NDA #	22-003; Suppl. 21; SDN 542.
Submission Date(s)	3/10/2016
Drug	Posaconazole
Trade Name	Noxafil®
Clinical Reviewer	Elizabeth O'Shaughnessy, M.D.
Acting Clinical Team Leader	Yuliya Yasinskaya, M.D.
Division	DAIP
Applicant	Merck
Relevant IND(s)	51,662
Submission Type	Labeling Supplement
Formulation, Strength(s)	Oral suspension 40 mg/mL
Indications	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. (2) The treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole**.**
Dosage and Administration	Prophylaxis of invasive *Aspergillus* and *Candida* infections: 200 mg TID. Treatment : Oropharyngeal Candidiasis: Loading dose of (b) (4) mg QD, then 100 mg QD for 13 days Refractory Oropharyngeal Candidiasis: 400 mg BID with a meal or with a nutritional supplement in patients who cannot tolerate a full meal

Introduction

Posaconazole (NOXAFIL®) 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 older. The Applicant submitted a labeling supplement on 3/10/16 which included revisions to subsection 8.4, USE IN SPECIFIC POPULATIONS, Pediatric Use and subsection 12.3, CLINICAL PHARMACOLOGY, Pharmacokinetics of the NOXAFIL® United States Prescribing Information (USPI).
In accordance with the Division's recommendation, the Applicant deleted the final two paragraphs in subsection 8.4 and included a brief summary of the results of the completed pediatric study, P03579/P032 entitled "*A Phase 1B study of the safety, tolerance, and pharmacokinetics of oral posaconazole in immunocompromised children with neutropenia*". Section 12.3 was also updated with a study description and a table of pharmacokinetic data (see Table 17 below) from Study P03579/P032.

(b) (4)

(b) (4)

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

Clinical Review of Proposed Labeling Revisions

The Applicant's proposed labeling revisions in subsections 8.4 and 12.3 are highlighted in track changes.

USE IN SPECIAL POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Noxafil injection in pediatric patients below the age of 18 years of age has not been established. Noxafil injection should not be used in pediatric patients because of nonclinical safety concerns *[see Nonclinical Toxicology (13.2)]*.

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

A total of 12 patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) of posaconazole oral suspension for prophylaxis of invasive fungal infections. The safety profile in these patients <18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these pediatric patients, the mean steady-state average posaconazole concentration (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)

(b) (4)

(b) (4)

CLINICAL PHARMACOLOGY

Subsection 12.3 Pharmacokinetics

Table 16: The Mean (%CV) [min-max] Posaconazole Steady-State Pharmacokinetic Parameters in Patients Following Oral Administration of Posaconazole Oral Suspension 200 mg TID and 400 mg BID

Dose*	Cavg (ng/mL)	AUC† (ng·hr/mL)	CL/F (L/hr)	V/F (L)	$t_{½}$ (hr)
200 mg TID‡ (n=252)	1103 (67) [21.5-3650]	ND§	ND§	ND§	ND§
200 mg TID¶ (n=215)	583 (65) [89.7-2200]	15,900 (62) [4100-56,100]	51.2 (54) [10.7-146]	2425 (39) [828-5702]	37.2 (39) [19.1-148]
400 mg BID# (n=23)	723 (86) [6.70-2256]	9093 (80) [1564-26,794]	76.1 (78) [14.9-256]	3088 (84) [407-13,140]	31.7 (42) [12.4-67.3]

Cavg = the average posaconazole concentration when measured at steady state
* Oral suspension administration
† $AUC_{(0\text{-}24\ hr)}$ for 200 mg TID and $AUC_{(0\text{-}12\ hr)}$ for 400 mg BID
‡ HSCT recipients with GVHD
§ Not done
¶ Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes
# Febrile neutropenic patients or patients with refractory invasive fungal infections, Cavg n=24
The variability in average plasma posaconazole concentrations in patients was relatively higher than that in healthy subjects.

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

(b) (4)

Clinical Reviewer's Comments / Recommendations

Study P03579/P032 was stopped early because it failed to meet its primary objective, i.e. ~90% subjects who were administered posaconazole suspension would reach steady-state Cavg between 500 ng/mL and 2500 ng/mL. This information should be clearly reflected in the label and the clinical reviewer has the following recommendations regarding the Applicant's proposed labeling changes:

1) Revise the Applicant's proposed wording in subsection 8.4 as follows: *"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 subjects instead of the pre-specified 90% of patients."*

2) In subsection 8.4, the inclusion of the age range, "birth to 12 years" is acceptable. The Sponsor deleted the final two paragraphs in section 8.4 as requested by the Division.

3) Delete (b) (4)

4) (b) (4) .

Note: The clinical recommendations are similar to the clinical pharmacology reviewer's recommendations. Please see review by Yongheng Zhang, Ph.D.

Comments to the Applicant

1) We recommend that you revise the wording in subsection 8.4 to indicate that Study P03579/P032 did not meet the pre-specified exposure target. For example,

"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 subjects instead of the pre-specified 90% of patients (b) (4)

2) We recommend that you remove the description o (b) (4)

3 (b) (4).

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/s/

ELIZABETH M OSHAUGHNESSY
07/18/2016

YULIYA I YASINSKAYA
07/20/2016