**NDA 214770**
**NDA 205053/S-012**
**NDA 205596/S-012**

**GENERAL ADVICE**

Merck Sharp & Dohme Corp.
a subsidiary of Merck & Co., Inc.
Attention: Deanne Jackson Rudd, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 North Sumneytown Pike
P.O. Box 1000, UG-2D-068
North Wales, PA 19454-2505

Dear Dr. Rudd:

Please refer to your new drug application (NDA) and your supplemental new drug applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Noxafil PowderMix (posaconazole) for delayed-release oral suspension, 300 mg per packet (NDA 214770), Noxafil (posaconazole) delayed-release tablets, 100 mg (NDA 205053/S-012) and Noxafil (posaconazole) injection, 300 mg/16.7 mL (18 mg/mL) (NDA 205596/S-012).

We also refer to our approval letter dated May 31, 2021, which contained the following errors:

1. The NDA number listed on page one was incorrectly listed as NDA 214470. The NDA number should have been listed as 214770.
2. A postmarketing requirement listed under **RELEASE FROM POSTMARKETING REQUIREMENTS** for NDA 205596 was listed as 2131-1 and should be 2132-1.
3. Carton and Container labeling for NDA 214770 was not attached and is appended to this communication.

This General Advice letter acknowledges the errors described above. The effective approval date will remain May 31, 2021, the date of the original letter.

If you have any questions, call Christopher L. Smith, PharmD, Regulatory Project Manager, at (301) 796-4851.

Sincerely,

*{See appended electronic signature page}*

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

**Attachment:**

- Carton and Container Labeling [**NDA 214770**]

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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SUMATHI NAMBIAR
06/02/2021 02:40:07 PM

**NDA 214470**
**NDA 205053/S-012**
**NDA 205596/S-012**

**NDA APPROVAL**
**SUPPLEMENT APPROVAL**

**FULLFILLMENT OF**
**POST MARKETING REQUIREMENTS**
**RELEASE FROM POSTMARKETING REQUIREMENTS**

Merck Sharp & Dohme Corp.
a subsidiary of Merck & Co., Inc.
Attention: Deanne Jackson Rudd, Ph.D.
Director, Global Regulatory Affairs and Clinical Safety
351 North Sumneytown Pike
P.O. Box 1000, UG-2D-068
North Wales, PA 19454-2505

Dear Dr. Rudd:

Please refer to your new drug application (NDA) and your supplemental new drug applications (sNDAs), dated and received July 31, 2020, and your amendments, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Noxafil PowderMix (posaconazole) for delayed-release oral suspension, 300 mg per packet (NDA 214770), Noxafil (posaconazole) delayed-release tablets, 100 mg (NDA 205053/S-012) and Noxafil (posaconazole) injection, 300 mg/16.7 mL (18 mg/mL) (NDA 205596/S-012).

This NDA and these prior approval new drug applications provide for the use of Noxafil PowderMix (posaconazole) for delayed-release oral suspension, Noxafil (posaconazole) delayed-release tablets, and Noxafil (posaconazole) injection, for the following:

| **NDA Number/ Supplement Number** | **Provide(s) for:** |
|---|---|
| NDA 214770 | The prophylaxis of invasive *Aspergillus* and *Candida* infections in pediatric patients 2 years of age and older (who weigh 40 kg or less) 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. |

| | |
|---|---|
| NDA 205053/ S-012 | Expansion of the approved 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 HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy, to include pediatric patients 2 years of age and older who weigh greater than 40 kg. |
| NDA 205596/ S-012 | Expansion of the approved indication of 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 HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy, to include pediatric patients 2 years of age and older. |

## APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

## 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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert and Instructions for Use) as well as annual reportable changes not included in the enclosed labeling. 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.*[2]

The SPL will be accessible via publicly available labeling repositories.

## CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling, for NDA 214770 for Noxafil PowderMix, that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product*

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

*Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214770**." Approval of this submission by FDA is not required before the labeling is used.

We note that the carton and container labeling for NDAs 205053 and 205596 remain unchanged from those currently approved.

## DATING PERIOD (NDA 214770)

Based on the stability data submitted to date, the expiry dating period for Noxafil PowderMix (posaconazole) for delayed-release oral suspension, shall be 36 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F).

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

You have fulfilled the pediatric study requirement for ages 2 years to less than 18 years for these applications.

A waiver was granted for children less than 2 years of age for all formulations.

## POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment for **NDA 214770**:

4072-1 Develop an appropriate administration method for Noxafil PowderMix (posaconazole) to support dosing in pediatric patients who weigh greater than 40 kg. Provide evidence that the design of the user interface supports dosing and administration of Noxafil PowderMix to patients who weigh greater than 40 kg and data to demonstrate that the entire dose can be delivered to these patients using the proposed method of administration (volume recovery and use-related risk analysis).

The timetable you submitted on May 26, 2021, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 06/2021 |
| Final Protocol Submission: | 07/2021 |
| Final Report/Use-Related Risk Analysis Submission: | 08/2021 |

4072-2 If based on the results of the above study, a human factors (HF) validation study is necessary to support the new administration method, conduct the HF validation study.

The timetable you submitted on May 26, 2021, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 11/2021 |
| Final Protocol Submission: | 02/2022 |
| Study/Trial Completion: | 05/2022 |
| Final Report Submission: | 06/2022 |

Changes to the dosage and administration for Noxafil PowderMix based on the results of the above studies should be submitted to the NDA as a prior approval supplement.

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

We remind you of your postmarketing commitment for **NDA 214770**:

4072-3 Develop a new dissolution method using constituted suspension samples for the Quality Control (QC) testing of the proposed drug product. Submit a method validation report and include additional dissolution data for constituted suspension samples from unexpired batches using (b) (4) to determine an appropriate paddle rotation speed.

The timetable you submitted on May 17, 2021, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Report Submission: | 08/2021 |

Changes in the dissolution method based on the results of this study should be submitted to NDA 214770 as a prior approval supplement before marketing any commercial drug product batches.

Submit clinical protocols to your IND 125097 for Noxafil PowderMix. 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**."

## FULFILLMENT OF POSTMARKETING REQUIREMENTS (PMRs)

We have received your submissions dated July 31, 2020, containg the final reports for the following PMRs listed in the November 25, 2013, approval letter for NDA 205053 Noxafil (posaconazole) delayed-release tablets, 100 mg and in the March 13, 2014, approval letter for NDA 205596 Noxafil (posaconazole) injection, 300 mg/16.7 mL.

**NDA 205053**

**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.

**NDA 205596**

**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.

We have reviewed your submissions and conclude that the above requirements were fulfilled.

## RELEASE FROM POSTMARKETING REQUIREMENTS

We have reviewed your submissions and have determined that you are released from the requirements below as they are no longer needed because the trial conducted to fulfill PMRs 2090-1 and 2131-1 was adequate to determine a pediatric dosing regimen for posaconazole (IV solution and the new age appropriate oral formulation).

**NDA 205053**

**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.

**NDA 205596**

**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.

This completes all your postmarketing requirements and postmarketing commitments acknowledged in our November 25, 2013 (NDA 205053) and March 13, 2014 (NDA 205596), letters.

## PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

## REPORTING REQUIREMENTS

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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, call Christopher L. Smith, PharmD, Regulatory Project Manager, at (301) 796-4851.

Sincerely,

*{See appended electronic signature page}*

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use

  Carton and Container Labeling **[NDA 214770 only]**

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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SUMATHI NAMBIAR
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