DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-003/S-007

Schering Corporation
Attention: Barbara Line Gunther MA, MBA
Associate Director & Liaison
Global Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Ms. Gunther:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

| Name of Drug Product | NDA Number | Supplement Number | Letter Date | Receipt Date |
|---|---|---|---|---|
| Noxafil® (posaconazole) Oral Suspension, 40mg/mL | 22-003 | S-007 | April 16, 2008 | April 18, 2008 |

We acknowledge receipt of your submissions dated August 14, November 7, and December 22, 2008.

This supplemental new drug application provides for revisions to the package insert (PI) and patient package insert (PPI) to add information regarding absorption and pharmacokinetic data.

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

The revisions to the package insert (PI) and patient package insert (PPI) are as follow (additions are noted with underline and deletions with ~~strikethrough~~):

1. Under the **CLINICAL PHARMACOLOGY/Pharmacokinetics/**Absorption subsection of the PI, the following wording was added:

   In 12 healthy volunteers who received a single 400 mg dose of NOXAFIL Oral Suspension in the fasted state, 5 minutes before, during, and 20 minutes after a high-fat meal in a 4-way crossover design, the coadministration of NOXAFIL with a high fat meal significantly increased the extent of absorption of posaconazole compared to in the fasted state. However, the magnitude of the food effect varied with timing of the meals. When NOXAFIL was administered during a high-fat meal, the mean $C_{max}$ and AUC increased by 339% and 382% compared to in the fasted state, respectively. When NOXAFIL was administered 20 minutes after a high-fat meal, the mean $C_{max}$ and AUC also increased by 333% and 387% compared to in the fasted state, respectively. When NOXAFIL was administered 5 minutes before a high-fat

meal, the mean $C_{max}$ and AUC increased by 96% and 111% compared to in the fasted state, respectively (See **DOSAGE AND ADMINISTRATION**).

In 12 healthy volunteers who received 400 mg BID and 200 mg QID of NOXAFIL Oral Suspension for 7 days in the fasted state and with liquid nutritional supplement (BOOST® Drink) in a 4-way crossover design, the administration of NOXAFIL 400 mg BID with BOOST increased the mean $C_{max}$ and AUC by 65% and 66%, respectively, compared to NOXAFIL 400 mg BID in the fasted state. However, when NOXAFIL 200 mg QID was administered with BOOST, the mean $C_{max}$ and AUC were not affected compared to NOXAFIL 200 mg QID in the fasted state.

In 12 healthy volunteers who received 400 mg BID and 200 mg QID of NOXAFIL Oral Suspension for 7 days in the fasted state and with liquid nutritional supplement (BOOST Drink) in a 4-way crossover design, the absorption of posaconazole was significantly increased when NOXAFIL was administered by dividing the total daily dose from 400 mg BID to 200 mg QID regardless of under fasted conditions or with liquid nutritional supplement. In the fasted state, the mean $C_{max}$ and AUC increased by 136% and 161%, respectively, when NOXAFIL was administered as 200 mg QID compared to 400 mg BID. When NOXAFIL was administered as 200 mg QID with BOOST, the mean $C_{max}$ and AUC increased by 44% and 54%, respectively, compared to 400 mg BID with BOOST.

In 12 healthy volunteers who received a single 400 mg dose of NOXAFIL Oral Suspension alone, or with ginger ale, or with esomeprazole, or both ginger ale and esomeprazole in the fasted state in a 4-way crossover design, the coadministration of NOXAFIL with ginger ale (carbonated acidic beverage) increased the mean $C_{max}$ and AUC by 92% and 70% compared to NOXAFIL alone, respectively. The coadministration of NOXAFIL with esomeprazole (proton pump inhibitor) decreased the mean $C_{max}$ and AUC by 46% and 32% compared to NOXAFIL alone, respectively. The coadministration of NOXAFIL with both ginger ale and esomeprazole decreased the mean $C_{max}$ and AUC by 33% and 21% compared to NOXAFIL alone, respectively (See **CLINICAL PHARMACOLOGY, Drug Interactions**, **PRECAUTIONS, Drug Interactions**, and **DOSAGE AND ADMINISTRATION**.

In 12 subjects who received single 400 mg dose of NOXAFIL Oral Suspension with BOOST, or with a prokinetic agent (metoclopramide 10 mg TID for 2 days) and BOOST, or with an anti-kinetic agent (loperamide 4 mg single dose) and BOOST in a 3-way crossover design, the coadministration of NOXAFIL with metoclopramide decreased the mean $C_{max}$ and AUC by 21% and 19%, respectively, compared to NOXAFIL alone. When NOXAFIL was coadministered with loperamide, the mean $C_{max}$ and AUC were decreased by 3% and increased by 11%, respectively, compared to NOXAFIL alone (See **CLINICAL PHARMACOLOGY, Drug Interactions** and **PRECAUTIONS, Drug Interactions**).

In 16 healthy volunteers who received a single 400 mg dose of NOXAFIL either orally or via an NG tube in a crossover design, the mean $C_{max}$ and AUC decreased by 19% and 23%, respectively, when NOXAFIL was administered via an NG tube compared to when POS was administered orally. In 5 subjects, the $C_{max}$ and AUC decreased substantially (range -27% to -53% and -33% to -51%, respectively) when NOXAFIL was administered via an NG tube compared to when NOXAFIL was administered orally. It is recommended to closely monitor patients for breakthrough fungal infections when NOXAFIL is administered via an NG tube

because a lower plasma exposure may be associated with an increase risk of treatment failure (See **CLINICAL PHARMACOLGY, Exposure Response Relationship**).

2. The second paragraph under the **CLINICAL PHARMACOLOGY/Exposure Response Relationship** subsection of the PI was revised as follows:

   To enhance the oral absorption of posaconazole and optimize plasma concentrations:
   - Each dose of NOXAFIL® Oral Suspension should be administered ~~with~~ during or immediately (i.e. within 20 minutes) following a full meal or liquid nutritional supplement. For patients who can not eat a full meal or tolerate an oral nutritional supplement, alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.
   - Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.
   - Co-administration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections. (See **CLINICAL PHARMACOLOGY, Drug Interactions.**)

3. The **CLINICAL PHARMACOLOGY/Pharmacokinetics in Special Populations**/Hepatic Insufficiency subsection of the PI was revised as follows:

   After a single oral dose of posaconazole 400 mg, the mean AUC was 43%, 27% and 21% higher in subjects with mild (Child-Pugh Class A, N=6), moderate (Child-Pugh Class B, N=6), and severe (Child-Pugh Class C, N=6) hepatic insufficiency, respectively, compared to subjects with normal hepatic function (N=18). Compared to subjects with normal hepatic function, the mean $C_{max}$ was 1% higher, 40% higher, and 34% lower in subjects with mild, moderate, and severe hepatic insufficiency, respectively. The mean apparent oral clearance (CL/F) was reduced by 18%, 36% and 28% in subjects with mild, moderate, and severe hepatic insufficiency, respectively, compared to subjects with normal hepatic function. The elimination half-life (t½) was 27 hours, 39 hours, 27 hours, and 43 hours in subjects with normal hepatic function, mild, moderate, and severe hepatic insufficiency, respectively.

   It is recommended that no dose adjustment of NOXAFIL is needed in patients with mild to severe hepatic insufficiency (Child-Pugh Class A, B, and C) (**See WARNINGS** and **DOSAGE AND ADMINISTRATION**).

   ~~The pharmacokinetic data in subjects with hepatic impairment was not sufficient to determine if dose adjustment is necessary in patients with hepatic dysfunction. It is recommended that posaconazole be used with caution in patients with hepatic impairment. (See **WARNINGS** and **DOSAGE AND ADMINISTRATION.**)~~

4. The **Drug Interactions**/Effect of Other Drugs on Posaconazole subsection of the PI was revised as follows:

   Posaconazole is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. A summary of drugs studied

clinically, which affect posaconazole concentrations, is provided in **Table 3** (see PRECAUTIONS, **Drug Interactions** section).

**TABLE 3. Summary of the Effect of Co-administered Drugs on Posaconazole in Healthy Volunteers**

| Co-administered Drug (Postulated Mechanism of Interaction) | Co-administered Drug Dose/Schedule | Posaconazole Dose/Schedule | Effect on Bioavailability of Posaconazole | | Recommendations |
|---|---|---|---|---|---|
| | | | Change in Mean $C_{max}$ (ratio estimate*; 90% CI of the ratio estimate) | Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate) | |
| Rifabutin (UDP-G Induction) | 300 mg QD x 17 days | 200 mg (tablets) QD × 10 days | ↓43% (0.57; 0.43-0.75) | ↓ 49% (0.51; 0.37-0.71) | Avoid concomitant use unless the benefit outweighs the risks. |
| Phenytoin (UDP-G Induction) | 200 mg QD x 10 days | 200 mg (tablets) QD × 10 days | ↓ 41% (0.59; 0.44-0.79) | ↓ 50% (0.50; 0.36-0.71) | Avoid concomitant use unless the benefit outweighs the risks. |
| Cimetidine (Alteration of Gastric pH) | 400 mg BID × 10 days | 200 mg (tablets) QD × 10 days | ↓ 39% (0.61; 0.53-0.70) | ↓ 39% (0.61; 0.54-0.69) | Avoid concomitant use unless the benefit outweighs the risks. |
| Efavirenz (UDP-G Induction) | 400 mg QD × 10 and 20 days | 400 mg (oral suspension) BID × 10 and 20 days | ↓45% (0.55; 0.47-0.66) | ↓ 50% (0.50; 0.43-0.60) | Avoid concomitant use unless the benefit outweighs the risks. |
| Esomeprazole (Increase in gastric pH) | 40 mg QAM × 3 days | 400 mg (oral suspension) single dose | ↓ 46% (0.54; 0.43-0.69) | ↓ 32% (0.68; 0.57-0.81) | Monitor closely for breakthrough fungal infections. |
| Metoclopramide (Increase in gastric motility) | 10 mg TID × 2 days | 400 mg (oral suspension) single dose | ↓ 21% (0.79; 0.72-0.87) | ↓ 19% (0.81; 0.72-0.91) | Monitor closely for breakthrough fungal infections |

*Ratio Estimate is the ratio of co-administered drug plus posaconazole to posaconazole alone for $C_{max}$ or AUC.

Co-administration of these drugs listed in **Table 3** with posaconazole may result in lower plasma concentrations of posaconazole.

No clinically relevant effect on posaconazole bioavailability and/or plasma concentrations was observed when administered with an antacid, glipizide, ritonavir, loperamide, or H2 receptor antagonists other than cimetidine~~, or proton pump inhibitors~~; therefore, no posaconazole dose adjustments are required when used concomitantly with these products.

5. The **PRECAUTIONS/Information for Patients** subsection of the PI was revised as follows:

Patients should be advised to:

- Take each dose of NOXAFIL® Oral Suspension ~~with~~ during or immediately (i.e. within 20 minutes) following a full meal or liquid nutritional supplement in order to enhance absorption.

- Inform their physician if they develop severe diarrhea or vomiting as these conditions may change blood levels of posaconazole.
- Inform their physician if they are taking other drugs or before they begin taking other drugs as certain drugs can change blood levels. (See **CLINICAL PHARMACOLOGY, Drug Interactions.**)

6. The **PRECAUTIONS/Drug Interactions** subsection of the PI was revised as follows:

A summary of significant drug interactions with posaconazole that have been studied clinically are provided in **Tables 8** and **9.** Appropriate precautions for the co-administration of these drugs with posaconazole are provided (see **CLINICAL PHARMACOLOGY/Drug Interactions** section**, CONTRAINDICATIONS** and **WARNINGS).**

**TABLE 8. Summary of the Effect of Co-administered Drugs on Posaconazole**

| Co-administered Drug | Recommendations |
|---|---|
| Cimetidine | Avoid concomitant use unless the benefit outweighs the risks. |
| Rifabutin | Avoid concomitant use unless the benefit outweighs the risks. |
| Phenytoin | Avoid concomitant use unless the benefit outweighs the risks. |
| Efavirenz | Avoid concomitant use unless the benefit outweighs the risks. |
| Esomeprazole | Monitor closely for breakthrough fungal infections. |
| Metoclopramide | Monitor closely for breakthrough fungal infections. |

Co-administration of these drugs listed in **Table 8** with posaconazole may result in lower plasma concentrations of posaconazole.

7. The **DOSAGE AND ADMINISTRATION** section of the PI was revised as follows:

| Indication | Dose and Duration of therapy |
|---|---|
| Prophylaxis of Invasive Fungal Infections | 200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression. |
| Oropharyngeal Candidiasis | Loading dose of 100 mg (2.5 mL) twice a day on the first day, then 100 mg (2.5 mL) once a day for 13 days. |
| Oropharyngeal Candidiasis Refractory to itraconazole and/or fluconazole | 400 mg (10 mL) twice a day. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response. |

Each dose of NOXAFIL® should be administered with a full meal or with a liquid nutritional supplement in patients who can not eat a full meal. (See **CLINICAL PHARMACOLOGY.**)

Alternatively, NOXAFIL may be taken with an acidic carbonated beverage (e.g. ginger ale).

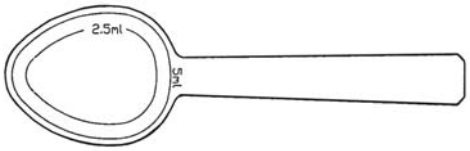
To enhance the oral absorption of posaconazole and optimize plasma concentrations:

- Each dose of NOXAFIL® Oral Suspension should be administered ~~with~~ during or immediately (i.e., within 20 minutes) following a full meal or liquid nutritional supplement. For patients who can not eat a full meal or tolerate an oral nutritional supplement, alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.

- Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.
- Co-administration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections. (See **CLINICAL PHARMACOLOGY, Drug Interactions section**).

Shake NOXAFIL® Oral Suspension well before use.

A measured dosing spoon is provided, marked for doses of 2.5 mL and 5 mL.




It is recommended that the spoon is rinsed with water after each administration and before storage.

8. The **DOSAGE AND ADMINISTRATION/**Hepatic Insufficiency subsection of the PI was revised as follows:

   No dose adjustment of NOXAFIL is needed in patients with mild to severe hepatic insufficiency (Child-Pugh Class A, B, and C). (See CLINICAL PHARMACOLOGY/Pharmacokinetics in Special Populations).

   ~~The pharmacokinetic data in subjects with hepatic impairment was not sufficient to determine if dose adjustment is necessary in patients with hepatic dysfunction. It is recommended that posaconazole be used with caution in patients with hepatic impairment. (See **CLINICAL PHARMACOLOGY** and **WARNINGS.**)~~

9. The following was added to the end of the PI label:

   BOOST® Drink is a registered trademark of Nestlé Healthcare Nutrition, Inc.

10. The **How do I take NOXAFIL?** section of the PPI was revised as follows:

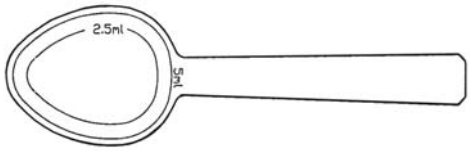
    - NOXAFIL® comes in cherry-flavored liquid form. Shake NOXAFIL Oral Suspension well before use.
    - Take NOXAFIL for as long as your doctor tells you. Take each dose of NOXAFIL ~~with~~ during or immediately (i.e. within 20 minutes) following a full meal, or with a liquid nutritional supplement if you are unable to eat a full meal. Alternatively, NOXAFIL may be taken with an acidic carbonated beverage (e.g. gingerale).

- Follow your doctor's instructions on when and how much of NOXAFIL you should take.

If you miss a dose of NOXAFIL, take it as soon as you remember.

- If you take too much NOXAFIL, call your doctor or poison control center immediately.
- Tell your doctor right away if you develop severe diarrhea or vomiting.

A measured dosing spoon is provided, marked for doses of 2.5 mL and 5 mL.




It is recommended that the spoon is rinsed with water after each administration and before storage.

## CONTENT OF LABELING

As soon as possible, please submit revised content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, SPL for approved NDA 22-003/S-007."

## LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., "Dear Health Care professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

## 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 Jacquelyn Smith, M.A., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert (PI)
Patient Package Insert (PPI)

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/s/

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Renata Albrecht

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