OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	22-003/SDN542
Submission Date(s):	March 10, 2016
PUDFA date	September 10, 2016
Drug	Posaconazole
Product/Formulation/Strength(s)	Noxafil (Posaconazole injection 18 mg/mL, delayed-release tablets 100 mg, and oral suspension 40 mg/mL)
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip Colangelo, Pharm D, Ph D
OCP Division	DCP4
OND Division	DAIP
Applicant	Merck
Submission Type	Labeling Supplement
Approved indication	*Injection, delayed-release tablets, and oral suspension* - prophylaxis of invasive Aspergillus and Candida infections in patients, (b) (4) who are at high risk of developing these infections due to being severely immunocompromised, such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy. *Oral suspension* - treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole.

Dose and Administration

Indication	Dose and Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	**Injection*:** Loading dose: 300 mg Noxafil injection intravenously twice a day on the first day. Maintenance dose: 300 mg Noxafil injection intravenously once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.1) **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. (2.2) **Oral Suspension‡:** 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.3)
Oropharyngeal Candidiasis (OPC)	**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. (2.3)
OPC Refractory (rOPC) 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. (2.3)

1. EXECUTIVE SUMMARY

NOXAFI® (posaconazole) oral suspension was approved in 2006 for the prophylaxis of invasive Aspergillus and Candida infections and the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. Posaconazole oral suspension is not approved for use in patients 13 years of age and younger.

The labeling supplement includes revisions to subsections **8.4, USE IN SPECIFIC POPULATIONS**, **Pediatric Use** *and*; **12.3, CLINICAL PHARMACOLOGY**, **Pharmacokinetics** of the NOXAFIL® United States Prescribing Information (USPI).

To support the labeling supplement, the Applicant provided a pediatric clinical study report (P03579/P032) titled "*Phase 1B study of the safety, tolerance, and pharmacokinetics of oral posaconazole in immunocompromised children with neutropenia*". The study was terminated early based on pharmacokinetic analysis demonstrating that the PK exposure target (90% of subjects achieving steady state C_{avg} of 500 -< 2500 ng/mL) was not met. In this study of 136 neutropenic pediatric patients 11 months to less than 18 years treated with posaconazole oral suspension, 70 subjects were evaluable for PK analyses at Day 7 (steady state), and only 50 % of those subjects (30% -80%, depending on the dosing cohort, *see Table below*) achieved steady state C_{avg} of 500 -< 2500 ng/mL.

Distribution of C_{avg} by Dose and Age Group at Day 7

Dose	Age Group	N	Cavg (ng/mL)				
			< 200	200 - <500	**500 - <2500**	2500 - <3650	>3650
12 mg/kg/day divided BID	2 to < 7 years	16	19% (3/16)	44% (7/16)	**31% (5/16)**	6% (1/16)	0
	7 to < 18 years	14	14% (2/14)	21% (3/14)	**65% (9/14)**	0	0
18 mg/kg/day divided BID	2 to < 7 years	12	25% (3/12)	25% (3/12)	**50% (6/12)**	0	0
	7 to < 18 years	12	8% (1/12)	25% (3/12)	**50% (6/12)**	8% (1/12)	8% (1/12)
18 mg/kg/day divided TID	2 to < 7 years	5	20% (1/5)	20% (1/5)	**60% (3/5)**	0	0
	7 to < 18 years	10	20% (2/10)	0	**80% (8/10)**	0	0
12 mg/kg/day divided TID	3 months to < 2 years	1	0	100% (1/1)	0	0	0

Numbers in parenthesis = (Number of subjects in category/Total number of subjects)
Numbers in **bold** = target C_{avg} range (500 - <2500 ng/mL) for ~90% of subjects

(b) (4)

- 28-3: Deferred pediatric study under PREA for the prophylaxis of invasive Aspergillus and Candida infections in patients, ages 2 to 12 year of age, who are at high risk of developing these infections. (Same as Written Request [WR] Study 2A or 2B).

1.1. Recommendation

The reviewer's revision to the proposed label changes (see Section **2**. below) needs to be conveyed to the sponsor.

(b) (4)

2. LABELING RECOMMENDATIONS

Sponsor Proposed Revisions in red and/or ~~strikethrough~~

Clinical Phaermacology Revisions noted in [ ] as bold font and yellow highlight, and/or ~~strikethrough~~

8.4 Pediatric Use

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

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). ~~In a study of 136 neutropenic pediatric patients 11 months to less than 18 years treated with posaconazole oral suspension,~~ (b) (4) ~~(12.3)].~~

[FDA revision: In a study of 136 neutropenic pediatric patients 11 months to less than 18 years treated with posaconazole oral suspension, the exposure target of steady-state posaconazole Cavg between 500 ng/mL and less than 2500 ng/mL was attained in approximately 50% of pediatric patients, instead of the pre-specified 90% of patients.]

(b) (4)

[FDA: proposed deletion accepted]

(b) (4)

[FDA: Sponsor proposed deletion accepted]

12. 3 Pharmacokinetics

(b) (4)

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/s/

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07/18/2016

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07/18/2016