



**Pediatric Focused Safety Review
Noxafil[®] (posaconazole)
Pediatric Advisory Committee Meeting
April 12, 2016**

**Amy M. Taylor, MD, MHS
Division of Pediatric and Maternal Health
Office of New Drugs/ ODE IV
Center for Drug Evaluation and Research
Food and Drug Administration**

Outline

- **Background Information**
- Pediatric Studies
- Drug Use Trends
- Safety
- Summary

Background Drug Information

Noxafil[®] (posaconazole)

- **Drug:** Noxafil[®] (posaconazole)
- **Formulations:** oral suspension (9/2006); delayed-release tablets (11/2013); injection (3/2014)
- **Sponsor:** Merck Sharp Dohme
- **Original Market Approval:** September 15, 2006 (oral suspension)
- **Therapeutic Category:** antifungal agent
- Approval of the delayed-release tablets initiated this safety review.

Background Drug Information, continued

Noxafil[®] (posaconazole)

Indications

- Prophylaxis of invasive *aspergillus* and *candida* infections
 - In patients who are at high risk of developing these infections
 - In severely immunocompromised patients
- Treatment of oropharyngeal candidiasis (OPC), including OPC refractory to itraconazole and/or fluconazole
- The safety and effectiveness of posaconazole in pediatric patients below the age of 13 years have not been established.
- The safety and effectiveness of Noxafil injection in pediatric patients below the age of 18 years of age have not been established.

Background Drug Information, continued

Noxafil[®] (posaconazole)

Safety labeling

Contraindications (section 4)

- Known hypersensitivity to posaconazole or other azole antifungal agents
- Contraindicated with sirolimus
- Contraindicated with CYP3A4 substrates that prolong the QT interval
- Contraindicated coadministration with HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4
- Contraindicated with use of ergot alkaloids

Background Drug Information, continued

Noxafil[®] (posaconazole)

Safety labeling continued

Warnings and Precautions (section 5)

- Arrhythmias and QT prolongation
 - Associated with prolongation of the QT interval and cases of torsades de pointes have been reported
- Renal impairment
 - Variable exposure with delayed-release tablets and oral suspension.
 - Injection should be avoided in patients with moderate or severe renal impairment unless an assessment of the benefit/risk to the patient justifies the use.
- Hepatic toxicity
 - Hepatic reactions such as mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and/or clinical hepatitis have been reported in clinical trials.

Background Drug Information, continued

Noxafil[®] (posaconazole)

Safety labeling continued

Warnings and Precautions (section 5) continued

- Calcineurin-inhibitor drug interactions
 - Increase in whole blood trough concentrations of cyclosporine and tacrolimus
- Use with midazolam
 - Increases midazolam plasma concentrations by approximately 5-fold

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Pediatric Studies

Noxafil[®] (posaconazole)

- Approval of posaconazole delayed-release tablets was based on bridging studies in adults which matched bioavailability and PK of delayed release tablets with the previously marketed suspension.
- Use of posaconazole oral suspension and delayed-release tablets in children is supported by evidence from adequate and well-controlled studies in adults as well as pharmacokinetic, safety, and bioavailability studies in adults.
- No new pediatric studies were conducted to support approval of posaconazole delayed-release tablets in pediatric patients.

Pediatric Studies Continued

Noxafil[®] (posaconazole)

Previously conducted pediatric studies

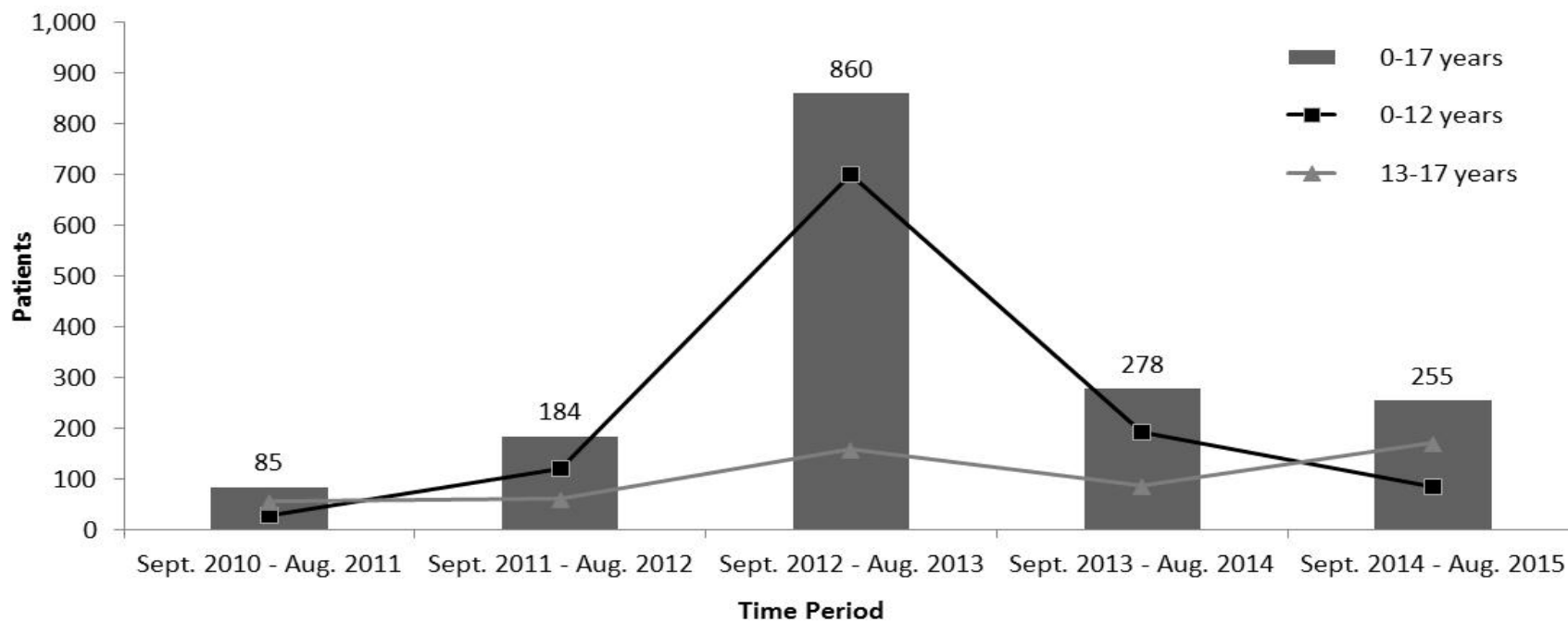
- Twelve patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) of posaconazole oral suspension for prophylaxis of invasive fungal infections. Safety profile appears similar to adults. The mean steady-state average posaconazole concentration was similar to adults.
- Sixteen patients 8 to 17 years of age were treated with 800 mg/day (400 mg twice a day or 200 mg four times a day) of posaconazole oral suspension in a study for another indication. The mean steady-state average posaconazole concentration was similar to adults.

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Pediatric Drug Utilization: Noxafil® (posaconazole)¹

Nationally Estimated Number of Pediatric Patients (0-17 years) Who Had A Hospital discharge Billing for Posaconazole from U.S. Non -Federal Inpatient and Outpatient Hospital settings, September 2010 through August 2015



¹Source: IMS Health, IHCareUS. September 2010 through August 2015. Extracted December 2015.

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Number* of Adult and Pediatric FDA Adverse Event Reporting System (FAERS) Cases with Posaconazole (September 15, 2006 through August 31, 2015)

	All reports (US)	Serious [†] (US)	Deaths (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; cases 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

Selection of Pediatric FAERS Cases

Total pediatric reports with a serious outcome reviewed (n=90)
– Pediatric reports with the outcome of death (n=18)

Excluded Reports (n=56)*

- Serious, labeled adverse events (n=33)
- Duplicates (n=22; including 5 deaths)
- Lack of temporal association (n=1)

Pediatric Case Series (n=34)

(including 13 deaths)

* These 56 reports were reviewed and excluded from case series for the stated reasons, including 33 reports associated with non-fatal, labeled adverse events.

Characteristics of Pediatric Case Series Noxafil[®] (posaconazole)

Characteristics of Pediatric Case Series with Posaconazole (N=34)

Age	0 - <2 years	1
	2 - <13 years	21
	13 - 17 years	12
Formulation	oral suspension	27
	delayed-release tablet	2
	Injection	1
	oral suspension and injection	1
Reported Indication*	Treatment	21
	Prophylaxis	10
	Prophylaxis and treatment	1
Serious Outcome [†]	Other	22
	Hospitalized	13
	Death	13
	Life-threatening	3
	Disability	1

* 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.

Fatal Pediatric Cases Noxafil® (posaconazole) (n=13)

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.

One example case:

- A 10 year old female with aplastic anemia developed invasive fungal infection. Two weeks after the start of antifungal treatment, she was started on posaconazole oral suspension. She improved and received a hematopoietic stem cell transplantation which failed. She received a second transplantation. Six weeks after the second transplant, she developed a disseminated adenovirus infection which led to her death. Death was attributed to the disseminated adenovirus infection and multi-organ failure.

Drug Interaction Adverse Events Noxafil[®] (posaconazole) (n=10)*

- Drug Interaction (n=10 including 1 fatal case – adverse event was not associated with death)
- Vincristine and posaconazole
 - Age range: 3-12 years
 - Oral suspension (n=10)
 - Reported adverse event
 - Drug interaction (n=5)
 - Paralytic ileus (n=3)
 - Inappropriate antidiuretic hormone secretion (SIADH) (n=3)
 - Brain edema (n=2)
 - Constipation (n=2)
 - Peripheral neuropathy (n=2)

*Some cases have more than one associated adverse event.

Drug Interaction Adverse Events Noxafil® (posaconazole) (n=10)

Vincristine - posaconazole drug interaction

- Posaconazole is a strong inhibitor of CYP3A4 and is labeled for a potential drug interaction with vincristine.
- Posaconazole can increase plasma concentrations of vincristine.
- Vincristine is labeled for neurologic toxicity, constipation, bowel obstruction, and SIADH.
- Vincristine is labeled for caution with use of posaconazole and other strong CYP3A inhibitors.

Serious Non-Fatal Unlabeled Adverse Events continued Noxafil® (posaconazole) (n=11)*

With the following adverse events causality could not be determined due to limited clinical details or case was confounded by underlying disease or concomitant medications

- Pancreatitis (n=2)
- Seizure (n=2)
- Gamma-glutamyltransferase increased (n=1)
- Gastrointestinal hemorrhage (n=1)
- Hepatic fibrosis (n=1)
- Hypertriglyceridemia (n=1)
- Hearing impaired (n=1)
- Memory impairment (n=1)
- Face edema (n=1)
- Hypoproteinemia (n=1)
- Proteinuria (n=1)
- Toxic encephalopathy (n=1)
- Tremor (n=1)

*Some cases have more than one associated adverse event.

Summary of Safety Review

Noxafil[®] (posaconazole)

- This concludes the pediatric focused safety review of FAERS reports.
- Safety signal of posaconazole – vincristine drug interaction
- FDA is evaluating this safety signal to determine if, and how, labeling may be modified, and will provide a report to the PAC at a future meeting.
- Following this evaluation, FDA recommends continuing routine, ongoing post-marketing safety monitoring.
- Does the committee concur?

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John Alexander, MD, MPH
Ethan D. Hausman, MD
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OSE

Timothy Jancel, PharmD, BCPS
LCDR Justin Mathew, PharmD
Kelly Cao, PharmD
Rajdeep Gill, PharmD
S. Christopher Jones, PharmD, MS, MPH
LCDR Grace Chai, PharmD

OPT

Judith Cope, MD, MPH
Robert "Skip" Nelson, MD, PhD
Amy Odegaard, MPH
Pam Weinel, MS, MBA, RN
LCDR Kenneth Quinto, MD, MPH