**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-003/S-002
NDA 22-003/S-006

Schering Corporation
Attention: Ms. Lisa Travis, MS, RAC
Director, Global Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Ms. Travis:

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

| **NDA #** | **Drug Product** | **Supplement Number** | **Date of supplement** | **Date of receipt** |
|---|---|---|---|---|
| 22-003 | Noxafil® (posaconazole) Oral Suspension, 40mg/mL. | S-002 | April 11, 2007 | April 12, 2007 |
| 22-003 | Noxafil® (posaconazole) Oral Suspension, 40mg/mL. | S-006 | February 15, 2008 | February 19, 2008 |

We acknowledge receipt of your submissions to NDA 22-003/S-002, dated:

| | | |
|---|---|---|
| April 18, 2007 | April 26, 2007 | February 8, 2008 |
| April 24, 2007 | November 21, 2007 | March 31, 2008 |

Supplemental new drug application NDA 22-003/S-002 provides for changes to the **CONTRAINDICATIONS** section and the **CLINICAL PHARMACOLOGY/ Drug Interactions** and **PRECAUTIONS/ Drug Interactions** subsections of the Noxafil labeling to provide information on interactions with various CYP3A4 substrates.

The "Changes Being Effected" supplemental new drug application, NDA 22-003/S-006, provides for changes to the **PRECAUTIONS/Drug Interactions** subsection of the labeling to reflect a possible interaction between posaconazole and digoxin.

The following revisions (~~strikethrough~~ = deleted and <u>underlined</u> = added) to the text for the package insert for Noxafil were proposed in these supplemental applications:

1. The following was added to the end of Table 3 in the **CLINICAL PHARMACOLOGY/Drug Interactions/Effect of Other Drugs on Posaconazole** subsection:

**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) | |
| 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. |

2. The first paragraph in the **CLINICAL PHARMACOLOGY/Drug Interactions/Effect of Posaconazole on Other Drugs** subsection was modified as follows:

*In vitro* studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4. A clinical study in healthy volunteers also indicates that posaconazole is a strong CYP3A4 inhibitor as evidenced by a >5-fold increase in midazolam AUC. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole. A summary of the drugs studied clinically, for which plasma concentrations were affected by posaconazole, is provided in **TABLE 4** (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS/Drug Interactions**).

3. Table 4 in the **CLINICAL PHARMACOLOGY/Drug Interactions/Effect of Posaconazole on Other Drugs** subsection was modified as follows:

**TABLE 4. Summary of the Effect of Posaconazole on Co-administered Drugs in Healthy Volunteers and Patients**

| **Co-administered Drug** (Postulated Mechanism of Interaction) | **Co-administered Drug Dose/Schedule** | **Posaconazole Dose/ Schedule** | **Effect on Bioavailability of Co-administered** | | **Recommendations** |
|---|---|---|---|---|---|
| | | | **Change in Mean $C_{max}$** (ratio estimate*; 90% CI of the ratio | **Change in Mean AUC** (ratio estimate *; 90% CI of | |
| Sirolimus (Inhibition of CYP3A4 by posaconazole) | 2 mg single oral dose | 400 mg (oral suspension) BID x 16 days | ↑ 572% (6.72; 5.62-8.03) | ↑ 788% (8.88; 7.26-10.9 | Coadministration of posaconazole with sirolimus is contraindicated (see **CONTRAINDICATIONS**). |
| Cyclosporine (Inhibition of CYP3A4 by posaconazole) | Stable maintenance dose in heart transplant recipients | 200 mg (tablets) QD x 10 days | ↑ cyclosporine whole blood trough concentrations<br><br>Cyclosporine dose reductions of up to 29% were required | | At initiation of posaconazole treatment, reduce the cyclosporine dose to approximately three-fourths of the original dose.<br><br>Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly. |

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| Tacrolimus (Inhibition of CYP3A4 by posaconazole) | 0.05 mg/kg single oral dose | 400 mg (oral suspension) BID × 7 days | ↑121% (2.21; 2.01-2.42) | ↑ 358% (4.58; 4.03-5.19) | At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose.<br><br>Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly. |
| Rifabutin (Inhibition of CYP3A4 by posaconazole) | 300 mg QD x 17 days | 200 mg (tablets) QD × 10 days | ↑ 31% (1.31; 1.10-1.57) | ↑ 72% (1.72; 1.51-1.95) | Avoid concomitant use unless the benefit outweighs the risks. If the drugs are co-administered, frequent monitoring of rifabutin adverse effects (eg, uveitis, leukopenia) should be performed. |

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| Midazolam (Inhibition of CYP3A4 by posaconazole) | Single 30 min IV infusion of 0.05 mg/kg<br><br>0.4 mg single IV dose[a]<br><br>2 mg single oral dose[a]<br><br>0.4 mg single IV dose[a] | 200 mg (tablets) QD x 10 days<br><br>200 mg (oral suspension) BID x 7 days<br><br>200 mg (oral suspension) BID x 7 days<br><br>400 mg (oral suspension) BID x 7 days | NA**<br><br>↑30% (1.3; 1.13-1.48)<br><br>↑126% (2.26; 2.02-2.53)<br><br>↑62% (1.62; 1.41-1.86) | ↑ 83% (1.83; 1.57-2.14)<br><br>↑362% (4.62; 4.02-5.3)<br><br>↑362% (4.59; 4.12-5.11)<br><br>↑524% (6.24; 5.43-7.16) | Frequent monitoring of adverse effects of benzodiazepines metabolized by CYP3A4 should be performed and dose reduction of these benzodiazepines should be considered during co-administration with posaconazole. |
| Phenytoin (Inhibition of CYP3A4 by posaconazole) | 200 mg QD PO x 10 days | 200 mg (tablets) QD x 10 days | ↑ 16% (1.16; 0.85-1.57) | ↑ 16% (1.16; 0.84-1.59) | Frequent monitoring of phenytoin concentrations should be performed while co-administered with posaconazole and dose reduction of phenytoin should be considered. |
| Ritonavir (Inhibition of CYP3A4 by posaconazole) | 100 mg QD x 14 days | 400 mg (oral suspension) BID x 7 days | ↑ 49% (1.49; 1.04-2.15) | ↑ 80% (1.8; 1.39-2.31) | Frequent monitoring of adverse effects and toxicity of ritonavir should be performed during co-administration with posaconazole. |

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|---|---|---|---|---|---|
| Atazanavir (Inhibition of CYP3A4 by posaconazole) | 300 mg QD x 14 days | 400 mg (oral suspension) BID x 7 days | ↑ 155% (2.55; 1.89-3.45) | ↑ 268% (3.68; 2.89-4.70) | Frequent monitoring of adverse effects and toxicity of Atazanavir should be performed during co-administration with posaconazole. |
| Atazanavir/ ritonavir boosted regimen (Inhibition of CYP3A4 by posaconazole) | 300 mg/100 mg QD x 14 days | 400 mg (oral suspension) BID x 7 days | ↑ 53% (153; 1.13-2.07) | ↑ 146% (2.46; 1.93-3.13) | |

*Ratio Estimate is the ratio of co-administered drug plus posaconazole to co-administered drug alone for $C_{max}$ or AUC.
**NA: Not applicable if administered as an IV.
[a] The mean terminal half-life of midazolam was increased from 3 hours to 8 to 10 hours during co-administration with posaconazole.

4. The paragraph below Table 4 in the **CLINICAL PHARMACOLOGY/Drug Interactions/Effect of Posaconazole on Other Drugs** subsection was modified as follows:

   Additional clinical studies demonstrated that no clinically significant effects on zidovudine, lamivudine, ritonavir, indinavir, or caffeine were observed when administered with posaconazole 200 mg QD; therefore, no dose adjustments are required for these co-administered drugs when co-administered with posaconazole 200 mg QD.

5. The following was added after the first paragraph in the **CONTRAINDICATIONS** section:

   Co-administration of NOXAFIL® (posaconazole) with sirolimus is contraindicated (See **CLINICAL PHARMACOLOGY/Drug Interactions** and **PRECAUTIONS/Drug Interactions**).

6. The **WARNINGS/ Cyclosporine drug interaction** subsection was modified as follows:

   Cases of elevated cyclosporine levels resulting in rare serious adverse events, including nephrotoxicity and leukoencephalopathy, and death were reported in clinical efficacy studies. Dose reduction and more frequent clinical monitoring of cyclosporine and~~,~~ tacrolimus, ~~and sirolimus~~ should be performed when posaconazole therapy is initiated (See **PRECAUTIONS/Drug Interactions**).

7. The **PRECAUTIONS/Information for Patients** subsection was modified as follows:

   Patients should be advised to:
   - Take each dose of NOXAFIL® Oral Suspension with 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~~ decrease the plasma concentrations 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~~ decrease the plasma concentrations of posaconazole. (See **CLINICAL PHARMACOLOGY/Drug Interactions.**)

8. The **PRECAUTIONS/Drug Interactions** subsection was modified 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, 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. |

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

**TABLE 9. Summary of the Effect of Posaconazole on Co-administered Drugs**

| Co-administered Drug | Recommendations |
|---|---|
| Sirolimus | Co-administration of posaconazole with sirolimus is contraindicated. (See **CLINICAL PHARMACOLOGY/Drug Interactions** and **CONTRAINDICAIONS**.) |
| Cyclosporine | Increased cyclosporine concentrations resulted in cyclosporine dose reductions in heart transplant patients co-administered posaconazole. At initiation of posaconazole treatment, reduce the cyclosporine dose to approximately three fourths of the original dose. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly. |

| Co-administered Drug | Recommendations |
|---|---|
| Tacrolimus | Posaconazole has been shown to increase $C_{max}$ and AUC of tacrolimus significantly. At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly. |
| Rifabutin | Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. However, if concomitant administration is required frequent monitoring of full blood counts and adverse events due to increased rifabutin levels (eg, uveitis, leukopenia) is recommended. |
| Midazolam | Frequent monitoring of adverse effects of benzodiazepines metabolized by CYP3A4 should be performed and dose reduction of these benzodiazepines should be considered during co-administration with posaconazole. |
| Phenytoin | Frequent monitoring of phenytoin concentrations should be performed while co-administered with posaconazole and dose reduction of phenytoin should be considered. |
| Atazanavir | Frequent monitoring of adverse effects and toxicity of atazanavir should be performed during co-administration with posaconazole. |
| Ritonavir | Frequent monitoring of adverse effects and toxicity of ritonavir should be performed during co-administration with posaconazole. |

Although not studied *in vitro* or *in vivo*, posaconazole may affect the plasma concentrations of the drugs or drug classes described in **TABLE 10**. Appropriate precautions for the co-administration of these drugs with posaconazole are provided (See **CONTRAINDICATIONS.**)

**TABLE 10. Drugs Not Studied in vitro or in vivo but Likely to Result in Significant Drug Interactions**

| Drug or Drug Class (CYP3A4 Substrates) | Recommendations |
|---|---|
| Terfenadine, Astemizole, Pimozide, Cisapride, Quinidine, Halofantrine | Increased plasma concentrations of these drugs can lead to QT prolongation with rare occurrences of torsade de pointes. **Co-administration with posaconazole is contraindicated**. (See **CONTRAINDICATIONS.**) |

| | |
|---|---|
| Ergot Alkaloids | Posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism. **Co-administration of posaconazole with ergot alkaloids is contraindicated**. (See **CONTRAINDICATIONS.**) |
| Vinca Alkaloids | Posaconazole may increase the plasma concentrations of vinca alkaloids (eg, vincristine and vinblastine) which may lead to neurotoxicity. Therefore, it is recommended that the dose adjustment of the vinca alkaloid be considered. |
| ~~Sirolimus~~ | ~~Frequent monitoring of sirolimus whole blood trough concentrations should be performed upon initiation, during co-administration, and at discontinuation of posaconazole treatment, with sirolimus doses reduced accordingly.~~ |
| HMG-CoA reductase inhibitors (statins) metabolized through CYP3A4 | It is recommended that dose reduction of statins be considered during co-administration. Increased statin concentrations in plasma can be associated with rhabdomyolysis. |
| Calcium Channel Blockers metabolized through CYP3A4 | Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during co-administration. Dose reduction of calcium channel blockers may be needed. |
| Digoxin | Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and posaconazole. Therefore, monitoring of digoxin plasma concentrations is recommended during co-administration. |

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

Within 21 days of the date of this letter, submit 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, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions "**SPL for approved supplement NDA 22-003/S-002 and NDA 22-003/S-006**."

If you issue a letter communicating important information about this drug product (i.e., a "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

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 question, call Jacquelyn Smith, 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

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/s/

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Renata Albrecht

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