

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205053Orig1s000

SUMMARY REVIEW

Deputy Division Director Decisional Memo

Date	(electronic stamp)
From	Katherine Laessig, MD
Subject	Deputy Division Director Decisional Memo
NDA #	205-053
Applicant Name	Merck Sharpe & Dohme Corp.
Date of Submission	January 25, 2013
PDUFA Goal Date	November 25, 2013
Established (USAN) Name	Posaconazole, tradename Noxafil®
Dosage Forms / Strength	100 mg delayed release tablets
Approved Indications	Prophylaxis of invasive <i>Aspergillus</i> and <i>Candida</i> 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 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	Mark Seggel
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 205-053 in support of a new formulation of posaconazole, 100 mg delayed release tablets. The proposed dose is a loading dose of 300 mg po bid on Day 1, followed by 300 mg po q d starting on Day 2 through the end of immunosuppression. 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, specifically neutropenic patients under treatment for acute myelogenous leukemia or myelodysplasia, as well as hematopoietic stem cell transplant patients with graft-versus-host disease. [REDACTED] (b) (4)

[REDACTED] The advantage of the delayed release tablet is that it only needs to be taken once daily and, according to the applicant, [REDACTED] (b) (4). This [REDACTED] (b) (4) oral suspension which must be taken multiple times a day and with food.

In support of this application, Merck has submitted a Phase 1/3B safety, tolerability, and PK study (Study P05615), as well as chemistry, manufacturing, and controls data to support the identity, strength, purity, and quality of the drug substance and drug product. In addition, the sponsor developed a dissolution test method in accordance with USP<71>, Delayed Release Dosage Forms.

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, Dr. Mark Seggel. He has concluded that the information provided by the applicant is sufficient to assure the identity, strength, purity, and quality of the drug, and that the proposed dissolution method and acceptance criterion are acceptable. The Office of Compliance has made a final recommendation of acceptable for the manufacturing establishments filed in this NDA on October 4, 2013. Therefore, from the CMC perspective, Dr. Seggel recommends approval of this application.

Drug substance CMC are currently filed under NDA 22-003 (posaconazole oral suspension). The specification for posaconazole drug substance used in the manufacture of the oral suspension has been found to be suitable for posaconazole used in the manufacture of the delayed release tablets.

The drug product consists of [REDACTED] (b) (4)

[REDACTED] and a non-functional film coating.

By limiting the dissolution of posaconazole in the acidic stomach environment, the uncontrolled precipitation in the small intestine is eliminated. Accordingly, one of the critical attributes of the drug product is its dissolution profile, which will be discussed further below.

Each capsule-shaped (oblong) tablet contains [REDACTED] (b) (4) 100 mg posaconazole [REDACTED] (b) (4). Other excipients in the tablet include additional [REDACTED] (b) (4) microcrystalline cellulose [REDACTED] (b) (4), hydroxypropyl cellulose [REDACTED] (b) (4), croscarmellose sodium [REDACTED] (b) (4) silicon dioxide [REDACTED] (b) (4), and magnesium stearate [REDACTED] (b) (4). The tablets are debossed on one side with "100" and have a non-functional Opadry II yellow film coating. Tablets are packaged in 60-count HDPE bottles with child-resistant closures.

Product manufacturing involves [REDACTED] (b) (4)

Twelve-month long term data on three primary stability batches and 24-36 month long term data from supporting stability batches show very little change in drug product quality. No significant changes were observed under accelerated conditions. Overall, the data support a 24-month expiry.

The applicant developed a dissolution test method using Apparatus II, paddles at 75 rpm. Because of the low solubility of posaconazole, polysorbate 80 is included in the buffer stage dissolution medium. The applicant agreed to implement FDA's recommended buffer stage acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 145 minutes (5 minutes for pH change plus 20 minutes after pH change). Based on evaluation of the provided data, the dissolution method was found to be acceptable by the ONDQA-Biopharmaceutics reviewer, Mark Seggel, and the test method and acceptance criteria will assure adequate and consistent product performance across batches.

3.0 Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Owen McMaster, found no nonclinical pharmacology or toxicology data that preclude approval of the posaconazole tablets. The regulatory requirements for pharmacology/toxicology studies for the tablets are fulfilled by referring to the nonclinical studies conducted under NDA [REDACTED] (b) (4). The applicant conducted two nonclinical pharmacokinetic studies to bridge the proposed tablet formulation of posaconazole to the current marketed oral suspension. Study DM27344 titled "SCH 56592: Plasma Pharmacokinetics of

SCH56592 in monkeys following a single oral or intravenous dose of various formulations” compared the pharmacokinetics of posaconazole in male cynomolgus monkeys. All three capsule formulations increased posaconazole exposure compared to the oral suspension. Subsequently, the pharmacokinetics of one tablet formulation, Tablet A, were compared to the HPMC-AS tablet in Study DM27489. AUC values for Tablet A were 2-3 times higher than those obtained with the HPMC-AS capsule. Adverse effects including emesis, soft feces, and increases in liver enzymes were similar to those seen with the marketed oral suspension and can be monitored in the clinic.

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 clinical program for posaconazole tablets was designed to demonstrate comparable systemic PK exposure and safety among similar patient populations for which the oral suspension has previously been approved. The exposure target was based upon the range of exposures achieved and the exposure-response relationship established in earlier controlled studies of the oral suspension, i.e.:

- Mean C_{min} at steady state levels ≥ 500 ng/mL or $AUC \geq 12,000$ hr•ng/mL in at least 90% of subjects
- Mean steady state $C_{min} \leq 2,500$ ng/mL or $AUC \leq 59,000$ hr•ng/mL;
- No subject with a mean steady state $C_{min} > 3,750$ ng/mL or with a steady state $AUC > 90,000$ hr•ng/mL

In study P05615, the steady state C_{min} following administration of posaconazole tablets at the proposed dosage regimen of 300 mg po bid on the first day, followed by 300 mg po qd on the second day and thereafter, fell within the predefined target exposure for greater than 90% of the 186 subjects for whom PK data were obtained. The steady state C_{min} was ≥ 500 ng/mL in 94.6% of subjects and was < 500 ng/mL in 5.4% of subjects. The mean C_{min} at steady state in 186 subjects treated with the 300 mg qd dose was $\leq 2,500$ ng/mL. Although there were six subjects with a $C_{min} > 3,750$ ng/mL, no significant safety issues were identified in these subjects. Thus, the proposed dosage regimen is acceptable.

The applicant had not conducted a food effect study at the time of submission of this application; therefore the product labeling will state that posaconazole tablets should be given with food, as for the oral suspension. [REDACTED] (b) (4)

5.0 Clinical Safety

The medical officer, Elizabeth O'Shaughnessy, recommends approval of posaconazole tablets for the current indication and the proposed dose and regimen. Her review evaluated the safety findings from Study P05615, which was a single arm study of the safety and tolerability of posaconazole tablets in 230 subjects with hematologic malignancies at risk of invasive fungal infections (IFI). Her conclusion is that the safety profile of the tablets is similar to that of the oral suspension.

The survival rate at Day 65 (survival visit) was high at > 90%. The incidence of breakthrough IFI was approximately 5% and similar to that previously reported in the two randomized prophylaxis trials of posaconazole oral suspension. There were two deaths in the 200 mg dose cohort and 20 deaths in the 300 mg dose cohort. Eighteen subjects died during the study period and two died after the survival visit at Day 65. The most common causes of death were infections, including sepsis and septic shock. One patient died from multiorgan failure, and one died from hepatic insufficiency.

The most common adverse reactions were nausea and diarrhea. Other adverse reactions included hepatotoxicity, a known toxicity of the azoles, with elevation of hepatic transaminases and hyperbilirubinemia, QTc prolongation, adrenal insufficiency, and drug-drug interactions. Five subjects developed treatment emergent hepatotoxicity and were discontinued from study drug.

Overall, posaconazole tablets were well tolerated. There did not appear to be a relationship between higher posaconazole exposures and a higher incidence of treatment related adverse reactions in this study. The medical officer concludes that the benefit of posaconazole in preventing life-threatening IFI outweighs the risk of adverse reactions in severely immunocompromised patients.

6.0 Pediatrics

Posaconazole tablets are not suitable for young children because they cannot consistently swallow tablets. This tablet formulation also may not be crushed or split. (b) (4)

In their proposed pediatric plan, the applicant plans to conduct a study of an IV solution, followed by the new age-appropriate oral formulation. The applicant requested a waiver for pediatric patients < 2 years of age, and a deferral for studies in patients > 2 to < 13 years of age. The adult studies of the oral suspension included subjects 13 years of age and older. The proposed pediatric plan was presented to the Pediatric Review Committee (PeRC) on October 3, 2013. PeRC recommended the waiver for patients < 1 year of age as hematologic

malignancies occur in children between the ages of 1 and 2 years. In addition, PeRC recommended an efficacy study if an appropriate pediatric dosing regimen cannot be determined from the study of the IV and new oral formulation. However, when this revision was proposed to the applicant, they stated that they had discussed the issue with investigators who reported that the incidence of ALL and AML in pediatric patients less than two years of age is very infrequent, and therefore antifungal prophylaxis is rarely used. The review team found this rationale to be acceptable and the Pediatric Research Equity Act (PREA) post marketing requirements (PMRs) were written accordingly.

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 conducted an inspection of the analytical sites and no 483 was issued or significant findings identified. Therefore, the data for the analytical portions of study P05615 are acceptable.

8.0 Recommended Regulatory Action

I concur with the recommendations 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 delayed release tablets for the previously granted indication of 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 recipients with graft-versus-host disease or those with hematologic malignancies with prolonged neutropenia from chemotherapy. There are two PREA PMRs to which the applicant has agreed as follows:

2090-1: Conduct a trial in patients, ages 2 to < 18 years, to evaluate the pharmacokinetic (PK), safety, and tolerability of two new formulations of posaconazole (IV solution and/or new age-appropriate oral formulation) in immunocompromised pediatric patients with known or expected neutropenia.

Final Protocol Submission: 09/30/14

Trial Completion: 06/30/17

Final Report Submission: 09/30/17

If the trial for PMR 2090-1 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 2090-2) will be required, provided a safe and tolerable dosage regimen can still be identified. If the trial for PMR 2090-1 is successful in determining a pediatric dosing regimen, you may request release from PMR 2090-2.

2090-2: Conduct a comparative, double-blind, randomized, multi-center trial, in patients ages 2 to < 18 years, to evaluate the safety, efficacy, and tolerability of posaconazole for the prophylaxis of invasive fungal infections (IFI) in pediatric patients with known or expected neutropenia.

Final Protocol Submission: 09/30/17

Trial Completion: 11/30/20

Final Report Submission: 03/31/21

Katherine A. Laessig, MD

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

/s/

KATHERINE A LAESSIG

11/25/2013