

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205053Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 205-053  
Supporting document/s: 1  
Applicant's letter date: January 24, 2013  
CDER stamp date: January 25, 2013  
Product: NOXAFIL<sup>®</sup> (posaconazole) Tablet  
Indication: Prophylaxis of invasive Aspergillus or 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 (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.  
Applicant: Merck Sharp and Dohme  
One Merck Drive  
P.O. Box 100  
Whitehouse Station, New Jersey 08889-0100  
Review Division: Division of Anti-infective Products  
Reviewer: Owen McMaster, Ph.D.  
Supervisor/Team Leader: Wendelyn Schmidt, Ph.D.  
Division Director: Sumathi Nambiar, M.D.  
Project Manager: Alison Rodgers

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205-053 are owned by Merck or are data for which Merck has obtained a written right of reference. Any information or data necessary for approval of NDA 205-053 that Merck does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Merck does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 205-053.

**1 Executive Summary**

**1.1 Recommendations**

**1.1.1 Approvability**

There are no nonclinical pharmacology or toxicology data that preclude the approval of NOXAFIL tablets.

**1.1.2 Additional Non Clinical Recommendations**

No additional nonclinical pharmacology or toxicology studies of NOXAFIL tablets are being recommended at this time.

**1.1.3 Labeling**

No labeling changes are being recommended at this time.

**1.2 Brief Discussion of Nonclinical Findings**

The regulatory requirement for Pharmacology and Toxicology studies for this NDA is fulfilled by referring to the nonclinical Pharmacology and Toxicology studies conducted under NDA (b) (4). The nonclinical data submitted with the current NDA consisted of two pharmacokinetics studies conducted to bridge the proposed tablet formulation of posaconazole (SCH56592) to the current marketed oral suspension. Administration of a single 60 mg oral dose of posaconazole (SCH56592) as a capsule or tablet increased SCH 56592 exposure when compared to the oral suspension. Dosing was well tolerated and, consistent with clinical data; single instances of emesis and soft feces were observed.

Study DM27344: ‘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 between the various formulations as listed in Table 1, below.

**Table 1 Description and Characterization of SCH 56592 Prototype Formulations**

| Group | Formulation              | Description      | Batch No. | SCH 56592 Concentration | Excipients |
|-------|--------------------------|------------------|-----------|-------------------------|------------|
| 1     | Oral Suspension          | Suspension       | 81713-111 | 40 mg/mL                | (b) (4)    |
| 2     | Solid Dispersion (b) (4) | Capsule          | 83471-106 | 60 mg/capsule           |            |
| 3     | Solid Dispersion (b) (4) | Capsule          | 83471-107 | 60 mg/capsule           |            |
| 4     | Semi-solid               | Capsule          | 83471-111 | 60 mg/capsule           |            |
| 5-6   | Solution for Injection   | (b) (4) Solution | 83073-127 | 2.5 mg/mL <sup>a</sup>  |            |

(b) (4)

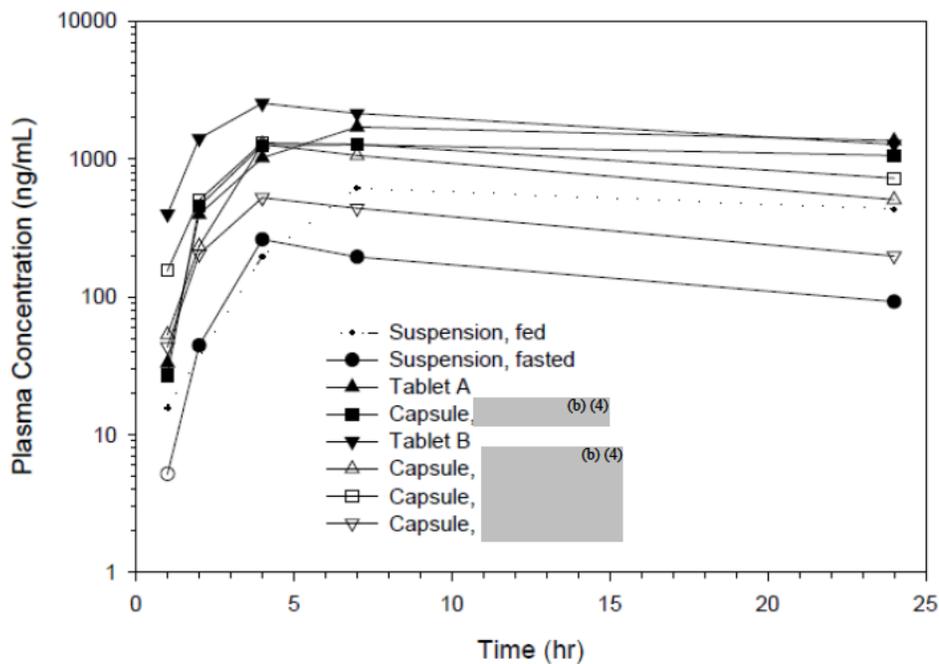
All three capsule formulations increased SCH 56592 exposure when compared to the marketed oral suspension (see Table 2, below). The most significant difference between the formulations was the presence and/or form of (b) (4)



Table 2. Mean (range) pharmacokinetic parameters of posaconazole following a single 60 mg oral administration of various formulations of posaconazole.

| Study        | Formulation                       | T <sub>max</sub> (hr) | C <sub>max</sub> (ng/mL) | AUC <sub>(0-t)</sub> (ng-hr/mL) | tf (hr)    |
|--------------|-----------------------------------|-----------------------|--------------------------|---------------------------------|------------|
| DM27344 (34) | Suspension <sup>a</sup>           | 4 (NA)                | 261 (190-332)            | 4950 (3140-6890)                | 48 (NA)    |
|              | Capsule (semi-solid) <sup>b</sup> | 4 (4-8)               | 531 (287-1060)           | 11400 (5360-18400)              | 60 (48-72) |
|              | Capsule (b) (4)                   | 4 (NA)                | 1280 (979-1460)          | 29600 (22500-37300)             | 84 (72-96) |
|              | Capsule (b) (4) <sup>d</sup>      | 4 (4-8)               | 1480 (1020-1840)         | 38400 (24100-51200)             | 84 (72-96) |
| DM27489 (40) | Tablet A <sup>e</sup>             | 7 (NA)                | 1710 (1330-2450)         | 69500 (49900-109000)            | 72 (NA)    |
|              | Capsule (b) (4)                   | 27 (4-48)             | 1690 (636-3420)          | 64000 (23200-127000)            | 72 (NA)    |
|              | Tablet B <sup>f</sup>             | 4 (NA)                | 2540 (1990-3270)         | 77700 (49600-125000)            | 72 (NA)    |

Figure 2. Plasma concentration-time profile during the first 24 Hours after oral administration of various formulations of posaconazole to monkeys.



The table below details the tablet composition for the intended market posaconazole tablet. This contains two forms of the (b) (4)

(b) (4)

| Components  | Quality Standard  | Function      | Amount per tablet (mg) |
|---|-------------------|---------------|------------------------|
| Posaconazole, (b) (4)                               | In-house standard | Active        | 100.0 (b) (4)          |
| Hypromellose Acetate Succinate <sup>a</sup> (b) (4) | NF                |               |                        |
| (b) (4)   | NF                |               |                        |
| Microcrystalline Cellulose                          | NF                |               |                        |
| Hydroxypropyl Cellulose                             | NF                |               |                        |
| Silicon Dioxide                                     | NF                |               |                        |
| Croscarmellose Sodium                               | NF                |               |                        |
| Magnesium Stearate                                  | NF                |               |                        |
| Film coating  |                   |               |                        |
| Opadry® II Yellow (b) (4)                           | In-house standard | Color coating | (b) (4)                |
| Coated Tablet Weight                                |                   |               | (b) (4)                |

Discussion and Conclusion

NOXAFIL® (Posaconazole) ORAL SUSPENSION 40 mg/mL is the currently marketed in the US and it is recommended to administer posaconazole with food to assure attainment of adequate plasma concentrations. Administration with a high fat meal increases the AUC by 2 to 4-fold compared to fasted patients. This NDA introduces a tablet form of posaconazole which was prepared using (b) (4)

This formulation limits the amount of SCH 56592 dissolved at low pH (b) (4) in the stomach and enhances the dissolution at neutral pH (b) (4) for maximal absorption in the small intestine. The data presented show that the tablet formulation significantly increased exposure to posaconazole, making it more likely that adequate plasma concentrations will be attained (b) (4).

Adverse effects (including emesis, soft feces and increases in liver enzymes) were similar to those observed with the oral suspension and can be monitored in the clinic. There are no data that would preclude the approval of NOXAFIL® (Posaconazole) TABLETS.

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/s/  
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OWEN G MCMASTER  
10/09/2013

WENDELYN J SCHMIDT  
10/09/2013

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205035

Applicant: Merck

Stamp Date: 1/25/2013

Drug Name: NOXAFIL<sup>®</sup> (posaconazole) Tablet NDA Type: Priority

On initial overview of the NDA/BLA application for filing:

|   | Content Parameter  | Yes | No | Comment   |
|---|--|-----|----|---|
| 1 | Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?  |     |    | N/A. No new pharmacology/toxicology data. Applicant will reference data submitted to NDA [REDACTED] (b) (4) |
| 2 | Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?   |     |    | N/A   |
| 3 | Is the pharmacology/toxicology section legible so that substantive review can begin?   |     |    | N/A   |
| 4 | Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?        | √   |    |   |
| 5 | If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA). | √   |    |   |
| 6 | Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?   | √   |    |   |
| 7 | Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?  |     |    | N/A   |
| 8 | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?  |     |    | N/A   |

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

|    | <b>Content Parameter</b>  | <b>Yes</b> | <b>No</b> | <b>Comment</b> |
|----|---|------------|-----------|----------------|
| 9  | Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57? | √          |           |                |
| 10 | Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)   | √          |           |                |
| 11 | Has the applicant addressed any abuse potential issues in the submission?   |            |           | N/A            |
| 12 | If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?   |            |           | N/A            |

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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Reviewing Pharmacologist Date

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Team Leader/Supervisor Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

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/s/  
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OWEN G MCMASTER  
03/17/2013

WENDELYN J SCHMIDT  
03/19/2013