated with voriconazole, developed an invasive fungal infection (recurrent *Aspergillus)* before a second BMT could be performed. Due to severe diarrhea while on posaconazole oral suspension, he was started on compassionate posaconazole injection (dose and frequency not reported) on 06-Feb-2015. On 13-Feb-2015, the patient was clinically stable with reduced fevers and tolerating posaconazole infusions with no adverse effects. Follow-up information received on 3-Mar-2015 reported the patient died on an unknown date. It was not reported if an autopsy was performed.

Reviewer Comments: *This case lacks clinical details and autopsy findings, which limits our causality assessment. The reporter did not provide an assessment of causal relationship between the use of posaconazole and death.*

FAERS Case #11050995, Italy, Literature Report[12] Initial FDA Received Date: 21-Apr-2015

Title: *(18)F-FDG PET/CT contribution to diagnosis and treatment response of rhino-orbital-cerebral mucormycosis.*

Case Narrative: A 13-year-old female completed chemotherapy for ALL three months after a left periorbital swelling associated with facial pain had appeared. An MRI scan revealed left orbital soft tissues edema, signs of left maxillary sinusitis, ethmoiditis, and left frontal lobe cerebritis. Nasal conchae surgical sweeping revealed fungal hyphae characteristic of mucormycosis. Systemic amphotericin B was started and after four weeks, an MRI scan and positron emission tomography–computed tomography (PET/CT) scan were performed. The MRI scan showed reduction of edema suggestive of response to treatment and signs of necrosis in the left emivolto and cerebritis in the left frontal lobe. The PET/CT scan showed progression of the disease with increased necrosis. The rest of the whole-body scan showed ^{18}F-FDG uptake in the skeleton due to activation of bone marrow as a consequence of amphotericin B nephrotoxicity. Treatment with amphotericin B was replaced with posaconazole (dose, route, and frequency not reported), but the patient died three months later. It was not reported if an autopsy was performed.

Reviewer Comments: *This literature report describes an immunocompromised patient with a complicated clinical course. Death was reportedly associated with infection (rhino-orbital-cerebral mucormycosis) unresponsive to antifungal therapy.*

3.3.3 Summary of Serious, Unlabeled, Non-Fatal Pediatric Cases (n=12)

In addition to the cases with vincristine and the fatal cases, 12 cases with serious outcomes and unlabeled adverse events were also selected for inclusion into the primary case series. Based on the available data, causality between these adverse events and posaconazole could not be determined. The cases either reported limited clinical details or were confounded by underlying disease processes or concomitant medications.

The unlabeled adverse events from these 12 cases included the following MedDRA preferred terms (PTs): pancreatitis (n=2), seizure (n=2), gamma-glutamyltransferase increased (n=1), gastrointestinal haemorrhage (n=1), hepatic fibrosis (n=1), hypertriglyceridaemia (n=1), hearing impaired (n=1), memory impairment (n=1), face oedema (n=1), hypoproteinaemia (n=1), proteinuria (n=1), toxic encephalopathy (n=1), and tremor (n=1).

Appendix C (Table C3) lists all the FAERS case numbers, FAERS version numbers, manufacturer control numbers, and summary case narratives.

4 DISCUSSION

The vast majority of patients who had a hospital billing for posaconazole from inpatient pharmacy setting were adult patients aged 18 years and older. Pediatric patients aged 0-17 accounted for approximately 2% of the total patients in 12-month period ending August 2015. Findings from this review should be interpreted in the context of the known limitations of the databases used. The analysis of sales distribution data showed the majority of posaconazole bottles/packages were distributed to the inpatient pharmacy setting. We focused our analysis on the non-federal inpatient hospital and outpatient ER setting; therefore, these estimates may not apply to other settings of care in which these products are used such as outpatient or mail/specialty pharmacy settings. The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time. All changes over time should be considered approximate and may be due to random error.

Within the primary FAERS case series (N=34), 13 cases reported a fatal outcome and 21 cases cited non-fatal outcomes that were also associated with serious, and unlabeled adverse events. Twenty-two of the 34 cases (65%) occurred in patients less than 13 years of age, which is off-label according to FDA-approved prescribing information. In addition, 18 of the 22 cases (82%) reporting a treatment indication for posaconazole occurred for the treatment of mold infections (mucormycosis, aspergillosis, or other molds) which is off-label according to FDA-approved labeling. Twenty-eight of the 34 cases (82%) were reported from outside the US. The low number of domestic cases is consistent with the low domestic use in pediatric patients. The six US cases included two patients greater than 13 years of age and four patients less than the approved 13 years of age and older (age range: 1.5 – 7 years). Three of the six US cases reported a posaconazole indication for the off-label treatment of mucormycosis (n=2) and aspergillosis (n=1).

DPV identified a pattern of cases (n=10) that primarily described unlabeled adverse events consistent with vincristine toxicity (e.g., paralytic ileus, inappropriate antidiuretic hormone secretion, peripheral neuropathy, seizure, etc.) when posaconazole was administered with vincristine. All 10 cases reported the use of vincristine or vincristine sulfate; there was no indication liposomal vincristine (vincristine sulfate liposome injection [Marqibo®]) was administered in any of the cases. The FAERS data show a temporal association, positive dechallenge in five (50%) of the cases, and a case (FAERS Case #7399499) that described seizures only when vincristine was administered with concomitant posaconazole. No seizures were observed when vincristine was administered without concomitant posaconazole on two other instances. The adverse events described in the FAERS cases are serious (e.g., life-threatening neurotoxicity requiring ICU or hospital admission, persistent seizures leading to respiratory compromise requiring mechanical ventilation, and grade III peripheral neuropathy). One of the cases (FAERS Case #6975058) reported an outcome of death, but the death was not directly related to the adverse events associated with the concomitant administration of posaconazole with vincristine.

There is mechanistic plausibility by which posaconazole can increase levels of vincristine when administered concomitantly; therefore, it is reasonable to suspect that posaconazole may have played a role in the adverse events. Posaconazole is a strong inhibitor of CYP3A4, and also inhibits P-gp.[13] Most of the vinca alkaloids are substrates of CYP3A4, and vincristine metabolism has been shown to be mediated by the CYP3A subfamily and it is a substrate for the efflux transporter P-glycoprotein (P-gp).[14] Although this potential drug-drug interaction has not been studied *in vivo*, posaconazole may increase vincristine exposure through the inhibition of two possible pathways (i.e., CYP3A4 and P-gp).

The increase in vincristine exposure caused by concomitant posaconazole administration may lead to the development of dose-dependent neurotoxicity, the predominant adverse effect of vincristine, many of

which were noted in the FAERS cases. Vincristine-induced neurotoxicity may consist of peripheral neuropathy, autonomic neuropathy, cranial nerve palsies, and central nervous system toxicity.[15] Peripheral neuropathy may present as paresthesias in the fingers and toes and the impairment and loss of deep tendon reflexes.[16-18] Autonomic neuropathy may present as abdominal pain, constipation, and paralytic ileus.[17] Central nervous system toxicity may present as the excessive release of antidiuretic hormone resulting in hyponatremia, mental confusion, and seizures.[19,20] Because these neurotoxic events are associated with vincristine, it is unknown whether these adverse events would have occurred with vincristine alone or whether posaconazole had an additive effect. However, since neurotoxicity is dose-dependent, and this purported drug-drug interaction is likely to result in increased vincristine exposure, we find the combined use of these drugs to be suspect.

Although the drug interaction of vincristine with posaconazole is included in the posaconazole labeling (Section 7 *Drug Interactions*), there is insufficient guidance for clinicians. For example, the label recommends to dose adjust the vinca alkaloid when administered with posaconazole, but it does not state how much to dose reduce the vinca alkaloid.[2] Furthermore, the posaconazole label conflicts with the vincristine sulfate liposome injection (Marqibo®) label which states to avoid use with strong CYP3A inhibitors such as posaconazole. It must be noted that there are differences in the pharmacokinetics of liposomal (Marqibo®) and non-liposomal vincristine sulfate. The slow clearance of Marqibo® contributes to a much higher area under the curve (AUC) for Marqibo® relative to non-liposomal vincristine sulfate.[14] In general, there is variability in the labeling across the class of azole antifungals and vincristine with respect to drug interactions (refer to Appendix D).

Two review articles[21,22] summarized the published literature in pediatric and adult patients for adverse events with the concomitant administration of vincristine with azole antifungals including ketoconazole, itraconazole, voriconazole, and posaconazole. Both literature review articles identified the same two pediatric cases reports[5,23] and one adult case report[24] with vincristine and posaconazole. The two pediatric literature case reports are included in this review (FAERS Case #7399499 and #7009054) and are summarized in Appendix C (Table C1). The adult case report described a 21-year-old male with ALL who developed bilateral foot paresthesias, generalized loss of deep tendon reflexes, and profound muscle weakness that had not substantially improved almost 5 months after the discontinuation of vincristine and posacoanzole.[24] In addition, both literature review articles[21,22] reported pediatric patients under 18 years of age accounted for the majority of published adverse event cases related to the drug interaction between vincristine and azole antifungals. Pana and Roilides[21] suggested the most reasonable explanations for the predominance of pediatric cases could be due to higher vincristine doses used in pediatric chemotherapy protocols compared to adults, or the different bioavailability of vincristine in the pediatric population and the immature pediatric nervous system, which might have an increased sensitivity to neurotoxic drugs. Moriyama et al.[22] suggested the predominance of pediatric cases was a reflection of the more frequent use of vincristine in pediatric malignancies, especially ALL. Due to the severity of many of the adverse events associated with azole-associated adverse events with vincristine, Pana and Roilides[21] concluded close monitoring is needed to detect early neurotoxicity, and prospective studies evaluating safety and efficacy of other antifungal treatments are needed. Moriyama et al.[22] recommended alternative (non-azole) antifungal agents if possible, and consultation with an infectious diseases physician and clinical pharmacist if concomitant administration of vincristine with an azole antifungal is required.

Our review of the FAERS database was limited to pediatric patients 0 to 17 years of age. Unfortunately, due to the limitations of the FAERS database, we are unable to calculate the incidence of an adverse event or compare adverse event rates among different age groups.

Given the serious outcomes of vincristine-induced neurologic toxicity reported in the FAERS cases and the plausible mechanism of drug-interaction between posaconazole and vincristine, it is important to provide more specific guidance on how much to dose reduce vinca alkaloids, if known, as well as more specific recommendations on monitoring for neurotoxicity. Also, consideration should be given to consistency among drug labels when there is a known a drug interaction for the respective drugs.

Additional information about this potential safety signal (i.e., serious outcomes associated with posaconazole and vincristine drug interaction) is needed to provide clinically relevant information to health care providers. Further evaluation through consultation with the FDA/CDER Office of Clinical Pharmacology and the Division of Hematology and Oncology Products are needed to inform FDA of the next steps (e.g., labeling revision). The FDA intends to open a Tracked Safety Issue (TSI) to document and evaluate this signal. The TSI team will determine if any regulatory action is needed.

5 CONCLUSION

A signal of vincristine-induced neurotoxicity (e.g., paralytic ileus, inappropriate antidiuretic hormone secretion, peripheral neuropathy, seizure, etc.) was noted in 10 cases with concomitant administration of posaconazole and vincristine. These serious and potentially life-threatening neurologic adverse events are unlabeled with respect to posaconazole. There is mechanistic plausibility (i.e., inhibitor of CYP3A4 and P-glycoprotein) by which posaconazole can increase plasma concentrations of vincristine when administered concomitantly; therefore, it is reasonable to suspect that posaconazole may have played a role in these adverse events.

None of the 13 fatal cases were directly associated with posaconazole. The majority of fatal cases detailed highly immunocompromised patients and deaths were associated with underlying disease progression or various infectious diseases.

Other than the cases of posaconazole and vincristine drug interaction, no other safety signals were identified in pediatric patients (0 to 17 years of age) exposed to posaconazole. The cases of non-fatal outcomes that were associated with serious, unlabeled adverse events were highly confounded or did not provide relevant information, such as time to onset or outcome of the adverse event, to establish the relationship between the adverse events and posaconazole. The remaining reported adverse events were considered in nature with the risks cited in the posaconazole product labeling; no increased severity or specific patterns were observed in these reports.

6 RECOMMENDATIONS

The Division of Pharmacovigilance II (DPV II) recommends further evaluation of the potential safety signal (i.e., serious outcomes associated with posaconazole and vincristine drug interaction) through consultation with the FDA/CDER Office of Clinical Pharmacology and the Division of Hematology and Oncology Products, to inform FDA of the next steps (e.g., labeling revision). Revisions to the label(s) and other regulatory actions will be considered, pending the additional information.

DPV II will continue routine postmarketing surveillance of all adverse events associated with the use of posaconazole in pediatric patients.

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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.

These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution. The amount of product purchased through these channels of distribution may be a possible surrogate for use, assuming facilities purchase drugs in quantities reflective of actual patient use.

IMS Health, Inpatient HealthCare Utilization System (IHCarUS)

The IMS, Inpatient HealthCare Utilization System (IHCarUS) provides hospital inpatient and outpatient emergency department encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from mid-2001, are collected weekly and monthly and are available 25-30 days after the end of each monthly period. This robust data set includes >620 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include >16 million patients and >65 million annual hospital encounters (including ED visits) representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. IMS' datasets are geographically representative, and include claims across all third-party payer types, including commercial insurers, Medicare, Medicare Part D, Medicaid and other payer types.

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, MANUFACTURER CONTROL NUMBERS, AND CASE DESCRIPTIONS FOR THE PEDIATRIC CASE SERIES WITH POSACONAZOLE (N=34)

TABLE C1. PEDIATRIC CASES WITH POSACONAZOLE AND VINCRISTINE (N=10)

FAERS Case# - Version#	Initial FDA Received Date	Manufacturer #	Age (years) Sex	Country	Underlying Medical Condition	Reported MedDRA Preferred Terms (PTs)
6689077-1	**19-Jun-2008**	**2008SP011339**	**3 Female**	**Israel**	**Leukemia (ALL)**	Ileus paralytic
Case Notes: Posaconazole OS 100 mg BID initiated for the treatment of invasive mucormycosis starting on 15-Apr-2008; vincristine sulfate administered on 11-May-2008. 3-year-old female developed invasive mucormycosis, involving the lung and sinuses, during chemotherapy for ALL. Concomitant mediations included vincristine (11-May-2008), methotrexate (11-May-2008), L-asparaginase (12-May-2008), leucovorin (12-May-2008), and liposomal amphotericin B (12-Apr-2008 to 6-May-2008). On 21-May-2008, she experienced paralytic ileus confirmed by x-ray. Posaconazole was continued and the event resolved after 10 days. ***Reviewer Comments:*** *Limited case details preclude a meaningful causality assessment. Vincristine sulfate is labeled for paralytic ileus, particularly in young pediatric patients. The reporter did not specify if vincristine was dose-reduced for this patient. Posaconazole is labeled as a strong CYP3A4 inhibitor and may increase vincristine exposure which may lead to neurotoxicity; therefore, dose adjustment of vincristine should be considered (Posaconazole labeling DRUG INTERACTIONS). Vincristine sulfate is labeled for paralytic ileus, particularly in young pediatric patients; ileus will reverse itself with temporary discontinuance of vincristine sulfate injection and with symptomatic care.*					
6975058-2	**13-Apr-2009**	**2009SP007606**	**12 Male**	**Chile**	**Leukemia (ALL)**	Blood alkaline phosphatase increased, Condition aggravated, Drug ineffective, Drug interaction, Ileus, Leukaemia, Nausea, Neoplasm malignant, Pain, Vomiting, Zygomycosis
Case Notes: Posaconazole 200 mg PO QID (OS presumed*) initiated for the treatment of mucormycosis starting on 24-Apr-2008; vincristine administered 28-Apr-2008 to 5-May-2008. A 12-year-old male was diagnosed with ALL in March 2008 and received chemotherapy from 17-Mar-2008 to 31-Mar-2008. On 2-Apr-2008, he developed febrile neutropenia thought to be associated with a break of urinary or oral mucosa (hard palate injury) and was started on amikacin, cloxacillin, and ceftazidime. On 7-Apr-2008, a necrotic lesion of the palate was noted and he was started on amphotericin B. Otorhinolaryngology showed zygomycetes fungal infection of the oral mucosa and endoscopic surgery was performed on (b) (6) pathology report consistent with mucormycosis. After surgery, he was transferred to the ICU and the amphotericin B dose was increased. On 24-Apr-2008, he was started on posaconazole 200 mg PO QID. He had nausea and vomiting, and chemotherapy was adjusted to weekly since 28-Apr-2008. On 5-May-2008, he presented with intense intestinal ileus and it was decided to discontinue vincristine because of a possible drug interaction with posaconazole. On 8-May-2008, posaconazole was temporarily discontinued because of lack of drug in the country. Posaconazole was restarted on 16-May-2008 using 400 mg PO BID (OS presumed*) to enhance the tolerance, and he recovered from vomiting. On 2-Jun-2008, alkaline phosphatase was elevated to 320 U/L (normal range: 10-49 U/L) while AST/ALT, total bilirubin, and direct bilirubin were within normal limits. Posaconazole was discontinued on 4-Jul-2008 when it was found the infection with zygomycetes increased. The clinical team determined the patient should be admitted for treatment of pain management and given amphotericin B to improve quality of life. The patient died in (b) (6) secondary to leukemia disease progression. It was not reported if an autopsy was performed, or the outcome of intense intestinal ileus. ***Reviewer Comments:*** *Vincristine sulfate is labeled for paralytic ileus, particularly in young pediatric patients. The reporter did not provide dates of vincristine administration, but according to the narrative, vincristine was given concomitantly with posaconazole. Based on the narrative, it is indeterminate if vincristine was dose-reduced during concomitant posaconazole administration due to the possible drug-drug interaction or due to nausea and vomiting. Vincristine sulfate is labeled for paralytic ileus, particularly in young pediatric patients; ileus will reverse itself with temporary discontinuance of vincristine sulfate injection and with symptomatic care.*					
7009054-1 ***Duplicate***	**21-May-2009** ***1-Oct-2007***	**272695** ***2007SP019246***	**9 Female**	**France**	**Leukemia (ALL)**	Brain oedema, Constipation, Drug interaction, Fusarium infection, Hypokalaemia, Hypophosphataemia, Inappropriate antidiuretic hormone secretion, Leukaemia recurrent, Metabolic encephalopathy, Neuropathy peripheral, Neurotoxicity, Neutropenia *Altered state of consciousness, Metabolic disorder, Hyponatraemia,*

6441936-2						*Somnolence, Seizure, Hemiparesis, Coma scale abnormal, Electroencephalogram abnormal*
Duplicate 7613834-1	***10-Sep-2010***	***2009SP012065***				*Seizure, Acute lymphocytic leukaemia, Fusarium infection, Abdominal pain, Neuropathy peripheral, Constipation, Neurotoxicity, Hyponatraemia, Drug interaction, Brain oedema, Neutropenia, Leukaemia recurrent, Encephalopathy, Hypokalaemia*
Duplicate 7879884-2	***9-Mar-2011***	***2011SP009941***				*Neurotoxicity, Seizure, Abdominal pain, Inappropriate antidiuretic hormone secretion, Drug interaction, Hypokalaemia, Neutropenia, Encephalopathy, Hypophosphataemia, Constipation, Neuropathy peripheral, Hyponatraemia, Fusarium infection*

Literature Report: **Eiden C, Palenzuela G, Hillaire-Buys D, et al. Posaconazole-increased vincristine neurotoxicity in a child: a case report. J Pediatr Hematol Oncol. 2009;31:292-5.**

Case Notes: Posaconazole 50 mg PO TID (OS presumed*) initiated for prophylaxis.

A 9-year-old female developed medullary ALL relapse in Jun-2007. Posaconazole was started five days prior to chemotherapy due to a past history of disseminated fusariosis in 2002. Four days before the start of systemic chemotherapy in 2007, she received intrathecal chemotherapy consisting of methotrexate, cytarabine, and prednisone. Induction protocol consisted of dexamethasone, asparaginase, vincristine (1.5 mg/m^2 for days one and six), and methotrexate. Six days after the second dose of vincristine, she presented with grade III peripheral neuropathy of the lower extremities, abdominal cramps, and constipation. An abdominal ultrasound and x-ray suggested fecal stasis without paralytic ileus. Seven days later, impaired consciousness, confusion, agitation, and drowsiness were observed. Posaconazole was discontinued and she was transferred to the PICU due to a decline in alertness with a Glasgow Coma Scale score of seven. EEG revealed nonspecific slow waves with posterior encephalopathy. CT scan of head showed cerebral edema. Methotrexate toxicity was first suspected, and aminophylline was administered. Severe hyponatremia was observed (115 mmol/L, normal range not reported) suggesting a syndrome of inappropriate secretion of antidiuretic hormone. Hypokalemia (2.5 mmol/L, normal range not reported) and hypophosphatemia (0.82 mmol/L, normal range not reported) were also observed without renal dysfunction. Sodium and potassium supplementation were administered. She then experienced an episode of seizures and was treated with fosphenytoin. Examination of the cardiorespiratory system was normal and plasma methotrexate levels were within expected range. After two days in the PICU, her Glasgow Coma Scale score was 11 with no focal neurologic findings present. In Jul-2007, chemotherapy was continued with a 30% dose-reduction of vincristine and cytarabine, without intrathecal methotrexate. Neutropenia resolved in 10 days and antifungal prophylaxis was not required. The authors concluded an interaction between posaconazole and vincristine may have played a role in the observed severe neurotoxicity.

Reviewer Comments: *Based on the temporal association, a causal relationship between many of the reported events and posaconazole cannot be excluded. The reporter did not specify if vincristine was initially dose-reduced for this patient during concomitant posaconazole administration. Posaconazole is labeled as a strong CYP3A4 inhibitor and may increase vincristine exposure which may lead to neurotoxicity; therefore, dose adjustment of vincristine should be considered (Posaconazole labeling DRUG INTERACTIONS). Vincristine sulfate is labeled for constipation, inappropriate antidiuretic hormone secretion, neuropathy, neurotoxicity, and hyponatremia.*

7399499-1	**26-May-2010**	**IN-BRISTOL-MYERS SQUIBB COMPANY-15107980**	**4 Male**	**India**	**Leukemia (ALL)**	Drug interaction, Inappropriate antidiuretic hormone secretion, Seizure, Zygomycosis

Representative case (See also page 12)

Literature Report: **Jain S, Kapoor G. Severe life threatening neurotoxicity in a child with acute lymphoblastic leukemia receiving posaconazole and vincristine. Pediatr Blood Cancer. 2010;54:783.**

Case Notes: Posaconazole 7 mg/kg/day (route and frequency not reported; OS presumed*) initiated for prophylaxis.

A 4-year-old male with ALL received induction therapy using Berlin-Frankfurt-Münster (BFM)-95 protocol.† On day 19 of this protocol, disseminated mucormycosis was detected that responded to amphotericin B. He underwent wedge resection of the pulmonary lesions and surgical debridement of the cutaneous lesions. Induction was completed with prednisolone, vincristine, and L-asparaginase. He achieved complete remission and subsequent chemotherapy per protocol. Posaconazole (7 mg/kg/day) was initiated for secondary prophylaxis during re-induction (route, frequency, and formulation were not reported). On day 20 of re-induction, he presented with repeated episodes of seizures. He had no past or family history of seizure disorder. He had been lethargic the past few days, but had no history of fever, constipation, diarrhea, or vomiting. Persistent seizures led to respiratory compromise requiring mechanical ventilation. Laboratory values revealed the following: sodium 99 mEq/L (normal range not reported), potassium 2.8 mEq/L (normal range not reported), and normal renal function. Serum osmolality was low (243 Osm/kg H_2O, normal range not reported), urinary osmolality was high (415 Osm/kg H_2O, normal range not reported), and urinary sodium was high (125 mEq/L, normal range not reported), thus confirming a diagnosis of syndrome of inappropriate antidiuretic hormone secretion. Baseline serum electrolytes prior to events were

reported as normal. MRI scan of the brain was performed the same day and found to be normal. Posaconazole was discontinued (date not reported) and seizures were treated with phenytoin, fluid restriction, and sodium and potassium supplementation. His biochemical parameters and mental status normalized and no other apparent cause of seizure was identified. He did not have further episodes of seizure or neurotoxicity when vincristine was subsequently administered alone without posaconazole.

Reviewer Comments: *Based on the temporal association, a causal relationship between posaconazole and the events of inappropriate antidiuretic hormone secretion and seizure cannot be excluded. The adverse events of seizure and neurotoxicity only occurred when vincristine was administered with concomitant posaconazole. The patient received vincristine before and after concomitant posaconazole administration without experiencing any episodes of seizure or neurotoxicity. It was not reported if vincristine was dose-reduced during concomitant administration with posaconazole. Posaconazole is labeled as a strong CYP3A4 inhibitor and may increase vincristine exposure which may lead to neurotoxicity; therefore, dose adjustment of vincristine should be considered (Posaconazole labeling DRUG INTERACTIONS). Vincristine sulfate is labeled for neurotoxicity, convulsions, and inappropriate antidiuretic hormone secretion.*

7746673-2	**2-Dec-2010**	**2010SP061640**	**6 Female**	**USA**	**Leukemia (ALL)**	Neuropathy peripheral

Case Notes: Posaconazole (dose, route and frequency not reported; OS presumed*) initiated for treatment of an unspecified fungal infection on 4-Nov-2010.

6-year-old female with a history of ALL, hypertension, and red man syndrome, started posaconazole on 4-Nov-2010. Afterwards, she was administered her monthly dose of vincristine sulfate. On the same day, she experienced an increase in peripheral neuropathy which lasted at least four to five days. Unspecified medical attention was sought. She was started on gabapentin for the neuropathy and recovered on an unknown date. The action taken with posaconazole was not reported. Concomitant medications included unspecified blood pressure medications, "ethradapin" (possibly isradipine), pantoprazole, enoxaparin, and filgrastim.

Reviewer Comments: *Limited case details precluded a meaningful causality assessment. Based on the temporal association, a causal relationship between the reported adverse events and posaconazole cannot be excluded. The reporter did not specify if vincristine was dose-reduced for this patient. Posaconazole is labeled as a strong CYP3A4 inhibitor and may increase vincristine exposure which may lead to neurotoxicity; therefore, dose adjustment of vincristine should be considered (Posaconazole labeling DRUG INTERACTIONS). Vincristine sulfate is labeled for neuropathy.*

9346442-1	**13-Jun-2013**	**IR-009507513-1306IRN005535**	**8 Male**	**Iran**	**Leukemia (ALL)**	Abdominal pain, Constipation, Drug interaction, Pain in jaw, Pancreatitis, Toxicity to various agents

Literature Report: **Alavi S, Ebadi M. Prolonged vincristine toxicity induced by concurrent posaconazole in a child with T-cell acute lymphoblastic leukemia. Iran J Med Sci. 2013;38:135-6.**

Case Notes: Posaconazole PO (dose and frequency not reported; OS presumed*) initiated for the treatment of an *Aspergillus niger* pulmonary infection.

8-year-old male with ALL was admitted with fever and neutropenia. Based on a chest CT scan, he was diagnosed with a pulmonary fungal infection. Treatment with conventional amphotericin B was started, but after two weeks, a chest CT scan showed no improvement of the pulmonary nodules. An open lung biopsy was performed and the biopsy specimen grew *A. niger*. On an unknown date, the combined treatment with caspofungin and liposomal amphotericin B led to clinical improvement and the patient was discharged after three weeks with oral posaconazole. He was then scheduled to receive his maintenance chemotherapy based on a routine protocol including vincristine (1.5 mg/m^2), doxorubicin, mercaptopurine, and prednisone. On an unknown date, he complained of severe jaw pain, disabling abdominal cramps and obstipation for eight days. Plain abdomen x-ray showed excessive intestinal gas without signs of obstruction, suggestive of paralytic ileus. After 10 days of conservative management, the patient had persistent jaw pain without defecation as well as abdominal pain. Abdominal ultrasonography of the pancreas illustrated an increased echo pattern. Laboratory investigations only showed an increased serum lipase level and ESR, but normal amylase level. On an unknown date, posaconazole was discontinued leading to the improvement of the symptoms within the next two days. The authors concluded peripheral neuropathy, manifesting as constipation and abdominal pain, can present in patients receiving vincristine and posaconazole.

Reviewer Comments: *Limited case details precluded a meaningful causality assessment. Based on the temporal association, a causal relationship between the reported events and posaconazole cannot be excluded. It was not reported if vincristine was dose-reduced for this patient. Posaconazole is labeled as a strong CYP3A4 inhibitor and may increase vincristine exposure which may lead to neurotoxicity; therefore, dose adjustment of vincristine should be considered (Posaconazole labeling DRUG INTERACTIONS). Vincristine sulfate is labeled for jaw pain, constipation, and paralytic ileus (particularly in young pediatric patients).*

9538433-2	**20-Sep-2013**	**FR-MERCK-1309FRA005309**	**12 Male**	**France**	**Leukemia (ALL)**	Paraesthesia

Case Notes: Posaconazole OS 200 mg PO TID initiated for prophylaxis starting in May-2013; vincristine sulfate administered on 5-Jul-2013 and 12-Jul-2013.

12-year-old male with ALL. In Oct-2012, induction treatment of ALL was performed with vincristine (2 mg [1.5 mg/m^2]), daunorubicin, and methotrexate. On 25-Feb-2013, he received nelarabine, cyclophosphamide, and etoposide. On 18-Mar-2013, he received vincristine, doxorubicin, and methotrexate. On 10-Apr-2013, he received nelarabine, cyclophosphamide, and etoposide. On 13-May-2013, he received nelarabine alone. In mid-May-2013, he started posaconazole for prophylaxis. On 3-Jun-2013, he received nelarabine, cyclophosphamide, and etoposide again, but residual disease was still positive. It was

decided to introduce sequential treatment with vincristine sulfate, liposomal daunorubicin, polyethylated glycol conjugated asparaginase, and dexamethasone. The dose of vincristine sulfate was reduced from 2 mg to 1.5 mg (1 mg/m²) due to concomitant administration with posaconazole. Since the beginning of the treatment cure, he complained of paresthesia (pins and needles) at the fingertips and was started on clonazepam. On 16-Jul-2013, persistence of paresthesia with permanent and sleeplessness pins and needles of the lower limbs, jaw, and upper limbs was reported. Gabapentin was started which improved paresthesia of the jaw, but there was a persistence in the limbs. Gabapentin was switched to amitriptylline and the dose of clonazepam increased. It was decided not to administer the third dose of vincristine on 19-Jun-2013. On 22-Jul-2013, limb paresthesia improved. Posaconazole was continued at the same dose during this time and the outcome of paresthesia was reported as recovered/resolved. ***Reviewer Comments:*** *Based on the temporal association, a causal relationship between paresthesia and posaconazole cannot be excluded. The reporter specified that the administered dose of vincristine was dose-reduced by 25% due to concomitant posaconazole. Posaconazole is labeled as a strong CYP3A4 inhibitor and may increase vincristine exposure which may lead to neurotoxicity; therefore, dose adjustment of vincristine should be considered (Posaconazole labeling DRUG INTERACTIONS). Vincristine sulfate and posaconazole are both labeled for paresthesia.*						
11039108-3	**16-Apr-2015**	**PL-MERCK-1504POL009164**	**3 Male**	**Poland**	**Leukemia (ALL)**	Ileus paralytic
Case Notes: Posaconazole OS 160 mg PO BID initiated from 6-Feb-2015 to 18-Feb-2015; vincristine sulfate administered on 30-Jan-2015, 8-Feb-2015, and 15-Feb-2015. 3-year-old male with ALL received three doses of vincristine sulfate on 30-Jan-2015 (1 mg), 8-Feb-2015 (1 mg), and 15-Feb-2015 (1 mg). Posaconazole was administered from 6-Feb-2015 to 18-Feb-2015 for an unreported indication. On 25-Feb-2015, seven days after posaconazole discontinuation (reason unspecified), he presented with abdomen flatulence, inability to defecate, and intense pain. Paralytic ileus was diagnosed and he was hospitalized on an unspecified date. The physician considered paralytic ileus to be life threatening and the patient recovered on an unspecified date. Concomitant medications included meropenem, IVIG, prednisone, sulfamethoxazole/trimethoprim, and amikacin. ***Reviewer Comments:*** *Based on the temporal association, a causal relationship between paralytic ileus and posaconazole cannot be excluded due to posaconazole's long terminal elimination half-life. The reporter did not specify if vincristine was dose-reduced for this patient. Posaconazole is labeled as a strong CYP3A4 inhibitor and may increase vincristine exposure which may lead to neurotoxicity; therefore, dose adjustment of vincristine should be considered (Posaconazole labeling DRUG INTERACTIONS). Vincristine sulfate is labeled for paralytic ileus, particularly in young pediatric patients; ileus will reverse itself with temporary discontinuance of vincristine sulfate injection and with symptomatic care.*						
11039110-2 ***Duplicate 11133732-1***	**16-Apr-2015**	**PL-MERCK-1504POL009371** ***PL-JNJFOC-20150515032***	**8 Female**	**Poland**	**Leukemia (ALL)**	Anxiety disorder, Brain oedema, Hallucination, Hallucination visual, Hypochloraemia, Hyponatraemia, Inappropriate antidiuretic hormone secretion, Mental disorder, Partial seizures, Polyuria *Anxiety, Convulsions local, Hallucination, Hallucination visual, Hypochloraemia, Hyponatraemia, Inappropriate antidiuretic hormone secretion, Polyuria*
Case Notes: Posaconazole OS 200 mg PO BID initiated for prophylaxis from 5-Mar-2015 to 14-Mar-2015; vincristine sulfate administered on 6-Mar-2015. 8-year-old female with ALL started posaconazole on 5-Mar-2015 and one dose of vincristine sulfate (1.4 mg) was administered on 6-Mar-2015. Other concomitant medications included tramadol, meropenem, piperacillin/tazobactam, prednisone, sulfamethoxazole/trimethoprim, and amikacin. On 13-Mar-2015, she experienced hypochloremia and on 14-Mar-2015, hyponatremia and focal convulsions. On an unspecified date, she experienced polyuria, inappropriate antidiuretic hormone secretion (cerebral edema), anxiety state, hallucinations, visual hallucinations, and productive symptoms. Posaconazole was discontinued on 14-Mar-2015, the next dose of vincristine was held, and she recovered three days after posaconazole discontinuation. The reporting physician considered the events as life-threatening and related to posaconazole, vincristine, and tramadol. ***Reviewer Comments:*** *Based on the temporal association, a causal relationship between the reported adverse events and posaconazole cannot be excluded. The reporter did not specify if vincristine was dose-reduced for this patient. Posaconazole is labeled as a strong CYP3A4 inhibitor and may increase vincristine exposure which may lead to neurotoxicity; therefore, dose adjustment of vincristine should be considered (Posaconazole labeling DRUG INTERACTIONS). Vincristine is labeled for inappropriate antidiuretic hormone secretion, hyponatremia, and polyuria.*						
11043139-2	**17-Apr-2015**	**PL-MERCK-1504POL016705**	**6 Male**	**Poland**	**Leukemia (ALL)**	Agranulocytosis, Drug interaction, Ileus paralytic
Case Notes: Posaconazole OS 220 mg PO BID initiated for prophylaxis from 29-Dec-2014 to 8-Jan-2015; vincristine sulfate administered once weekly from 17-Dec-2014 to 6-Jan-2015. 6-year-old male vincristine sulfate (1.5 mg) once weekly from 17-Dec-2014 to 6-Jan-2015 for the treatment of ALL. Posaconazole was started on 29-Dec-2014. On 7-Jan-2015, he experienced paralytic ileus which was confirmed by abdominal ultrasound. Posaconazole was discontinued on 8-Jan-2015 and paralytic ileus subsided and eventually resolved on an unknown date in 2015. On 23-Mar-2015, he experienced agranulocytosis but the outcome was unknown. The reporter thought paralytic ileus was related to the interaction between posaconazole and vincristine. Concomitant medications included prednisone, sulfamethoxazole/trimethoprim, ramipril, hydrochlorothiazide, and amlodipine. ***Reviewer Comments:*** *Based on the temporal association, a causal relationship between paralytic ileus and posaconazole cannot be excluded. The reporter did not specify if vincristine was dose-reduced for this*						

patient. Posaconazole is labeled as a strong CYP3A4 inhibitor and may increase vincristine exposure which may lead to neurotoxicity; therefore, dose adjustment of vincristine should be considered (Posaconazole labeling DRUG INTERACTIONS). Agranulocytosis occurred approximately 74 days after posaconazole discontinuation (lack of temporal relationship). Vincristine sulfate is labeled for paralytic ileus, particularly in young pediatric patients; ileus will reverse itself with temporary discontinuance of vincristine sulfate injection and with symptomatic care.

[*]Specific formulation not reported; selection based on date of administration and description of reported dose, route, or frequency

[†]This regimen may consist of prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, mesna, cytarabine, mercaptopurine, and methotrexate

Abbreviations: ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CT, computerized tomography; CYP450, cytochrome P450 enzymes; EEG, electroencephalogram; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; OS, oral suspension; PEG, PICU, pediatric intensive care unit; PO, by mouth; QID, four times daily; TID, three times daily

TABLE C2. FATAL PEDIATRIC CASES WITH POSACONAZOLE (N=13)

FAERS Case# - Version#	Manufacturer Control #
6161759-1	2006SP003807
6800724-2	2008SP021029
6975058-2	2009SP007606
7022019-1	2009SP008238
7252749-2	US-MERCK-1001USA00917
7959150-3 *Duplicate 7978749-1* *Duplicate 7996117-1* *Duplicate 8575390-1*	PT-MYLANLABS-2011S1010004 *PT-WATSON-2011-07243* *2011SP023910* *PT-ASTELLAS-2012EU003595*
8886217-1 *Duplicate 8737914-3* *Duplicate 8902763-3*	PHHY2012US099584 *US-009507513-1208USA006209* *US-RANBAXY-2012US-61932*
9720098-1 *Duplicate* 9725783-1	ES-MERCK-1311ESP007264 *ES-ASTELLAS-2013US012419*
9776700-1	PHHY2013US146416
10030949-2	HU-MERCK-1403HUN008325
10792393-1	US-009507513-1502USA004742
10899669-1	AU-MERCK-1503AUS001523
11050995-3	IT-ASTELLAS-2015US012661

TABLE C3. PEDIATRIC CASE SERIES WITH UNLABELED ADVERSE EVENTS AND POSACONAZOLE (N=12)						
FAERS Case# - Version#	**Initial FDA Received Date**	**Manufacturer #**	**Age (years) Sex**	**Reporter Country**	**Underlying Medical Condition**	**Reported MedDRA Preferred Terms (PTs)**
6287333-2	**28-Mar-2007**	**2007SP005109**	**7 Male**	**USA**	**Leukemia (ALL)**	Aspergillus infection, Condition aggravated, Disease recurrence, Pancreatitis, Pulmonary mass
Case Notes: Posaconazole 200 mg PO QID (OS presumed*) initiated for treatment of bronchopulmonary aspergillosis for one dose, then restarted later on 200 mg PO TID, 100 mg PO TID, then 100 mg PO BID. 7-year-old male with relapsed ALL was admitted to the hospital (b) (6) due to neutropenic fever and chills. Within a few hours of the first dose of posaconazole (200 mg), amylase and lipase increased from within normal range of 56 and 57, to 175 to 987, respectively (units and normal range unspecified throughout report). By 12-Mar-2007, amylase and lipase were 224 and 1754, respectively. Posaconazole was held until 15-Mar-2007, but then resumed at a reduced dose of 200 mg PO TID since amylase and lipase decrease to 93 and 312, respectively. On 16-Mar-2007, amylase and lipase increased to 128 and 476 , respectively. The posaconazole dose was reduced to 100 mg PO TID for two days. Amylase and lipase remained steady, but on 25-Mar and 26-Mar-2007, an increase in amylase (180) and lipase (1040) occurred, and the posaconazole dose was reduced to 100 mg PO BID. Amylase and lipase on 30-Mar-2007 decreased to 140 and 843, respectively. A chest scan revealed one of the pulmonary masses to be decreasing in size and posaconazole was continued. The reporting pharmacist considered the increase in amylase and lipase due to possible pancreatitis. Concomitant medications included multiple antibiotics including meropenem (other drugs and dates not reported), TPN and other medications (drugs and dates not reported). Relevant medical history included leukemia, hyperbilirubinemia, hepatitis, and hepatic failure. ***Reviewer Comments:*** *Posaconazole is not labeled for pancreatitis. Based on the temporal association, a causal relationship between pancreatitis and posaconazole cannot be excluded; however, pancreatitis is confounded by underlying disease processes, concomitant medications, and TPN.*						
6635729-3	**22-Apr-2008**	**2008SP007060**	**10 Male**	**Italy**	**Not reported**	Pancreatitis
Case Notes: Posaconazole 400 mg PO QD (OS presumed*) initiated for the treatment of an unspecified pulmonary infection from 20-Feb-2008 to 20-Mar-2008. One month after starting posaconazole, he developed nausea, vomiting, and abdominal pain without fever. On 20-Mar-2008, he underwent an abdominal echography which revealed pancreatitis. Lipase test showed an increased value of 2103 mU/mL (normal range: 114-286 mU/mL), he was hospitalized, and posaconazole was discontinued. Prior to this episode, he did not have a history of gallstones or hypertriglyceridemia. The only concomitant medication reported was sulfamethoxazole/trimethoprim (dates, dose, and frequency not reported). Posaconazole and sulfamethoxazole/trimethoprim were withdrawn on 20-Mar-2008. He was hospitalized from (b) (6) to (b) (6) and underwent fasting and parenteral nutrition. At the time of the report, pancreatitis was considered resolved. On an unspecified date, later tests of amylase, lipase, and abdominal echography were normal. ***Reviewer Comments:*** *Posaconazole is not labeled for pancreatitis. Based on the temporal association, a causal relationship between the reported events and posaconazole cannot be excluded; however, pancreatitis is confounded by concomitant administration with sulfamethoxazole/trimethoprim which is labeled for pancreatitis.*						
6781120-2	**12-Sep-2008**	**2008SP019059**	**6 Male**	**Netherlands**	**Leukemia (ALL)**	Toxic encephalopathy
Case Notes: Posaconazole 200 mg PO QID (OS presumed*) for the treatment of invasive mucormycosis starting in Aug-2008. In Oct-2007, the patient received SKION ALL-10 protocol, which can consist of prednisone, vincristine, daunorubicin, asparaginase, cyclophosphamide, cytarabine, mercaptopurine, and intrathecal methotrexate. On an unspecified date in Aug-2008, he initiated posaconazole for the treatment of invasive mucormycosis of the lung and possibly liver. On (b) (6) he experienced a tonic clonic seizure, was hospitalized, and treated with levetiracetam. Concomitant medications included sulfamethoxazole/trimethoprim, ciprofloxacin, and paracetamol. An EEG performed after hospitalization revealed no abnormalities. MRI showed multifocal bilateral hyper-intense signal of the grey substance with meningeal coloring at some places. It was reported that the image suggested toxic encephalopathy due to chemotherapy (methotrexate). At the time of the report, the outcome of tonic clonic seizure was unknown. ***Reviewer Comments:*** *Limited case details precluded a meaningful causality assessment. Posaconazole is not labeled for toxic encephalopathy. Based on the temporal association, a causal relationship between the reported events and posaconazole cannot be excluded; however, the reported adverse event may be due to underlying disease processes, concurrent disease states, and recently received or concomitant medications including intrathecal methotrexate and ciprofloxacin.*						
7049760-2	**2-Jul-2009**	**2009SP013987**	**15 Female**	**France**	**Leukemia (ALL)**	Agitation, Drug interaction, Hypertriglyceridaemia

Duplicate 7117126-1	***17-Sep-2009***	***FR-ROCHE-656368***				*Drug interaction, Hypertriglyceridaemia*
Case Notes: Posaconazole 200 mg PO TID (OS presumed*) initiated for prophylaxis from 30-May-2009 to 7-Jun-2009. 15-year-old female with ALL, BMT, behavior disorder, epilepsy, and mental retardation. Concomitant medications included acyclovir, clonazepam, cyclosporine, dexbrompheniramine, enoxaparin, insulin, lamotrigine, mycophenolate, nomegestrol, omeprazole, phenoxymethylpenicillin, sulfamethoxazole/trimethoprim, and ursodiol. On 7-Jun-2009, hypertriglyceridemia occurred with a reported triglyceride level of 11.68 mmol/L (normal range not reported). Pancreatic workup to rule-out pancreatitis found amylase at 46 IU/L (normal range not reported) and lipase at 30 IU/L (normal range not reported). Also on 7-Jun-2009, she received fenofibrate 67 mg TID for hypertriglyceridemia, and the following medications were discontinued: posaconazole, clonazepam, cyclosporine, and nomegestrol. One month after these drugs were discontinued, triglyceride levels normalized. Posaconazole was reintroduced at the same dose on 30-Jun-2009, but the outcome was not reported. ***Reviewer Comments:*** *Posaconazole is not labeled for hypertriglyceridemia, and agitation occurred prior to initiation of posaconazole. Based on the temporal association, a causal relationship between hypertriglyceridemia and posaconazole cannot be excluded; however, hypertriglyceridemia may be due to underlying disease processes and concomitant medications including cyclosporine which is labeled for hypertriglyceridemia.*						
7346234-2	**19-Mar-2010**	**2010SP016087**	**12 Male**	**Russia**	**Hematologic disease**	Gastrointestinal haemorrhage
Case Notes: Posaconazole 800 mg/day in divided doses (OS presumed*) initiated for prophylaxis from 12-Mar-2010 to 13-Mar-2010. 12-year-old male with unspecified hematologic disease. During the morning of 12-Mar-2010, he took three doses (exact dose, route, and frequency unspecified). Later that evening, he experienced liquid stool. The following day, another two doses were administered for a total of 800 mg in five doses. Later on 13-Mar-2010, the patient experienced intestinal bleeding and posaconazole was discontinued the same day. The outcomes of the events were not reported. ***Reviewer Comments:*** *Limited case details precluded a meaningful causality assessment. Based on the temporal association, a causal relationship between the reported event and posaconazole cannot be excluded.*						
7613825-1	**10-Sep-2010**	**2008SP023801**	**15 Male**	**Germany**	**Lymphoma**	Gamma-glutamyltransferase increased, Hepatic fibrosis
Case Notes: Posaconazole initiated for treatment of aspergillosis (dose, route and frequency unspecified; OS presumed*). 15-year-old male with history of relapsed T-cell lymphoma and BMT in 2007 with aspergillosis. At the time of the report, he was taking unspecified medications for aspergillosis and other unspecified medications. On an unknown date, he commenced treatment with posaconazole for aspergillosis and developed hepatic fibrosis. On an unknown date, tests revealed elevated GGT with values ranging from 200-400 U/L (normal range unspecified) and transaminases were not increased. The physician considered the event reversible since it was not hepatic cirrhosis. The outcomes of these events were not reported. ***Reviewer Comments:*** *Limited case details precluded a meaningful causality assessment. Although not specifically labeled for elevation in GGT or hepatic fibrosis, posaconazole is labeled for hepatic reactions including clinical hepatitis and more severe reactions including cholestasis or hepatic failure including deaths in patients with serious underlying medical conditions (e.g., hematologic malignancy).*						
7634309-1	**30-Sep-2010**	**2010SP051344**	**13 Female**	**Peru**	**Not reported**	Tachycardia, Seizure
Case Notes: Posaconazole initiated for treatment of resistant candidiasis on 20-Sep-2010 (dose, route and frequency unspecified; OS presumed*). Patient with no preexisting neurological history started posaconazole for the treatment of resistant candidiasis. Eight hours after the administration of posaconazole, she experienced seizures. On 21-Sep-2010, she experienced unspecified tachycardia that spontaneously disappeared. Outcomes for both events were unknown. Posaconazole was discontinued on an unknown date in Sep-2010. ***Reviewer Comments:*** *Limited case details precluded a meaningful causality assessment. Posaconazole is not labeled for seizure.*						
7751385-1	**7-Dec-2010**	**2010SP062650**	**11 Female**	**France**	**Cystic fibrosis**	Drug level decreased, Tremor
Case Notes: Posaconazole 400 mg BID (PO and OS presumed*) initiated for the treatment of *Aspergillus fumigatus* from 11-Oct-2010 to 9-Nov-2010. 11-year-old female with cystic fibrosis diagnosed at 22 months of age. On 27-Sep-2010, she started itraconazole for *A. fumigatus* that was present in her expectorations. On 11-Oct-2010, she was changed to posaconazole due to a better minimum inhibitory concentration. On 27-Oct-2010, the concentration of posaconazole was found to be lower than the targeted values and the dose was increased from 400 mg BID to 600 mg BID. On 9-Nov-2010, she presented with tremor of her four extremities. Posaconazole was discontinued and changed to voriconazole and the event resolved. ***Reviewer Comments:*** *Limited case details precluded a meaningful causality assessment. Based on the temporal association, a causal relationship between the reported adverse event of tremor and posaconazole*						

cannot be excluded. Posaconazole is not labeled for tremor.						
8854942-1	**23-Oct-2012**	**SE-009507513-1210SWE006385**	**11 Male**	**Sweden**	**Medulloblastoma**	Hearing impaired
Case Notes: Posaconazole OS 400 mg PO BID initiated for treatment of suspected pulmonary mucormycosis. 11-year-old male with relapsed medulloblastoma and a prior history of hearing impairment. Medulloblastoma was treated initially according to the common medulloblastoma protocol in Sweden followed by temozolomide monotherapy. Unspecified intrathecal chemotherapy was also administered. On an unknown date in 2012, he started posaconazole for suspected pulmonary mucormycosis and beta-glucan test was positive. Blood posaconazole concentration was 1.06 (units and reference range not reported). On an unknown date in 2012, he experienced aggravation of previously existing hearing impairment. He specified that he could not hear at all on the left ear and his hearing on the right ear was severely impaired. On unknown date, posaconazole was discontinued due to hearing impairment. The outcome was reported as "not recovered/resolved". Concomitant medications included bevacizumab, celecoxib, fenofibrate, and an unspecified drug similar to thalidomide. ***Reviewer Comments:*** *Limited case details precluded a meaningful causality assessment. Posaconazole is not labeled for hearing impairment; however, hearing impairment is confounded by disease processes, concomitant medications including intrathecal chemotherapy, and concomitant celecoxib which is labeled for deafness and tinnitus.*						
9602255-1	**3-Oct-2013**	**KAD201309-001263**	**5 Male**	**India**	**Solid organ transplant (liver)**	Drug effect decreased, Seizure, Product use issue, Immunosuppression
Literature Report: **Rao S, Choudhury S, Chandrashekar V, et al. Cladophialophora bantiana causing brain abscess in a child following liver transplant-a case report [abstract]. Pediatr Transplant. 2013;17 Suppl 1:83.** ***Case Notes:*** Posaconazole PO (dose and route not reported; OS presumed*) initiated for treatment of *Cladophialophora bantiana.* 5-year-old male underwent living donor liver transplant for biliary cirrhosis secondary to biliary atresia. On the 34th day post-transplant, he developed a right-sided focal seizure. CT showed a left frontal lobe brain lesion. The brain abscess was aspirated and *C. bantiana* identified. Liposomal amphotericin B was initiated and immunosuppression reduced; however, response was poor and there was clinical and radiological worsening. Craniotomy and debridement of the abscess was performed on day 60 post-transplant. Intralesional amphotericin B was administered and followed by a three week course of IV amphotericin and voriconazole. Clinical and radiological improvement was noted and he was discharged on oral posaconazole. He continued to remain asymptomatic and antifungal therapy was stopped six months later. Within three weeks of posaconazole discontinuation, he had another convulsion and imaging suggested a progression of the lesion. Flucytosine and voriconazole were initiated, but these had to be stopped due to severe gastrointestinal side effects after two months. Oral posaconazole was restarted and the patient was two years post-transplant and remained symptom free. However, the patient still had significant lesions on MRI, and it is likely that the patient had active disease. ***Reviewer Comments:*** *Posaconazole is not labeled for seizure; however, seizure occurred prior to posaconazole initiation and approximately three weeks after posaconazole discontinuation. Based on the available data, there is not a reasonable basis for concluding posaconazole caused seizure in this case.*						
10226397-2	**09-Jun-2014**	**DE-009507513-1405DEU011890**	**17 Female**	**Germany**	**Leukemia (AML)**	Memory Impairment
Case Notes: Posaconazole DRT 200 mg PO TID initiated for prophylaxis from 12-Apr-2014 to 16-May-2014. Short-term memory impairment occurred approximately one month after starting posaconazole and resolved after posaconazole discontinuation. Concomitant medications included chemotherapy (AML-BFM 2012 protocol) and teicoplanin. ***Reviewer Comments:*** *Limited case details precluded a meaningful causality assessment. Based on the temporal association, a causal relationship between the reported events and posaconazole cannot be excluded. Posaconazole is not labeled for memory impairment; however, memory impairment is confounded by underlying disease processes and concomitant medications including chemotherapy. Of note, the last report stated "oral tablet, 200 mg, three times daily" which is consistent with the approved dosing of posaconazole OS and not the DRT. It is unknown if this was a transcription error, medication error, or intentional off-label dosing of the DRT.*						
11385889-2	**17-Aug-2015**	**FR-009507513-1507FRA008758**	**5 Male**	**France**	**Leukemia (ALL)**	Body temperature increased, Drug intolerance, Face oedema, Hypoproteinaemia, Off label use, Proteinuria
Case Notes: Posaconazole DRT 300 mg PO QD initiated for prophylaxis from 4-May-2015 to 11-Jul-2015. 5-year-old male with deep aplasia induced by courses of strong chemotherapies with baseline hypoproteinemia appeared to experience accentuated hypoproteinemia when taking posaconazole. Concomitant medications included imatinib and acyclovir. On 9-Jul-2015, he presented with hypoproteinemia, hypoalbuminemia, and facial edema; ethmoiditis was suspected but was ruled out by brain and sinus CT scan. On an unknown date in Jul-2015, he presented with proteinuria. Posaconazole was discontinued on 11-Jul-2105 due to persistence of facial edema and proteinuria. On 14-Jul-2015 facial edema abated and proteinuria						

normalized the following day.

Reviewer Comments: *Based on the temporal association, a causal relationship between the reported adverse events and posaconazole cannot be excluded. Posaconazole is not labeled for face edema, hypoproteinemia, or proteinuria; however, these adverse events are confounded by courses of unspecified chemotherapy, preexisting hypoproteinemia, and concomitant medications including imatinib which is labeled for hypoproteinemia and facial edema. Although not specifically labeled for face edema, posaconazole is labeled for edema, edema legs, and edema peripheral.*

*Specific formulation not reported; selection based on date of administration and description of reported dose, route, or frequency

Abbreviations: ALL, acute lymphoblastic leukemia; BID, twice daily, BMT; bone marrow transplant; CT, computerized tomography; DRT, delayed-release tablet; EEG, electroencephalogram; HSCT, hematopoietic stem cell transplantation; IV, intravenous; MRI, magnetic resonance imaging; OS, oral suspension; PO, by mouth; QD, once daily; QID, four times daily; TID, three times daily; TPN, total parenteral nutrition

8.4 APPENDIX D. PRODUCT LABELING FOR SELECT AZOLE ANTIFUNGALS AND VINCRISTINE

Product labeling describing the interaction of the following azole antifungals with vincristine, or of vincristine with azole antifungals.

Noxafil® (Posaconazole) Labeling[a]

Drug Interactions, Vinca Alkaloids

Most of the vinca alkaloids are substrates of CYP3A4. Posaconazole may increase the plasma concentrations of vinca alkaloids (e.g., vincristine and vinblastine) which may lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered.

Sporanox® (Itraconazole) Labeling[b]

Drug Interactions, Vinca Alkaloids

Use with caution

Diflucan® (Fluconazole) Labeling[c]

Drug Interactions, Vinca Alkaloids

Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g., vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vfend® (Voriconazole) Labeling[d]

Drug Interactions, Vinca Alkaloids

Not studied *in vitro* or *in vivo*, but drug plasma exposure likely to be increased. Frequent monitoring for adverse events and toxicity (i.e., neurotoxicity) related to vinca alkaloids. Adjustment of vinca alkaloid dosage may be needed.

Vincristine Sulfate Labeling[e]

PRECAUTIONS, Drug Interactions

Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vincristine sulfate with itraconazole (a known inhibitor of the metabolic pathway) has been reported to cause an earlier onset and/or an increased severity of neuromuscular side effects (see ADVERSE REACTIONS). This interaction is presumed to be related to inhibition of the metabolism of vincristine.

Marqibo® (Vincristine Sulfate Liposome) Labeling[f]

Unlike vincristine sulfate, the safety and effectiveness of Marqibo® in pediatric patients has not been established.

Drug Interactions

Vincristine sulfate, the active agent in Marqibo, is a substrate for cytochrome P450 3A isozymes (CYP3A); therefore, the concomitant use of strong CYP3A inhibitors should be avoided (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin). Vincristine sulfate, the active agent in Marqibo, is also a substrate for P-glycoprotein (P-gp). The effect of concomitant use of potent P-gp inhibitors or inducers has not been investigated; it is likely that these agents will alter the pharmacokinetics or pharmacodynamics of Marqibo. Therefore the concomitant use of potent P-gp inhibitors or inducers should be avoided.

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[a] Noxafil® (posaconazole), NDAs 022003, 205053, 205596 – Approved Product Label. Drugs@FDA Database. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022003s018s020,0205053s002s004,0205596s001s003lbl.pdf. Accessed: January 2016.

[b] Sporanox® (itraconazole), NDA 20083. Drugs@FDA Database. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020083s058,020657s033lbl.pdf. Accessed January 2016.

[c] Diflucan® (fluconazole), NDA 019949. . Drugs@FDA Database. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019949s060,020090s044lbl.pdf. Accessed January 2016.

[d] Vfend® (voriconazole), NDA 21266. Drugs@FDA Database. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021266s038,021267s047,021630s028lbl.pdf. Accessed January 2016.

[e] Vincristine sulfate, ANDA 71484. Drugs@FDA Database. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/071484s042lbl.pdf. Accessed January 2016.

[f] Marqibo® (vincristine sulfate liposome injection), NDA 202497. Drugs@FDA Database. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202497s000lbl.pdf. Accessed January 2016.

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/s/

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03/03/2016

JUSTIN A MATHEW
03/03/2016

RAJDEEP K GILL
03/03/2016
Drug use data has been cleared by data vendors.

KELLY Y CAO
03/03/2016

GRACE CHAI
03/03/2016

STEVEN C JONES
03/04/2016