DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205596

**NDA APPROVAL**

Merck Sharp & Dohme Corp.
Attention: Laurie J. MacDonald, MD
Executive Director, Global Regulatory Affairs
351 North Sumneytown Pike, P.O. Box 1000
MAILSTOP UG2D68
North Wales, PA 19454-2505

Dear Dr. MacDonald:

Please refer to your New Drug Application (NDA) dated September 13, 2013, received September 13, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Noxafil (posaconazole) injection, 18 mg/mL.

We acknowledge receipt of your amendments dated October 14, and 24, and December 12 (2), 2013, and January 3, and 8, and February 13, 25, 27 (2), and 28, and March 13 (2), 2014.

This new drug application provides for the use of Noxafil (posaconazole) injection, 18 mg/mL for prophylaxis of invasive *Aspergillus* and *Candida* 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 (HSCT) recipients with graft versus host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

## WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

## CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 205596**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than 2 years because necessary studies are impossible or highly impracticable. This is because antifungal prophylaxis is rarely used in immunocompromised patients with hematologic malignancies in the age group less than 2 years of age.

We are deferring submission of your pediatric studies for ages 2 to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act/FDCA. These required studies are listed below.

**2132-1**: 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 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, you may request release from PMR 2132-2.

**2132-2:** 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

Submit the protocol(s) to your IND 75061, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

**2132-3:** 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.

The timetable you submitted on March 13, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: June 2014
Interim Report Submission: June 2015
Interim Report Submission: June 2016
Interim Report Submission: June 2017
Study Completion: June 2018
Final Report Submission: September 2018*

*Final report will include 3 year stability test time-point for 10 batches

**2132-4:** 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 timetable you submitted on March 13, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 6/30/14
Study Completion: 12/31/14
Final Report Submission: 3/31/15

Submit clinical protocols to your IND 75061, for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

## REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

*{See appended electronic signature page}*

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

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

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/s/

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KATHERINE A LAESSIG
03/13/2014