# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205596Orig1s000

# CROSS DISCIPLINE TEAM LEADER REVIEW

# CROSS DISCIPLINE TEAM LEADER REVIEW

| | |
|---|---|
| **Date** | February 24, 2014 |
| **From** | Philip M. Colangelo, Pharm.D, Ph.D |
| **Subject** | Cross Discipline Team Leader Review |
| **NDA #** | 205-596 |
| **Applicant** | Merck, Sharpe, and Dohme, Corp. |
| **Date of Submission** | September 13, 2013 |
| **PDUFA Goal Date** | March 13, 2014; Priority Review |
| **Proprietary Name / Established (USAN) names** | NOXAFIL® (Posaconazole) Injection |
| **Dosage forms / Strength** | Posaconazole intravenous solution 18 mg/mL (300 mg/vial) |
| **Proposed Indication(s)** | Prophylaxis of invasive *Aspergillosis* and *Candida* infections in patients 18 years of age and older |
| **Recommended Action:** | Approval |

## 1. Introduction

Merck, Sharpe, and Dohme, Corp. submitted an NDA application for Noxafil® Injection (Posaconazole intravenous solution 18 mg/mL). Posaconazole (POS) was developed initially as an oral suspension and subsequently approved in 2006 under NDA 22-003 (Schering-Plough Pharmaceuticals) for the prevention of invasive fungal infections (IFIs) in immunocompromised patients 13 years of age and older, specifically, neutropenic patients under treatment for acute myelogenous leukemia (AML) or myelodysplasia (MDS), as well as hematopoietic stem-cell transplant (HSCT) patients with graft versus host disease (GVHD). Noxafil delayed release oral tablet was recently approved in November 2013 under NDA 205-053 for the same indication.

Although the oral formulations of POS (i.e., Noxafil Delayed Release Tablets and Oral Suspension) are effective to prevent IFIs, the use of POS is however limited by the lack of an intravenous formulation for patients who are unable to take an oral medication. To meet the needs of these patients, the sponsor developed an intravenous formulation of POS, and the NDA was granted a priority review. The proposed indication for Noxafil Injection in this NDA is similar to that of both the oral suspension and the delayed release, except for the age limit, i.e., Noxafil Injection is indicated for the prophylaxis of invasive *Aspergillosis* and *Candida* infections in patients 18 years of age and older, who are at high risk of developing these IFIs due to being severely immunocompromised, such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

The clinical program for Noxafil Injection was designed to demonstrate comparable systemic PK exposure and safety among similar patient populations for which the POS Oral Suspension has already been approved (see above). The PK exposure target was based upon the range of POS systemic exposures achieved and the exposure-response relationship established in the earlier efficacy and safety studies of POS Oral Suspension. At the time of the NDA submission for the Oral Suspension, both the FDA and the previous sponsor (Schering-Plough) had agreed upon the range of PK target exposures for posaconazole to achieve an adequate level of efficacy (i.e., prevention of break-through IFIs) and safety. In this current NDA submission, the sponsor conducted a Phase 1B/3 safety, tolerability, and PK Study P05525 that showed the proposed dosage regimen of Noxafil Injection (i.e., Loading Dose: 300 mg BID on Day 1; Maintenance Dose: 300 mg QD on Day 2 and thereafter, given by slow 90-minute infusion via a central venous line) provided systemic PK exposure to POS within this pre-defined target PK exposure range, without safety issues, in patients with AML and in HSCT recipients, indicating that the proposed dosage regimen of Noxafil Injection is acceptable for the prophylaxis of invasive fungal infections.

## 2. Background

Posaconazole is a triazole antifungal agent available as an immediate release oral suspension or a recently approved delayed release oral tablet. POS blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. The resulting accumulation of methylated sterol precursors and depletion of ergosterol within the cell membrane weakens the structure and function of the fungal cell membrane. This process may be responsible for the antifungal activity of posaconazole.

The proposed indications of Noxafil Oral Suspension and Delayed Release Tablets are prophylaxis of invasive aspergillus and candida infections in patients 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

**Proposed dosage and administration for Noxafil Injection**
**Indication:**
Prophylaxis of invasive *Aspergillosis* and *Candida* infections in patients 18 years of age and older
**Dosage Regimen and Duration of Therapy:**
Loading Dose: 300 mg twice a day (BID) on the first day (Day 1) given as a slow 90-minute infusion via a central venous line
Maintenance Dose: 300 mg once a day (QD) on Day 2 and thereafter given as a slow 90-minute infusion via a central venous line
Duration of therapy is based on recovery from neutropenia or immunosuppression.

## 3. CMC/Device

**Drug Substance**

As per the Chemistry / Quality review of Xuhong Li, Ph.D, the majority of the drug substance information for Noxafil Injection was referenced to the approved NDA 22-003 for Noxafil Oral Suspension. For POS IV solution, the applicant uses the same drug substance approved for POS oral suspension and delayed release tablets, with bacterial endotoxins and microbiological examination

added to control the drug substance as parenteral grade. The synthesis and characterization of POS is documented within NDA 22-003 for Noxafil Oral Suspension.

POS drug substance has low aqueous solubility (no more than 1µg/mL in an aqueous media with pH higher than 5) and two pKa values at (b) (4). The (b) (4) of the drug substance presented a challenge for the development of the Noxafil injection formulation that was overcome by (b) (4). The use of beta-cyclodextrin for Noxafil Injection is similar to that of other intravenous azole formulations that are already FDA approved (i.e., Itraconazole, Voriconazole).

## Drug Product

Noxafil Injection, also known as Posaconazole Concentrate Solution for Infusion, contains 18 mg POS per mL. The drug product is a single-dose unpreserved sterile solution that is formulated with Betadex Sulfobutyl Ether Sodium (SBECD) as (b) (4), Disodium Edetate (EDTA) as (b) (4) and hydrochloric acid/sodium hydroxide for pH adjustment. The target deliverable volume (label claim) is 16.7 mL, corresponding to 300 mg/vial. The drug product is to be diluted in 0.9 % saline or 5% dextrose solution prior to administration by IV infusion.

Shelf-life stability and compatibility studies for Noxafil injection were acceptable, as per Dr. Li. However, in terms of drug product specifications, Dr. Li noted that several tests, including a pH test, have not been proposed to be included in the drug product shelf life specification. The proposed drug product is an intravenous solution and pH is one of the important quality attributes for this dosage form. Therefore, the Agency recommended the applicant to include pH testing as part of both release and shelf life specification for the drug product. On February 20, 2014, the applicant agreed to include the pH test in both release and stability specifications, and stated that the revised documents (the drug product specification and stability protocols) will be submitted to the NDA by February 25, 2014. The revised specification will be documented in DARRTS along with the EES recommendation for this NDA (once received from the Office of Compliance) via an addendum to this review.

In summary, the CMC / Quality reviewer finds that this NDA has generally provided sufficient information on raw material controls, manufacturing processes and process controls, test methods, specifications, batch data and stability data for assuring consistent product quality of the drug substance and drug product. In addition, the product quality microbiology review (dated February 14, 2014, in DARRTS) has recommended approval of this NDA from the quality microbiology viewpoint. However, there are labeling issues that are still pending and a site recommendation from the Office of Compliance has not been made as of the date of the CMC review. Therefore, from the CMC perspective, this NDA is not recommended for approval at this time until an acceptable recommendation for all manufacturing facilities is received from the Office of Compliance. As CDTL reviewer, I concur with this assessment. Refer to the CMC / Quality review by Xuhong Li, Ph.D dated February 20, 2014 for more information.

## Biopharmaceutics Assessment

Since the drug product in this NDA, Noxafil Injection, will be given intravenously there are no Biopharmaceutics issues, and no review was conducted.

## 4. Nonclinical Pharmacology/Toxicology

As per the review of Owen McMaster, Ph.D, the Pharmacology and Toxicology studies submitted to support Noxafil Injection represent an abbreviated toxicology program. Many nonclinical Pharmacology and Toxicology studies of posaconazole were conducted under the respective NDAs that supported the approval of Noxafil Oral Suspension and Delayed Release Tablets. Some of the data from these studies are described in the approved labeling for both formulations.

The identical posaconazole drug substance approved for the Noxafil Oral Suspension formulation is used in the IV solution formulation. Thus, there are no outstanding concerns regarding impurities or degradants associated with the Noxafil Injection drug product. All impurities have been qualified or are controlled to within acceptable limits. Dr. McMaster concluded that the toxicity profile of Noxafil Injection is similar to the other oral posaconazole formulations except that the SBECD excipient in Noxafil Injection results in kidney effects that are not found in the oral formulations that do not contain SBECD. In addition, Noxafil Injection is associated with increased ventricular volumes in the brains of very young dogs (2 to 8 weeks of age) when dosed at 10 mg/kg/day for 6 weeks. Noxafil Injection is therefore being restricted to patients 18 years of age and older. There are no nonclinical data that would preclude the approval of Noxafil Injection for use as prophylaxis of invasive *Aspergillus* or *Candida* infections in patients, 18 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised. As CDTL reviewer, I concur with this assessment. Refer to the Nonclinical Pharmacology / Toxicology review by Owen G. McMaster, Ph.D dated February 27, 2014 for more information.

## 5. Clinical Pharmacology

As per the Clinical Pharmacology review of Seong Jang, Ph.D, the main Clinical Pharmacology issue that needed to be addressed in this NDA for Noxafil Injection was the adequacy of the proposed Noxafil Injection dosage regimen to attain the same pre-defined target PK exposure range that was shown to be associated with acceptable efficacy and safety for Noxafil Oral Suspension.

The proposed dosing regimen of Noxafil Injection for the prophylaxis of IFIs is a loading dose of 300 mg BID on Day 1, then 300 mg QD on Day 2, and thereafter. The Phase 1B/3 study (Study P05520) was designed to demonstrate that this dosing regimen will provide POS exposure within the pre-defined target exposure range in patients 18 years of age and older with IFIs. The exposure target was determined based upon the range of exposures achieved with Noxafil Oral Suspension in the NFA safety and efficacy trials, as well as the exposure-response relationship found in earlier controlled studies of Noxafil Oral Suspension:

•Mean steady-state POS Cmin ≥500 ng/mL or AUC ≥12,000 hr•ng/mL in at least 90% of subjects;
•Mean steady-state POS Cmin ≤2,500 ng/mL or AUC ≤59,000 hr•ng/mL;
•No subject with a mean steady-state POS Cmin >3,750 ng/mL or with a steady-state AUC >90,000 hr•ng/mL.

In Study P05520, the steady state POS Cmin following administration of Noxafil Injection 300 mg QD fell within the pre-defined target exposure (Table 1). The steady state POS Cmin was ≥500 ng/mL in 92.7% of patients (190 out of 205 patients treated with 300 mg QD Noxafil injection); 7.3% (15/205) of patients had steady-state POS Cmin <500 ng/mL. The mean Cmin at steady-state in 205 patients treated with 300 mg QD Noxafil injection was ≤2,500 ng/mL (i.e., 1085 ng/mL). There was no patient with a steady state Cmin above 3,650 ng/mL. There was one patient with a steady state POS Cmin <200 ng/mL. Accordingly, the proposed dosage regimen for Noxafil injection is acceptable to the Clinical
Pharmacology review team for the prophylaxis of invasive fungal infections.

**Table 1.** Distribution of POS Cmin (ng/mL) measured at the earliest Day (i.e., after Day 3) in each patient after administration of 300 mg Noxafil Injection BID on Day 1, followed by 300 mg Noxafil Injection QD on Day 2 to high-risk patients fir IFIs (Study P05520: Cmin PK-evaluable population in Cohorts 2 and 3). Data are expressed as Cmin values at each percentile.

| N | Mean | SD | Min | 5th[a] | 10th[a] | 25th[a] | Median | 75th[a] | 90th[a] | 95th[a] | Max[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 205 | 1085 | 446 | 180 | 412 | 544 | 777 | 1050 | 1340 | 1720 | 1920 | 2330 |

[a]: Percentiles

*Infusion via Central Venous Line*
Noxafil injection is to be administered via a central venous line based on local infusion-site reactions identified initially in preclinical studies and more definitively in the first clinical study in healthy volunteers (Study P04985). Infusion through a peripheral venous line over 30 min has been evaluated only as a single 300 mg dose in healthy volunteers. Multiple dosing via a peripheral venous line to healthy volunteers resulted in infusion site AEs, and discontinuation of the infusion.

In Study P05520 Noxafil injection was administered via a central venous line by slow intravenous infusion over 90 minutes. Accordingly, the labeling will recommend that Noxafil injection is to be given in the same manner as was done in Study P05520. If a central venous catheter is not available, Noxafil Injection may be administered through a peripheral venous catheter by slow intravenous infusion over 30 minutes only as a 300 mg single dose. Intravenous bolus administration of Noxafil injection has not been evaluated, and will not be recommended in the labeling.

*Renal Impairment*
Noxafil Injection contains the excipient (b) (4) sulfobutyl ether beta-cyclodextrin (SBECD), and plasma levels of SBECD are known to accumulate in subjects with renal impairment. Therefore, patients with moderate to severe renal impairment (CrCL <50 mL/min) were excluded from the Phase 1b/3 Study P05520 and no PK or safety data are available for use of Noxafil injection in patients with moderate to severe renal impairment. Therefore, the labeling will recommend to avoid use of Noxafil Injection in patients with moderate to severe renal impairment. This recommendation mirrors that for IV voriconazole (Vfend®), which also contains SBECD, and the approved labeling for Vfend for Injection recommends to avoid intravenous administration in patients with moderate to severe renal impairment (CrCL<50 ml/min). The total amount of SBECD in Noxafil Injection does not exceed that in the IV formulation of voriconazole.

The Clinical Pharmacology information provided by the applicant in this NDA submission for Noxafil Injection was deemed acceptable by the Clinical Pharmacology Reviewer, and the review of the data

submitted in this NDA supports the approval of Noxafil injection for prophylaxis of invasive fungal infections in patients 18 years of age and older. As CDTL reviewer, I concur with the Clinical Pharmacology assessments. Refer to the Clinical Pharmacology review by Seong Jang, Ph.D dated February 19, 2014 for further information.

## 6. Clinical Microbiology

No new clinical microbiology data were submitted with this application, and there were no sponsor proposed changes to the Microbiology section of the existing Noxafil Oral Suspension and Delayed Release Tablets labeling. As CDTL reviewer, I concur with this assessment. Refer to the Microbiology review by Lynette Berkley, Ph.D dated December 18, 2013 for further information.

## 7. Clinical Assessment

Study P05520 was a single-arm, uncontrolled, open-label, multicenter study of the safety, tolerability, and PK of Noxafil Injection used as prophylaxis in 268 adult patients aged 18 years and older with hematologic malignancies at high risk for IFIs. The duration of prophylaxis with Noxafil Injection will depend on the length of time a patient remains at risk for invasive fungal infections (IFIs). The dosing regimen of Noxafil Injection for the patients in Study P05520 who received the 300 mg dose (Cohorts 2 and 3) was 300 mg IV BID on Day 1, followed by 300 mg IV QD on Days 2 through 14. Patients in Cohort 2 were to then receive 14 days of 400 mg Noxafil Oral Suspension at 400 mg BID. For Cohort 3 patients, Noxafil Injection was given 300 mg IV BID on Day 1, followed by 300 mg IV QD for at least 5 days, followed by Noxafil Oral Suspension either at 200 mg TID or 400 mg BID to complete 28 days of treatment. In the 300 mg dose Cohorts the mean duration of therapy was 23 days. A total of 227 (96%) of subjects completed ≥ 5 days

As per the Clinical reviewer, Elizabeth O'Shaughnessy, MD, the study was reviewed primarily for safety and tolerability of Noxafil Injection in the target population of patients with hematologic malignancies at risk for IFI. This study was not statistically powered for efficacy; there was no primary efficacy endpoint. Survival outcome at Day 65 was a secondary efficacy endpoint. As per Dr. O'Shaughnessy's review, the survival rate at Day 65 (survival visit) was high at >90%. The incidence of breakthrough IFI in this trial was approximately 1% and was lower than previously reported in two randomized prophylaxis trials of posaconazole oral suspension.

Overall, Dr. O'Shaughnessy noted that Noxafil Injection was well tolerated when administered over 90 minutes via a central line, and it had an acceptable safety profile within the range of systemic POS exposures achieved in Study P05520. The safety data indicate that Noxafil injection has a similar safety profile to Noxafil Oral Suspension and Delayed Release Tablets. The most common adverse reaction associated with Noxafil Injection was diarrhea. Other reported adverse reactions, associated with the azole class of antifungal drugs, included hepatotoxicity with elevation of hepatic transaminases and hyperbilirubinemia, and QTc interval prolongation. Six (2%) of the patients had hepatic function test results that met the criteria for Hy's Law during treatment with Noxafil Injection. The attribution of adverse reactions including hepatotoxicity was confounded by symptoms related to

the patients' underlying hematologic malignancies and myelosuppressive drug regimens. There was one case of acute renal failure associated with Gram-negative sepsis. There was one case of asymptomatic QTc interval prolongation (QTc >500 msec) which led to discontinuation of study drug and resolved off study drug. There were no reports of adrenal insufficiency.

The Medical Officer recommends that Noxafil Injection be approved for the prophylaxis of invasive fungal (i.e., *Aspergillus* and *Candida*) infections in adults, 18 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised. As CDTL reviewer, I concur with this assessment. Refer to the Clinical review by Elizabeth O'Shaughnessy, MD dated February 27, 2014 for further information.

## 9. Advisory Committee Meeting

No Advisory Committee Meeting was held for this NDA.

## 10. Pediatrics

The sponsor (Merck) is requesting a waiver for pediatric patients < 2 years of age and a deferral for studies in pediatric patients > 2 to < 18 years of age. However, in a meeting that was held with DAIP and the Pediatric Review Committee (PeRC) on October 2, 2013, PeRC recommended that a waiver be granted for patients < 1 year of age, instead of < 2 years, because cases of hematological malignancies do occur in children between the ages of 1 to 2 years of age. When this recommendation was proposed to the sponsor in 2014, the sponsor stated that they had discussed the issue with investigators who reported that the incidence of acute malignancies in pediatric patients less than two years of age is very infrequent, and therefore antifungal prophylaxis is rarely used. The DAIP review team found this rationale to be acceptable and the Pediatric Research Equity Act (PREA) post marketing requirements (PMRs) were written accordingly to waive studies in pediatric patients < 2 years of age.

In their pediatric plan, the sponsor proposes to conduct the following study to evaluate the safety, tolerability, and PK of two new formulations of posaconazole in immunocompromised pediatric patients with known or expected neutropenia:

> **Study A (PMR 2132-1):** A trial to evaluate the PK, safety, and tolerability of two new formulations of posaconazole (i.e., IV solution, followed by sequential use of the new age-appropriate oral formulation) in immunocompromised pediatric patients with known or expected neutropenia between the ages of 2 to < 18 years of age.

The dosing regimens for the IV and new age-appropriate oral formulations in pediatrics will be determined based on attaining the same target POS PK exposure ranges (i.e, steady-state Cmin and steady-state AUC) as that which has already been agreed upon by DAIP and the sponsors for Noxafil Oral Suspension (Schering-Plough), Delayed Release Tablets (Merck), and Injection (Merck).

PeRC also recommended that an efficacy study (see **Study B** below) be requested if an appropriate pediatric dosage regimen cannot be determined for the IV and new age-appropriate oral formulations of POS in the PK **Study A** proposed by the sponsor.

> **Study B (PMR 2132-2):** A comparative, double-blind, randomized, multi-center study to evaluate the safety, efficacy, and tolerability of posaconazole (b) (4) for the prophylaxis of invasive fungal infections (IFIs) in pediatric patients with known or expected neutropenia between the ages of 2 to < 18 years.

As CDTL reviewer, I concur with this assessment by PeRC.

**11. Other Relevant Regulatory Issues**

There are no outstanding regulatory issues for this NDA application.

**12. Labeling**

The sponsor has modified the approved labeling for Noxafil Oral Suspension and Delayed Release Tablets to add information for Noxafil Injection in physician's labeling rule (PLR) format. As CDTL reviewer, I concur with the labeling revisions made by the sponsor and subsequent revisions made by the Division (DAIP).

**13. Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

  As the CDTL reviewer, I concur with the assessments made by the review team and recommend approval of this NDA 205-596 for Noxafil Injection.

- Risk Benefit Assessment

  Noxafil is currently marketed as an Oral Suspension and Delayed Release Tablets for the prophylaxis of invasive fungal infections (IFIs) in immunocompromised patients, specifically neutropenic patients undergoing treatment for acute myelogenous leukemia (AML) or myelodysplasia (MDS), as well as hematopoietic stem-cell transplant (HSCT) patients with graft-versus-host disease (GVHD). Although Noxafil Oral Suspension and Delayed Release Tablets are effective in the prevention of such IFIs, their use is limited by the lack of an intravenous formulation for patients who are unable to take an oral medication. To meet the needs of these patients, the sponsor has developed an intravenous formulation of POS. Overall, Noxafil Injection was well tolerated, and within the range of the pre-specified targeted systemic PK exposures that were observed in the open-label Phase 3 safety, tolerability, and PK Study P05520, there does not appear to be an association of higher posaconazole concentrations with a higher incidence of treatment-related adverse reactions following administration of Noxafil Injection. Noxafil Injection appears to have an acceptable safety profile that is similar to the safety profile reported for

the oral formulations of Noxafil. The potential benefit of Noxafil Injection in preventing life-threatening invasive fungal infections outweighs the risk of adverse reactions in severely immunocompromised patients. Overall, as the CDTL reviewer, I feel that the benefits of Noxafil injection outweigh the risks.

- Recommendation for Post-Marketing Risk Management Activities

  There are no recommendations for post-marketing risk management activities.

- Recommendation for Other Postmarketing Study Commitments

  The recommendations for post-marketing commitments for Noxafil Injection are the same as those for Noxafil Delayed Release Tablets (NDA 205-053), which is the development of Noxafil Injection and an acceptable oral formulation of POS for the prophylaxis of IFIs in pediatric patients at high risk for such infections. Please see **Section 10. Pediatrics**, page 7 of this CDTL Memo for more details.

- Recommended Comments to Applicant

  There are no comments for the applicant.

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

---

/s/

---

PHILIP M COLANGELO
03/18/2014