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RESEARCH**

APPLICATION NUMBER:

205596Orig1s000

SUMMARY REVIEW

Deputy Division Director Decisional Memo

Date	(electronic stamp)
From	Katherine Laessig, MD
Subject	Deputy Division Director Decisional Memo
NDA #	205-596
Applicant Name	Merck Sharpe & Dohme Corp.
Date of Submission	September 13, 2013
PDUFA Goal Date	March 13, 2014
Established (USAN) Name	Posaconazole, tradename Noxafil®
Dosage Forms / Strength	Posaconazole intravenous solution 18 mg/mL (300 mg/vial)
Approved Indications	Prophylaxis of invasive <i>Aspergillus</i> and <i>Candida</i> infections in patients 18 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 recipients with graft-versus-host disease or those with hematologic malignancies with prolonged neutropenia from chemotherapy
Recommended Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package including:	
Medical Officer Review	Elizabeth O'Shaughnessy
Statistical Review	Cheryl Dixon
Pharmacology Toxicology Review	Owen McMaster
Product Quality Reviews	Xuhong Li, Vinayak Pawar
Microbiology Review	Lynette Berkeley
Clinical Pharmacology Reviews	Seong Jang
CDTL Review	Philip Colangelo
Labeling Reviews	Aleksander Winiarski, Christine Corser, Sharon Williams

OND=Office of New Drugs
 CDTL=Cross-Discipline Team Leader

1.0 Background

Merck has submitted NDA 205-596 in support of a new formulation of posaconazole, 18 mg/mL intravenous solution. The proposed dose is a loading dose of 300 mg intravenously (IV) bid on Day 1, followed by 300 mg IV q d starting on Day 2 and

thereafter, given by a slow 90-minute infusion through a central venous line. Posaconazole is a member of the class of azole antifungal drugs that act via inhibition of the synthesis of ergosterol, a key component of the fungal cell membrane. Specifically, posaconazole inhibits the cytochrome P450 enzyme lanosterol 14 α -demethylase responsible for the conversion of lanosterol to ergosterol. 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.

Posaconazole was first approved as an oral suspension in 2006 under NDA 22-033 for the prevention of invasive fungal infections in immunocompromised patients 13 years of age and older, specifically neutropenic patients under treatment for acute myelogenous leukemia or myelodysplasia, as well as hematopoietic stem cell transplant patients with graft-versus-host disease. A delayed release tablet formulation was approved in November 2013 (NDA 205-053). Merck is seeking the same indication for the intravenous solution, however only in patients 18 years of age and older. The restriction to 18 years of age and older is due to findings of ventricular dilatation in young dogs, which is discussed in the nonclinical pharmacology/toxicology section below.

In support of this application, Merck has submitted a Phase 1/3B safety, tolerability, and PK study (Study P05525), as well as chemistry, manufacturing, and controls data to support the identity, strength, purity, and quality of the drug substance and drug product.

This memo will summarize important findings and conclusions by review discipline. Note there is no new clinical microbiology or efficacy information in this application. For further details, please refer to discipline specific reviews and the CDTL memo by Philip Colangelo, PharmD, PhD.

2.0 Product Quality

The adequacy of the chemistry, manufacturing, and control (CMC) information contained in this application has been reviewed by the product quality reviewer, Xuhong Li, and the product quality microbiology reviewer, Vinayak Pawar. They have concluded that the information provided by the applicant is generally sufficient to assure the identity, strength, purity, and quality of the drug. The Office of Compliance has made a final recommendation of acceptable for the manufacturing establishments filed in this NDA on February 27, 2014. Although Dr. Pawar recommends approval of this application, Drs. Li, Matecka, Madurawe, and Mikskiski do not because of particulates noted in some Noxafil infusion solutions, as will be described further below. For complete information,

please refer to Dr. Li's CMC review dated February 20, 2014 and the addendum dated March 13, 2014.

The applicant uses the same drug substance approved for posaconazole oral suspension for the posaconazole injection, with bacterial endotoxins and microbiological examination added to control the drug substance as parenteral grade. The majority of the drug substance information was referenced to the approved NDA for Noxafil® Oral Suspension. Posaconazole drug substance has a low aqueous solubility of no more than 1 mcg/mL in an aqueous media with pH higher than 5 and two pKa values of (b) (4). (b) (4) the excipient sulfobutyl ether beta-cyclodextrin (SBECD) was added. The use of beta-cyclodextrin is also found in other intravenous azole formulations that are FDA-approved, including itraconazole and voriconazole.

The drug product is a single-dose, unpreserved, sterile solution that is formulated with SBECD as noted above, disodium edetate (EDTA) as a (b) (4) and hydrochloric acid/sodium hydroxide for pH adjustment. The drug product manufacturing process involves (b) (4).

The drug product is sterilized by (b) (4) a 20 mL Type I glass vial and closed with bromobutyl rubber stopper and aluminum seal. The target deliverable volume (per the product label) is 16.7 mL, corresponding to 300 mg/vial. The target fill volume is controlled at (b) (4), which contains (b) (4) to ensure that there is enough drug product solution available for withdrawal from the vial for delivery. The drug product is to be diluted in 0.9% saline or 5% dextrose solution prior to administration by IV infusion.

The drug product specifications include the following attributes: description, color, identification, assay, degradation products, pH, particulate matter, volume of injection in container, bacterial endotoxins, and sterility. Although the applicant did not include a pH test in the application, Merck agreed to include the pH test as part of the release and shelf life specification for the drug product during the review cycle. Data provided in the NDA showed that Noxafil infusion solutions prepared in D5W and 0.9% NS frequently exceeded USP <788> limits for particulate matter in large volume injections, a potential safety issue. Notably, the applicant originally included the recommendation (b) (4)

(b) (4) In use compatibility studies showed that the posaconazole admixtures were stable for up to 120 minutes of infusion after 24 hour storage in admixture containers at room temperature and 5°C. (b) (4)

(b) (4) using the clinical studies (a 0.22 µm filter was

recommended); however, they submitted data on February 27, 2014 that reportedly demonstrated the absence of any particles since 2009. The applicant stated that the failed results in the original NDA were due to improper handling. However, the information provided was not determined to be sufficient to rule out particulate formation in Noxafil infusion solutions. But the data provided do demonstrate that when Noxafil infusion solutions are passed through an inline filter, post-catheter solutions meet USP<788> requirements for large volume parenteral solutions with no potency loss.

The clinical and CMC reviewers, including division and office management, met several times and had three teleconferences with the applicant to discuss the particulate issue and implications for use of posaconazole injection. An initial plan was to have the applicant copackage posaconazole injection with an inline filter. However, discussions with the applicant and members of CDER's Drug Shortage team that is comprised of a number of pharmacists indicated that this was not feasible as different hospitals may use IV infusion sets that might not be compatible with the filter. In addition, the applicant stated that it could take (b) (4) months for copackaging to be accomplished for marketing purposes. After further dialogue among the review team members, it was decided that posaconazole injection could be approved with labeling stating that Noxafil injection must be administered through a 0.22 micron polyethersulfone (PES) or polyvinylidene difluoride (PVDF) filter. In an addendum to the ONDQA primary review dated March 13, 2014, ONDQA continues to recommend that the filter should be copackaged with Noxafil injection, and the package insert and carton include prominent wording regarding the requirement for filter usage. Per CMC reviewers' recommendations to evaluate the potential for particulate matter formation and to determine whether further risk mitigation strategies are needed, the applicant has been asked and agreed to the following two PMCs:

1. Provide USP <788> test results using both Method 1 and Method 2 for the diluted infusion solutions of posaconazole injection in D5W and normal saline at drug product release and at annual stability test time points for 10 commercial batches of the drug product, Noxafil Injection, 300 mg.
2. Conduct and provide the results of a detailed root-cause analysis of the particulate formation reported in Section 3.2.P.2.6 of the NDA for infusion solutions of posaconazole in 5% Dextrose and normal saline. This analysis should include evaluation of conditions under which particulates can be formed, the potential causes for the observed precipitation, an evaluation of whether particulate matter is more likely to appear in infusion solutions of newly manufactured batches of posaconazole injection, and if "batch aging" is likely to reduce particulates. Use

both USP<788> Method 1 and Method 2 in your analysis. For particulates observed, identify the particulate matter.

The proposed 36 month shelf life for the drug product when stored under refrigeration ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$) is supported by the stability data provided. The drug product is stable when exposed to light for up to 30 days at ambient conditions and the secondary container box is able to protect the product from light under storage conditions.

Dr. Vinayak Pawar reviewed the product quality microbiology information for this application. He determined that the applicant has met regulatory expectations with regard to the test method, acceptance criteria, and verification of the suitability of use of the bacterial endotoxins and sterility tests that will be performed on the drug substance. In addition, regulatory expectations were met with respect to validation of the process to demonstrate container closure integrity of the primary packaging system, for validation of the sterilization process for the manufacturing equipment and process simulations in support of the (b) (4) manufacture of the drug product, the test methods, acceptance criteria, and the approved stability program to support the newly formulated drug product's microbiological quality throughout its shelf life.

3.0 Nonclinical Pharmacology/Toxicology

The nonclinical reviewer, Owen McMaster, found no nonclinical pharmacology or toxicology data that preclude the approval of Noxafil injection. Many nonclinical pharmacology and toxicology studies of posaconazole were conducted under the NDAs that supported approval of the delayed release tablets and the oral suspension.

The nonclinical data submitted with the current NDA included a one month monkey study, a three month dog study, and a six week study in juvenile dogs. In the one month monkey study, higher doses were associated with findings similar to those seen in previous posaconazole studies including findings in the adrenal glands of increased weight, single cell necrosis, lymphohistiocytic infiltrates, congestion, hemorrhage, edema, decreased vacuolation, and hyperplasia/hypertrophy of the zona fasciculata and atrophy of the zona reticularis and zona glomerulosa. Thyroid glands showed increased weight and increased colloid. Phospholipidosis was also observed. The NOAEL was 4 mg/kg/d. Although the exposure at the clinical dose is higher than the exposure at the NOAEL, the patients would only be exposed to about one-third the exposures associated with adverse effects in monkeys.

The six-week study in juvenile beagles revealed ventricular dilatation in posaconazole-treated animals at the end of dosing in 5/8 posaconazole-treated animals compared to 0/8 placebo treated animals and 0/8 vehicle treated animals. At the end of the five month

recovery period, 1/8 of the posaconazole treated animals and 1/8 placebo treated animals continued to have ventricular dilatation. The three month follow-up study was subsequently conducted in older dogs and used MRI to assess the effect of posaconazole on the lateral ventricle. In contrast to the study in younger dogs, treatment of older dogs with three months of posaconazole showed no statistically significant difference in ventricular volume when compared to control animals. The applicant proposed labeling to address these findings, and limitation of the indicated population to 18 years of age and older. Dr. McMaster finds this approach acceptable.

4.0 Clinical Pharmacology

The clinical pharmacology reviewer, Seong Jang, finds that from a clinical pharmacology perspective, the data provided are acceptable to support the approval of posaconazole tablets. The proposed dosing regimen is a loading dose of 300 mg bid on the first day, then 300 mg qd thereafter. This dosing regimen was evaluated in a Phase 1B/3 study (Study P05520) designed to demonstrate that this regimen provides a posaconazole exposure that is in the range of exposures achieved with the oral suspension product in safety and efficacy trials, as well as the exposure response relationship found in earlier controlled studies of Noxafil oral suspension.

The exposure targets are:

- Mean steady state C_{\min} of approximately 1200 ng/mL, with at least 90% of the subjects between 500 ng/mL and 2500 ng/mL
- No subject with C_{\min} at steady state above 3650 ng/mL
- No subject with C_{\min} at steady state below 200 ng/mL

In general, the steady state C_{\min} following Noxafil injection 300 mg qd fell within the predefined target exposure. The steady state C_{\min} was ≥ 500 ng/mL in 92.7% of subjects (190/205); 7.3% of subjects had a steady state C_{\min} was < 500 ng/mL. The mean steady state C_{\min} was ≤ 2500 ng/mL (i.e. 1085 ng/mL). There was no patient with a steady state C_{\min} of > 3650 ng/mL. There was one subject with a steady state C_{\min} of < 200 ng/mL. According, the proposed dose and regimen of Noxafil injection is supported by the data from Study P05520.

Noxafil injection is labeled to be delivered via a central venous line based on local infusion site reactions identified initially in nonclinical studies and in the first clinical study in healthy volunteers. Multiple dosing via a peripheral line resulted in infusion site

adverse reactions. In study P05520, Noxafil injection was administered via a central venous line by slow infusion over 90 minutes and is labeled as such.

Since Noxafil injection contains the excipient SBECD and plasma levels of this cyclodextrin are known to accumulate in subjects with renal impairment, no data are available for use of Noxafil in patients with moderate to severe renal impairment and will be labeled accordingly.

5.0 Clinical Safety

The medical officer, Elizabeth O'Shaughnessy, recommends approval of posaconazole injection for the current indication and the proposed dose and regimen. Her review evaluated the safety findings in 72 healthy volunteers and 268 subjects with hematologic malignancies at risk for invasive fungal infections. Posaconazole 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 exposures achieved in Study P05520. The safety data indicate that it has a similar safety profile to the oral suspension and delayed release tablets.

The survival rate at Day 65 was high at >90%. The incidence of invasive fungal infections was approximately 1%. There were two deaths in cohort (subjects received 200 mg IV once or placebo IV) and one death in the 200 mg multidose cohort 1. In the 300 mg multidose cohorts, there were 19 (8%) deaths. The most common cause of death was sepsis/septic shock. One patient developed acute liver failure and died; posaconazole IV could have contributed to the hepatic injury however, it is more likely that death was due to Gram negative sepsis and progression of underlying acute myeloid leukemia.

The most common adverse reaction was diarrhea. Other reported adverse reactions included hepatotoxicity and QTc prolongation. Six patients had liver parameters that met the criteria for Hy's Law during treatment with posaconazole. However, attribution of these adverse reactions was confounded by comorbidities and administration of concomitant medications. There was one case of asymptomatic QT prolongation (>500 msec) leading to discontinuation of study drug. The QT prolongation resolved off study drug.

Within the range of exposures studied in P05520, there doesn't appear to be an association between higher posaconazole exposures and adverse drug reactions. Therefore, posaconazole has an acceptable safety profile that is similar to the oral formulations and the benefit of prevention of invasive fungal infections outweighs the risk of adverse reactions in the severely immunocompromised patient population.

Because of the particulates seen in some of the posaconazole admixtures, Dr. O'Shaughnessy concurs with the CMC reviewers that the use of an inline filter should be recommended in the package insert. I concur with this recommendation as well.

6.0 Pediatrics

The applicant requested a waiver for pediatric patients < 2 years of age and a deferral for studies in patients > 2 to < (b) (4) years of age. The Division presented the plan to the Pediatric Review Committee on January 29, 2014. PeRC recommended that the same PMRs for the posaconazole tablet would be sufficient for the intravenous solution. Therefore, the following pediatric required studies will be included in the action letter:

1. 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 and < 18 years of age.

If the trial for PMR 2132-1 fails to find a pediatric dosing regimen that provides pediatric patients with exposures similar to those in adult patients, then the following efficacy trial (PMR 2132-2) will be required, provided a safe and tolerable dosage regimen can still be identified. If the trial for PMR 2132-1 is successful in determining a pediatric dosing regimen, then the applicant may request release from PMR 2132-2.

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

7.0 Other Regulatory Issues

This application was not presented to the Anti-Infective Advisory Committee as it is not an NME and there were no major issues requiring advisory committee input.

The package insert, carton and container labeling have been reviewed by SEALD, OPDP, DMEPA, and the patient labeling group and their comments incorporated, as appropriate.

The Office of Scientific Investigations concluded that an inspection was not necessary as Study P05520 was conducted at approximately the same time as Study P05615 that was found to be acceptable for the support of the oral suspension. In addition, the same assay validations were used and OSI has inspected (b) (4) on several previous

occasions without noting any significant observations. Therefore, the data for the analytical portions of study P05520 are acceptable.

8.0 Recommended Regulatory Action

I concur with the recommendations of most of the review team and the CDTL that this application may be approved as the applicant has provided adequate information to support the safety, pharmacology (proposed dose and dosing regimen), and chemistry, manufacturing, and controls of the posaconazole injection for the previously granted indication of prophylaxis of invasive *Aspergillus* and *Candida* infections, with the distinction that the injectable formulation will be labeled only for patients 18 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 recipients with graft-versus-host disease or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

However, I disagree with the recommendations from the ONDQA team that the product should be copackaged with an inline filter to mitigate the risk from particulates as this would significantly delay the availability of a product for vulnerable patients with hematologic malignancies or stem cell transplants who are unable to take oral antifungal prophylaxis, which was the reason this application was granted a priority review initially. Copackaging an inline filter with the product does not guarantee that the copackaged filter would be used any more often than one available at a hospital. As noted above, the copackaged filter may not be compatible with IV infusion sets available at any given hospital. Also, the indicated patient population is frequently receiving other medications via an inline filter and therefore the likelihood that Noxafil injection would be administered without a filter is small. The small risk of exposure to particulates should a filter not be used or fail does not outweigh the benefit of prevention of invasive *Aspergillus* or *Candida* infections that are potentially fatal. Including the recommendation for an inline filter in the product labeling, routine pharmacovigilance to monitor for adverse outcomes related to particulates related to lack of use of or failure of an inline filter and the two CMC PMCs are adequate to allow for the safe use of Noxafil injection for the indicated patient population. There are two PREA PMRs to which the applicant has agreed, as discussed above.

Katherine A. Laessig, M.D.

APPEARS THIS WAY ON
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KATHERINE A LAESSIG
03/13/2014