CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-027

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER: 22-003

NAME OF APPLICANT / NDA HOLDER: Schering Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): NOXAFIL®

ACTIVE INGREDIENT(S)	STRENGTH(S)
Posaconazole	40 mg. Posaconazole per mL

DOSAGE FORM: Oral Suspension

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,661,151	August 26, 1997	August 26, 2014

d. Name of Patent Owner: SCHERING CORPORATION

Address *(of Patent Owner)*: 2000 Galloping Hill Road
City/State: Kenilworth, New Jersey
ZIP Code: 07033-0530
FAX Number *(if available)*: 908-298-5388
Telephone Number: 908-298-4000
E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ The applicant, Schering Corp., has a place of business within the U.S.

Address *(of agent or representative named in 1.e.)*:
City/State:
ZIP Code:
FAX Number *(if available)*:
Telephone Number:
E-Mail Address *(if available)*:

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? See Attachment 1	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes	☐ No
4.2 Claim Number (*as listed in the patent*): 9 and 13	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* See Attachment 2.		

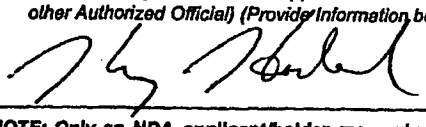
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	12/20/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Henry Hadad	
Address Patent Department K-6-1 Mailstop 1990 2000 Galloping Hill Road	City/State Kenilworth, New Jersey
ZIP Code 07033-0530	Telephone Number 908-298-2906
FAX Number *(if available)* 908-298-5388	E-Mail Address *(if available)* henry.hadad@spcorp.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Form FDA 3542a
Noxafil ®/NDA No. 22-003
USPN 5,661,151

ATTACHMENT 1

Item 2.1:

Because U.S. Patent No. 5,661,151 claims the drug substance for which approval is sought, it qualifies for listing on that basis and thus Question 2.1 is answered affirmatively. Accordingly, we do not address Questions 2.2, 2.3 or 2.4 on the Form concerning other forms of the drug substance.

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
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For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 22-003

NAME OF APPLICANT / NDA HOLDER: Schering Corporation

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TRADE NAME (OR PROPOSED TRADE NAME): NOXAFIL®

ACTIVE INGREDIENT(S)	STRENGTH(S)
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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,703,079	December 30, 1997	December 30, 2014

d. Name of Patent Owner: SCHERING CORPORATION

Address *(of Patent Owner)*: 2000 Galloping Hill Road
City/State: Kenilworth, New Jersey
ZIP Code: 07033-0530
FAX Number *(if available)*: 908-298-5388
Telephone Number: 908-298-4000
E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ The applicant, Schering Corp., has a place of business within the U.S.

Address *(of agent or representative named in 1.e.)*:
City/State:
ZIP Code:
FAX Number *(if available)*:
Telephone Number:
E-Mail Address *(if available)*:

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? See Attachment 1	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☒ Yes	☐ No
4.2 Claim Number (*as listed in the patent*) 8	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* See Attachment 2.		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

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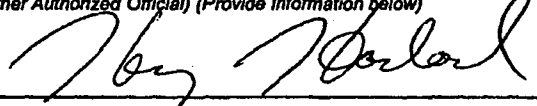
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	12/20/05

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Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name: Henry Hadad	
Address: Patent Department K-6-1 Mailstop 1990 2000 Galloping Hill Road	City/State: Kenilworth, New Jersey
ZIP Code: 07033-0530	Telephone Number: 908-298-2906
FAX Number *(if available)*: 908-298-5388	E-Mail Address *(if available)*: henry.hadad@spcorp.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Form FDA 3542a
Noxafil ®/NDA No. 22-003
USPN 5,703,079

ATTACHMENT 1

Item 2.1:

Because U.S. Patent No. 5,703,079 claims the drug substance for which approval is sought, it qualifies for listing on that basis and thus Question 2.1 is answered affirmatively. Accordingly, we do not address Questions 2.2, 2.3 or 2.4 on the Form concerning other forms of the drug substance.

__2__ Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

EXCLUSIVITY SUMMARY

NDA # 22-003 SUPPL # N/A HFD # 590

Trade Name Noxafil

Generic Name posaconazole

Applicant Name Schering Corporation

Approval Date, If Known June 22, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Kristen Miller, Pharm.D.
Title: Regulatory Health Project Manager
Date: May 30, 2006

Name of Office/Division Director signing form: Renata Albrecht, M.D.
Title: Director, Division of Special Pathogen and Transplant Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Exclusivity

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

/s/

Renata Albrecht
5/31/2006 02:14:13 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA: 22-027 **Supplement Type (e.g. SE5):** N/A **Supplement Number:**

Stamp Date: December 22, 2005 **PDUFA Action Date:** October 22, 2006

HFD-590 **Trade and generic names/dosage form:** Noxafil (posaconazole) Oral Suspension

Applicant: Schering Corporation **Therapeutic Class:** Systemic Antifungal (7030410)

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for these applications: 1

Indications:
Treatment of oropharyngeal candidiasis

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

X **No: Please check all that apply:** ____**Partial Waiver** __X__**Deferred** ____**Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.** 0 **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.** 18 **Tanner Stage**_____

Reason for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 6/22/2011

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Kristen Miller, Pharm.D.
Regulatory Project Manager

cc: NDA 22-027 and HFD-960/ Grace Carmouze
(revised 12-22-03)
FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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

/s/

Kristen Miller
5/30/2006 09:14:37 AM

Schering Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Thomas Haverty, M.D.

Group Vice President, Global Clinical Operations

APPEARS THIS WAY
ON ORIGINAL

NDA 22-027 Noxafil® (posaconazole)
oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to fluconazole or itraconazole

Division Director Review

Application Type	NDA 22-027
Submission Date	December 21, 2005
PDUFA Goal Date	October 22, 2006
Team Leader	Leonard Sacks, MD
Director	Renata Albrecht, MD
Review Completion Date	October 20, 2006
Established Name	Posaconazole
Trade Name	Noxafil®
Therapeutic Class	Antifungal Agent
Applicant	Schering-Plough Research Institute
Priority Designation	S
Formulation	Oral Suspension (40 mg/mL) in 4 oz bottle
Dosing Regimen	(see below)
Proposed Indication	oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and fluconazole (See **MICROBIOLOGY** and **CLINICAL STUDIES**).
Intended Population	Patients 13 years of age and older

Recommendations:

This application should be approved and the following text added to the INDICATIONS AND USAGE section of the labeling,

> "NOXAFIL (posaconazole) is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole (See **MICROBIOLOGY** and **CLINICAL STUDIES**)."

The treatment regimen is 100 mg PO BID on the first day, and 100 mg PO QD for 13 days for oropharyngeal candidiasis (OPC). The dosage regimen for OPC refractory to itraconazole or fluconazole is 400 mg PO BID. Duration of therapy in the latter should be based on the severity of the patient's underlying disease and clinical response. In clinical trials, patients with refractory disease received an average of approximately 100 days of treatment, with some patients receiving up to approximately 600 days of treatment.

Postmarketing Commitments:

None

Pediatric requirement under PREA:

Pediatric studies in patients 0-12 years of age with OPC are deferred under PREA until October 20, 2011.

Background – oropharyngeal candidiasis

Oropharyngeal candidiasis is an opportunistic infection caused primarily by *Candida albicans*, although other species of *Candida*, such as *C. glabrata, C. krusei, C. tropicalis, C. parapsilosis C. kefyr* and others can also be responsible for the infection. OPC can be seen in a variety of clinical settings, including

diabetes mellitus, patients receiving drugs such as corticosteroids or chemotherapeutic agents, patients with nutritional deficiencies (iron anemia, malnutrition), and local oral pathology such as xerostomia or dentures. OPC is also seen in immunocompromised patients, such as HIV-infected patients particularly with low CD4 counts (e.g., less than 100 cells/mL). The spontaneous resolution or cure of OPC is low, efficacy with drugs such as nystatin is around 50% and efficacy with fluconazole reaches 80-90%. [1] In a review of the literature by Patton et al [2], two trials comparing nystatin to fluconazole are presented and show a statistically significant difference between the drugs. In one trial the efficacy of fluconazole is 87% vs 52% in nystatin. In the other study, the efficacy is 80% and 29%, respectively. These studies show that the difference between the treatment arms range from 35% to 49%.

The following text is excerpted from the CLINICAL STUDIES section of the Diflucan package insert describing OPC:

> **Clinical cure at the end of treatment was reported for 86% of fluconazole treated patients compared to 46% of nystatin treated patients. Mycologically, 76% of fluconazole treated patients had the infecting organism eradicated compared to 11% for nystatin treated patients.**

	Fluconazole	**Nystatin**
Enrolled	96	90
Clinical Cure	76/88 (86%)	36/78 (46%)
Mycological eradication*	55/72 (76%)	6/54 (11%)

> *** Subjects without follow-up cultures for any reason were considered nonevaluable for mycological response.**

> **The proportion of patients with clinical relapse 2 weeks after the end of treatment was 14% for subjects receiving DIFLUCAN and 16% for subjects receiving nystatin. At 4 weeks after the end of treatment the percentages of patients with clinical relapse were 22% for DIFLUCAN and 23% for nystatin.**

In providing a justification for their proposed inferiority margin of 15%, the company cited studies comparing fluconazole vs nystatin and calculated a 95% CI for the differences between fluconazole vs nystatin (-53%, -27%) noting that a confidence interval of 15% preserves approximately half of that benefit. In fact, as seen in the study results below, in essentially all analyses of the mITT and per protocol populations, including evalution at the end of treatment (14 days) and at 4 weeks after the completion of therapy, the lower limit of the calculated confidence interval is 10%.

As stated in the review for NDA 22-003, "Therapeutic advances in the fields of oncology and transplantation have led to new treatment options for patients, but many of the involved treatments (such as chemotherapy in oncologic diseases or immunosuppressive agents to prevent transplant rejection) result in compromised immunity. As a result of impaired immune function, these patients are at risk for opportunistic infections. "....fungal infections are particularly problematic in immunocompromised patients. The two major fungal species responsible for these infections are *Candida* spp. and *Aspergillus* spp." OPC has the potential to cause significant morbidity, and is often seen in association with esophageal candidiasis, as in the trial submitted in this NDA.

Diflucan (fluconazole), the control drug in the OPC studies, is approved for the treatment of OPC. Itraconazole, ketoconazole, nystatin are also approved while none of the echinocandins have this indication. Caspofungin carries information in the CLINICAL STUDIES section indicating that OPC patients had an inferior outcome on caspofungin compared to fluconazole.

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[1] Horgan MM and WG Powderly, Chapter 21, Oral Fungal Infections. in Clinical Mycology, Elias J Anaissie, MR McGinnis and MA Pfaller, editors. Churchill Livingstone 2003.

[2] Patton LL et al A systematic review of the effectiveness of antifungal drugs for the prevention and treatment of oropharyngeal candidiasis in HIV-positive patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:170-9. [study developed under RTI/UNC EPC under contract to the Agency for Healthcare Research and Quality]

However, while azole treatment has been successful in the treatment of OPC and other *Candida* infections, *Candida* isolates resistant to these azoles have developed. In the non-comparative clinical studies submitted in this application, the definition of refractory OPC was patients who did not respond to at least 10 days of treatment with either fluconazole 100 mg or itraconazole 200 mg.

Synopsis of Efficacy and Safety:

Efficacy (See reviews by Drs Alivisatos and Dixon)
NDA 22-027 contains data from four clinical studies in support of the efficacy of posaconazole in OPC (2 comparative trials) and refractory OPC (2 noncomparative trials) :

- **Study C/I97-331**, a Phase 3 trial of OPC comparing posaconazole suspension (100 mg PO BID on day 1, 100 QD for 13 days) vs fluconazole (100 mg PO BID on day 1, 100 QD for 13 days). This evaluator blinded trial was done at 44 centers; 20% of patients were from the US. Patients were evaluated at the end of therapy (EOT) and again 4 weeks after completing treatment (See Tables below Patients' clinical symptoms were scored on a scale of 0-3, plaques were quantitated on a scale of 0-3, and cultures were judged negative if there were 0 CFU/mL. [The original protocol stated that cultures with < or equal to 20 CFU/mL would be interpreted as showing mycological success.]

Clinical Response at End of 14 Days of Therapy, StudyC/I97-331 (source, review by Dr Dixon)

	posaconazole	fluconazole	Difference and 95% CI*
MITT	155/169 (91.7)	148/160 (92.5)	-0.8 (-7.2, 5.6)
Cure	138	132	
Improvement	17	16	
Protocol Evaluable	139/143 (97.2)	130/135 (96.3)	0.9 (-4.0, 5.8)
Cure	125	116	
Improvement	14	14	

*A difference (posaconazole- fluconazole) and 95% confidence interval is reported.

Clinical Response at Follow-up in Study C/I97-331 (source, review by Dr Dixon)

	MITT		Protocol Evaluable	
	posaconazole n=169	fluconazole n=160	posaconazole n=143	fluconazole n=135
Cure	95	81	83	72
Improved	3	3	3	3
Relapse	45	52	43	46
Indeterminate	12	12	10	9
Previous Failure	14	12	4	5

Mycologic Response C/I97-331 (source, review by Dr Dixon)

	MITT		Protocol Evaluable	
	posaconazole n=169	fluconazole n=160	posaconazole n=143	fluconazole n=135
End of Therapy				
Eradicated	88 (52.1)	80 (50.0)	79 (55.2)	72 (53.3)
Superinfection	18	19	14	17
Persistent	50	50	47	42
Presumed Persistent	3	4	1	2
Indeterminate	10	7	2	2

Difference and 95% CI*	2.1 (-9.3, 13.5)		1.9 (-10.5, 14.3)	
Follow-up				
Eradicated	25 (14.8)	13 (8.1)	23 (16.0)	13 (9.6)
New infection	3	3	2	3
Relapse	49	51	46	47
Indeterminate	11	13	8	9
Previous Failure	81	80	64	63
Difference and 95% CI*	6.7 (-0.7, 14.1)		6.4 (-2.1, 14.9)	

*A difference (posaconazole- fluconazole) in eradication rates and 95% confidence interval is reported.

- **Study C/I96-209** was a Phase 2 dose ranging study of OPC comparing 4 doses of posaconazole oral capsule (50 mg, 100mg, 200 mg, and 400 mg) to fluconazole. In this trial, all patients received a 400 mg PO loading dose of posaconazole, and the study did not show a dose response. In the 200 mg arm, there were anomalously low results. The 100 mg and 400 mg data, however, were comparable to fluconazole and this trial provided supportive evidence of efficacy (See Table below)

Clinical Response at End of Therapy and Follow-up, MITT Population, Study C/I96-209 (source, review by Dr Dixon)

	posaconazole 50 mg	**posaconazole 100 mg**	**posaconazole 200 mg**	**posaconazole 400 mg**	**fluconazole**
# Patients	86	91	85	92	83
End of Therapy					
Success	73 (84.9)	79 (86.8)	65 (76.5)	80 (87.0)	74 (89.2)
Cure	64	73	63	76	69
Improvement	9	6	2	4	5
Difference* (95.2% CI)	-4.3 (-15.7, 7.1)	-2.4 (-13.3, 8.5)	-12.7 (-25.2, -0.2)	-2.2 (-13.0, 8.6)	
Follow-up					
Success	35 (40.7)	41 (45.1)	35 (41.2)	45 (48.9)	39 (47.0)
Relapse	24	27	19	25	23
Previous Failure	13	12	20	12	9
Indeterminate	14	11	11	10	12

*A difference (posaconazole- fluconazole) in success rates and 95.2% confidence interval is reported.

Mycologic Eradication at End of Therapy, MITT Population Study C/I96-209 (source, review by Dr Dixon)

posaconazole 50 mg	**posaconazole 100 mg**	**posaconazole 200 mg**	**posaconazole 400 mg**	**fluconazole**
29/86 (33.7)	31/91 (34.1)	27/85 (31.8)	33/92 (35.9)	33/83 (39.7)

- **Study C/I97-330** was a study of refractory OPC. Patients received posaconazole 400 mg PO BID for 3 days, and continued treatment with 400 mg QD (the regimen was amended after the first 103 patients to be 400 mg PO BID continuously). Patients were treated for 28 days and treatment could be extended to 3 months. Evaluation of response was done at 4 weeks. Although 199 patients were screened, and the company considered 176 evaluable, the division considered 96 evaluable because a stricter definition for refractory OPC was used. Specifically, patients who received at least 10 days of the approved fluconazole or itraconazole treatment regimen within 14 days of enrolling in the study were classified as having refractory OPC. The company reported a success rate of 132/176 (75%), The Division calculated a success rate of 66/89 (74.2%). The outcome in patients enrolled pre-amendment and post-amendment was similar (73.3% vs 75%). This study served as the primary data for refractory OPC.

- **Study P00298** was also a non-comparative trial in patients with refractory OPC. Although 100 HIV infected patients were enrolled, 60 of these were from study C/I97-330, and 40 were newly enrolled. The average duration of treatment was 100 days, some patients in this trial received posaconazole 400 mg BID PO for up to 15 months. The company reported a success rate among the 100 patients of 85.6%. A similar success rate was seen in the 40 newly enrolled patients.

Collectively, the data from these four studies support the efficacy of posaconazole in the treatment of OPC and refractory OPC. The information from the Phase 3 study and data supporting the refractory OPC approval will be included in the CLINICAL STUDIES section. The text of this section is provided below:

Treatment of Oropharyngeal Candidiasis (OPC)

Study 3 was a randomized, controlled, evaluator-blinded study in HIV-infected patients with oropharyngeal candidiasis. Patients were treated with posaconazole or fluconazole oral suspension (both posaconazole and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

Clinical and mycological outcomes were assessed after 14 days of treatment and at 4 weeks after the end of treatment. Patients who received at least one dose of study medication and had a positive oral swish culture of *Candida* species at baseline were included in the analyses (**TABLE 7**). The majority of the subjects had *C. albicans* as the baseline pathogen.

Clinical success at Day 14 (complete or partial resolution of all ulcers and/or plaques and symptoms) and clinical relapse rates (recurrence of signs or symptoms after initial cure or improvement) 4 weeks after the end of treatment were similar between the treatment arms (**TABLE 7**).

Mycologic eradication rates (absence of colony forming units in quantitative culture at the end of therapy, day 14), as well as mycologic relapse rates (4 weeks after the end of treatment) were also similar between the treatment arms (see **TABLE 7**).

TABLE 7. Clinical Success, Mycological Eradication and Relapse Rates in Oropharyngeal Candidiasis

	Posaconazole	**Fluconazole**
Clinical Success at End of Therapy (Day 14)	155/169 (91.7%)	148/160 (92.5%)
Clinical Relapse (4 Weeks after End of Therapy)	45/155 (29.0%)	52/148 (35.1%)
Mycological Eradication (absence of CFU) at End of Therapy (Day 14)	88/169 (52.1%)	80/160 (50.0%)
Mycological Relapse (4 Weeks after End of Treatment	49/88 (55.6%)	51/80 (63.7%)

Mycologic response rates, using a criterion for success as a post-treatment quantitative culture with $\leq$20 colony forming units (CFU/mL) were also similar between the two groups (posaconazole 68.0%, fluconazole 68.1%). The clinical significance of this finding is unknown.

Treatment of Oropharyngeal Candidiasis Refractory to Treatment with Fluconazole or Itraconazole

Study 4 was a non-comparative study of posaconazole oral suspension in HIV-infected subjects with OPC that was refractory to treatment with fluconazole or itraconazole. An episode of OPC was considered refractory if there was failure to improve or worsening of OPC after a standard course of therapy with fluconazole ≥100 mg/day for at least 10 consecutive days or itraconazole 200 mg/day for at least 10 consecutive days and treatment with either fluconazole or itraconazole had not been discontinued for more than 14 days prior to treatment with posaconazole. Eighty-nine subjects met these criteria for refractory infection.

Forty-five subjects with refractory OPC were treated with posaconazole 400 mg BID for three days, followed by 400 mg QD for 25 days with an option for further treatment during a 3-month maintenance period. Following a dosing amendment, a further 44 subjects were treated with posaconazole 400 mg BID for twenty-eight days. The efficacy of posaconazole was assessed by the clinical success (cure or improvement) rate after 4 weeks of treatment. The clinical success rate was 74.2% (66/89). The clinical success rates for both the original and the amended dosing regimens were similar (73.3% and 75.0%, respectively).

Safety

The safety from these four OPC studies as well as two prophylaxis studies (Studies CI98-316 & PO1899) and data on patients treated for various refractory fungal infections were previously reviewed under NDA 22-003 (issued AP letter for prophylaxis on September 15, 2006). In the OPC studies, 356/557 (64%) reported ADR compared to 175/262 (67%) in the fluconazole arms. The most frequently seen events were gastrointestinal – nausea, vomiting, diarrhea; other events were headaches and fever.

As part of the approval of NDA 22-003, the company agreed to follow TTP, PE and microangiopathic adverse events in the post marketing period. The data for this application had been previously reviewed as therefore, there are no new safety signals identified.

The following information regarding safety is included in the package insert.

Overview of Adverse Events in HIV infected subjects with OPC:

In two randomized comparative studies in OPC, the safety of posaconazole at a dose of ≤ 400 mg QD in 557 HIV infected patients was compared to the safety of fluconazole in 262 HIV-infected patients at a dose of 100 mg QD.

An additional 239 HIV infected patients with refractory OPC received posaconazole in 2 non-comparative trials for refractory OPC (rOPC). 149 of these subjects received the 800 mg/day dose and the remainder received the ≤ 400 QD dose.

TABLE 14 presents Treatment Emergent Adverse Events of Clinical Significance in the comparative and non-comparative studies of OPC.

TABLE 14. Treatment Emergent Adverse Events of Clinical Significance in OPC studies

	Number (%) of Subjects		
	Controlled OPC Pool		Refractory OPC Pool
	POS n=557	FLZ n=262	POS n=239
Subjects Reporting any Adverse Event[a]	356 (64)	175 (67)	221 (92)
Body as a Whole - General Disorders			
Fever	34 (6)	22 (8)	82 (34)
Headache	44 (8)	23 (9)	47 (20)
Anorexia	10 (2)	4 (2)	46 (19)
Fatigue	18 (3)	12 (5)	31 (13)
Asthenia	9 (2)	5 (2)	31 (13)
Rigors	2 (<1)	4 (2)	29 (12)
Pain	4 (1)	2 (1)	27 (11)
Disorders of Blood and Lymphatic System			
Neutropenia	21 (4)	8 (3)	39 (16)
Anemia	11 (2)	5 (2)	34 (14)

	Number (%) of Subjects		
	Controlled OPC Pool		Refractory OPC Pool
Neutropenia Aggravated	0	0	5 (2)
Gastro-Intestinal System Disorders			
Diarrhea	58 (10)	34 (13)	70 (29)
Nausea	48 (9)	30 (11)	70 (29)
Vomiting	37 (7)	18 (7)	67 (28)
Abdominal Pain	27 (5)	17 (6)	43 (18)
Infection and Infestations			
Candidiasis, Oral	3 (1)	1 (<1)	28 (12)
Herpes Simplex	16 (3)	8 (3)	26 (11)
Pneumonia	17 (3)	6 (2)	25 (10)
Liver and Biliary System Disorders			
Bilirubinemia	6 (1)	2 (1)	6 (3)
Hepatic Enzymes Increased	1 (<1)	1 (<1)	8 (3)
Hepatic Function Abnormal	8 (1)	4 (2)	0
Hepatitis	3 (1)	0	5 (2)
Hepatomegaly	0	0	8 (3)
Jaundice	0	0	4 (2)
SGOT Increased	8 (1)	5 (2)	6 (3)
SGPT Increased	6 (1)	5 (2)	6 (3)
Metabolic and Nutritional Disorders			
Weight Decrease	4 (1)	2 (1)	33 (14)
Dehydration	4 (1)	7 (3)	27 (11)
Hypokalemia	6 (1)	3 (1)	15 (6)
Platelet, Bleeding and Clotting Disorders			
Thrombocytopenia	4 (1)	1 (<1)	12 (5)
Psychiatric Disorders			
Insomnia	8 (1)	3 (1)	39 (16)
Renal & Urinary System Disorders			
Renal Failure Acute	0	0	7 (3)
Respiratory System Disorders			
Coughing	18 (3)	11 (4)	60 (25)
Dyspnea	8 (1)	8 (3)	28 (12)
Skin and Subcutaneous Tissue Disorders			
Rash	15 (3)	10 (4)	36 (15)
Sweating Increased	13 (2)	5 (2)	23 (10)

OPC=oropharyngeal candidiasis; POS=posaconazole; FLZ=fluconazole;
SGOT=serum glutamic oxaloacetic transaminase (same as AST); SGPT=serum glutamic pyruvic transaminase (same as ALT).
[a]: Number of subjects reporting treatment-emergent adverse events at least once during the study, without regard to relationship to treatment. Subjects may have reported more than one event.

Treatment related, treatment emergent events observed in patients with OPC at an incidence of ≥ 2% are shown in TABLE 15.

TABLE 15. Treatment Related, Adverse Events (Any Grade) ≥ 2%

	Number (%) of Subjects		
	Controlled OPC Pool		Refractory OPC Pool
	POS	FLZ	POS
Adverse Event	n=557	n=262	n=239
Subjects Reporting any Adverse Event[a]	150 (27)	70 (27)	135 (56)
Body As A Whole - General Disorders			
Headache	16 (3)	5 (2)	18 (8)
Anorexia	6 (1)	1 (<1)	7 (3)
Asthenia	4 (1)	2 (1)	6 (3)
Dizziness	9 (2)	5 (2)	8 (3)
Fatigue	8 (1)	5 (2)	7 (3)
Fever	10 (2)	1 (<1)	6 (3)
Central and Periph Nerv System			
Somnolence	4 (1)	5 (2)	3 (1)
Disorders of Blood and Lymphatic System			
Neutropenia	10 (2)	4 (2)	20 (8)
Anemia	2 (<1)	0	6 (3)
Gastro-Intestinal System Disorders			
Diarrhea	19 (3)	13 (5)	26 (11)

	Number (%) of Subjects		
	Controlled OPC Pool		Refractory OPC Pool
Nausea	27 (5)	18 (7)	20 (8)
Vomiting	20 (4)	4 (2)	16 (7)
Abdominal Pain	10 (2)	8 (3)	12 (5)
Flatulence	6 (1)	0	11 (5)
Mouth Dry	7 (1)	6 (2)	5 (2)
Liver and Biliary System Disorders			
Hepatic Enzymes Increased	1 (<1)	0	5 (2)
Hepatic Function Abnormal	3 (1)	4 (2)	0
Metabolic and Nutritional Disorders			
Phosphatase Alkaline Increased	3 (1)	3 (1)	5 (2)
Musculo-Skeletal System Disorders			
Myalgia	1 (<1)	0	4 (2)
Platelet, Bleeding and Clotting Disorders			
Thrombocytopenia	3 (1)	0	4 (2)
Psychiatric Disorders			
Insomnia	3 (1)	0	6 (3)
Skin and Subcutaneous Tissue Disorders			
Rash	8 (1)	4 (2)	10 (4)
Pruritus	6 (1)	2 (1)	5 (2)

OPC=oropharyngeal candidiasis; POS=posaconazole; FLZ=fluconazole;
SGOT=serum glutamic oxaloacetic transaminase (same as AST); SGPT=serum glutamic pyruvic transaminase (same as ALT).
[a]: Number of subjects reporting treatment-related adverse events at least once during the study, without regard to relationship to treatment. Subjects may have reported more than one event.

Adverse events were reported more frequently in the pool of patients with refractory OPC Among these highly immunocompromised patients with advanced HIV disease, serious adverse events (SAEs) were reported in 55% (132/239). The most commonly reported SAEs were fever (13%) and neutropenia (10%).

Treatment-related SAEs were reported for 14% (34/239) of these patients and included neutropenia (5%) and abdominal pain (2%). Posaconazole was discontinued in two patients who developed neutropenia that was considered serious and treatment-related. All other reported treatment-related SAEs occurred in ≤1% of subjects on posaconazole.

Uncommon and rare treatment related serious or medically significant adverse events reported during clinical trials in prophylaxis, OPC/rOPC or other indications with posaconazole have included adrenal insufficiency, allergic and/or hypersensitivity reactions.

In addition, a **Patient Package Insert** is being approved with this application. It summarizes important information regarding posaconazole, notably the significant interaction with cyclosporine that has resulted in deaths in 3 patients in the NDA databases. It instructs patients to inform their doctors if they are taking immunosuppressants like cyclosporine, tacrolimus or sirolimus since serious and rarely, fatal toxicity from cyclosporine has occurred when used together with posaconazole. For this reason, dose reduction and monitoring of blood levels is necessary for concurrent use of these immnosuppressive agents. Information is also included on the possible increase in frequency of blood clots among cancer or stem cell transplant patients treated with cyclosporine or tacrolimus and posaconazole.

Microbiology
Although the company wishes to i [redacted], in the Microbiology subsection of the labeling, clinical data for isolates other than *Candida albicans* are few and isolated in mixed culture. Therefore, the Division has only included the following information in the approved labeling.

Activity in vitro and in vivo

Posaconazole has shown in vitro activity against *Aspergillus fumigatus* and *Candida albicans*, including *Candida albicans* isolates from patients refractory to itraconazole or fluconazole or both drugs (See **CLINICAL STUDIES** and **INDICATIONS AND USAGE.**)

Chemistry

No new information

Clinical Pharmacology
No new information

Pharmacology / Toxicology
No new information

Division of Scientific Investigations
Three investigator sites were inspected. These investigators participated in both the OPC and refractory OPC studies. The inspections resulted in NAI recommendations for Dr Jacobson and Skiest, while a VAI recommendation was made for Dr Brosgart. The recommendation from DSI was that no major deficiencies were noted to compromise the integrity of the data, and the data reviewed were thus considered acceptable.

Summary
In summary, based on the results of these two comparative studies (Studies CI97-331 & C/I96-209), and two non-comparative studies (C/I97-330 and P00298), together with in vitro, animal study data, and supportive clinical data previously reviewed under ——— there is substantial evidence that posaconazole is effective in the treatment of OPC and refractory OPC.

The safety profile for posaconazole has been adequately described in the product label and a patient package insert is also being approved as part of this action.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Renata Albrecht
10/20/2006 12:53:13 PM
MEDICAL OFFICER

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE:

TO: Kristen Miller, Regulatory Project Manager
Maureen Tierney, M.D., Clinical Reviewer
Division of Special Pathogen and Transplant Products, HFD-590

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Karen M. Storms
Consumer Safety Officer
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 22-027

NME: Yes

APPLICANT: Schering Corporation

DRUG: NOXAFIL (posaconazole)

THERAPEUTIC CLASSIFICATION: (Priority Review)

INDICATION: Treatment of oropharyngeal candidiasis.

CONSULTATION REQUEST DATE: July 20, 2006

DIVISION ACTION GOAL DATE: September 22, 2006

PDUFA DATE: October 22, 2006

I. BACKGROUND:

Oropharyngeal candidiasis (OPC) is the most common opportunistic infection in HIV-infected patients. It occurs in up to 93% of these patients over the course of their illness. Furthermore, the incidence of oropharyngeal fungal infections (OFI) increases as CD_4+ lymphocyte count decreases, more than 60% of patients with less than 100 CD_4+ cells/mm^3 develop an OFI each year and over half of these patients develop recurrent OFI.

Posaconazole (SCH 56592) is a broad-spectrum triazole antifungal compound that contains a triazole analog active ingredient that is chemically similar to the broad-spectrum compounds fluconazole and itraconazole currently marketed in the United States. The antifungal mode of action of posaconazole is the selective inhibition of the alpha-demethylase P450 cytochrome system (CYP51A) involved in ergosterol biosynthesis of yeasts and filamentous fungi.

Protocol PC96-209
This was a Phase 2, safety and efficacy study for dose selection, using 2 interim analyses. This randomized (5 arms), active control, parallel-group, multicenter double-blind, and double-dummy study, was designed to compare SCH 56592 at different dose levels with fluconazole in the treatment of OPC in HIV-positive subjects. If the highest dose was shown to be at least equivalent of fluconazole, then this study was to serve as a phase III trial. Subjects received SCH 56592 capsules or fluconazole encapsulated tablets orally with meals. Subjects randomized to one of the 4 doses of SCH 56592 received 400 mg BID on Day 1, followed by one of the following 4 QD maintenance regimens on Days 2-14, 50, 100, 200, or 400 mg. Subjects randomized to fluconazole, received 200 mg on the first day followed by QD doses of 100 mg for 13 days.

Protocol C97-331
This was a Phase III, evaluator-blinded, multicenter study comparing the efficacy and safety of posaconazole (POZ) suspension versus fluconazole (FLZ) suspension for the treatment of OPC in HIV-infection subjects. The projected enrollment was 240 evaluable subjects from approximately 36 study sites. During the treatment phase, eligible subjects took an oral suspension of either POZ or FLZ: 200 mg on Day 1, followed by 100 mg once daily for the next 13 days.

Protocol C/I97-330:

This was a Phase III, noncomparative, open-label, multicenter study of POS in HIV-infected subject with oral and/or esophageal candidiasis that was unresponsive to standard treatment with oral fluconazole (FLZ) or itraconazole (ITZ). During the treatment period, eligible subject received POS oral suspension, 400 mg twice daily for 3 days, followed by 400 mg once daily for 25 days or 400 mg twice daily for 28 days, i.e., Day 1 through Day 29. The acute treatment period consisted of Study Day 1 through Study Day 29 and was the focus of most of the analyses. The maintenance period included in the Original Protocol (400 mg twice daily, three times weekly for 3 months) was discontinued in favor of a separate protocol (Protocol No. P00298) to evaluate the impact of long-term treatment with POS.

Protocol P00298:

This is a Phase III, noncomparative, open-label, multicenter study of POS in HIV- infected subjects with oral or esophageal candidiasis refractory to other azole antifungal agents. During the acute treatment phase, subjects received POS oral suspension, 400 mg twice a day (BID), for up to 3 months. Subjects with a clinical response of cure were observed for up to 1 month during an untreated follow-up period. Subject who remained cured at the end of follow-up were discontinued from the study. Subject who relapsed during follow-up or who showed improvement at the end of the treatment phase were eligible for the maintenance phase, continuing treatment with POS 400 mg BID for up to 12 months. Subjects were assessed monthly during the treatment and maintenance phases, and at the end of the follow-up period. Subjects were required to provide written informed consent before entering the treatment and maintenance phases, then at 3-month intervals during maintenance.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol #	Insp. Date	EIR Received Date	Field Classification
Brosgart	Berkeley, CA	C96-209 C97-330	8/7-14/06	Pending	VAI*
Jacobson	Berkeley, CA	C97-331 P00298 C97-330		Pending	NAI*
Skiest	Dallas, TX	C97-331 C96-209 00298 C97-330	8/8-8/14/06	Pending	NAI*

*Classification based on review of the Form FDA 483

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. **Protocol C97-330**

1. Carol Brosgart, M.D., Berkeley, CA 94705 (site 18)

   a. At this site, three subjects were randomized and enrolled into the study. An audit of three subjects' records was conducted and found adequate documentation that all subjects were available for the duration of the study. Data listings were accurate when compared to corresponding case report forms and laboratory data.

   b. There were no known limitations of the inspection; EIR pending.

   c. General observations/commentary:

      A Form FDA 483, Inspectional Observations, was not issued at the conclusion of the inspection. All subjects signed informed consent prior to receiving study drug.

   d. Assessment of data integrity: Based on preliminary information received from the field via e-mail, data for this site appear acceptable.

2. Susan Jacobson, M.D., Berkeley, CA 94705 (site 07)

   a. At this site, three subjects were randomized and enrolled. An audit of three subjects' records was conducted and found adequate documentation that all subjects were available for the duration of the study. Data listings were accurate when compared to corresponding case report forms and laboratory data.

   b. There were no known limitations of the inspection; EIR pending.

   c. General observations/commentary:

      A Form FDA 483, Inspectional Observations, was not issued at the conclusion of the inspection. All subjects received informed consent prior to receiving study drug.

d. Assessment of data integrity: Based on preliminary information received from the field via e-mail, data for this site appear acceptable.

D. Protocol P00298

1. Susan Jacobson, M.D., Berkeley, CA 94705 (site 07)

   a. At this site, seven subjects were randomized and enrolled into the study. An audit of three subjects' records was conducted and found data listings were accurate when compared to the corresponding case report forms and laboratory test values. There was adequate documentation to show that all subjects were available for the duration of their participation in the study.

   b. There were no known limitations of the inspection; EIR pending.

   c. General observations/commentary:

      A Form FDA 483, Inspectional Observations, was not issued at the conclusion of the inspection. All subjects signed informed consent prior to receiving study drug.

   d. Assessment of data integrity: Based on preliminary information received from the field via e-mail, data for this site appear acceptable.

2. Daniel J. Skiest, M.D., Dallas, TX 75235 (site 19)

   a. At this site, six subjects were randomized and enrolled into the study. An audit of two subjects' records was conducted and found data listings were accurate when compared to corresponding case report forms, laboratory test values and test article accountability.

   b. There were no known limitations of the inspection; EIR pending.

   c. General observations/commentary:

      A Form FDA 483, Inspectional Observations, was not issued at the conclusion of the inspection. Adverse events and serious adverse events were accurately reported. All subjects received informed consent prior to receiving study drug.

   d. Assessment of data integrity: Based on preliminary information received from the field via e-mail, data for this site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

With the limited information provided for the three above mentioned sites, no major deficiencies were noted that could compromise the integrity of the data. Thus, the data reviewed is acceptable. Should the inspection report contain information that would affect the application, it will be forwarded to the Review Division.

{See appended electronic signature page}

Karen M. Storms
Consumer Safety Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Karen Storms
9/11/2006 12:16:27 PM
CSO

Leslie Ball
9/12/2006 06:58:36 PM
MEDICAL OFFICER

DSI CONSULT: Request for Clinical Inspections

Date: July 20, 2006

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

From: Kristen Miller, Regulatory Project Manager, HFD-590
Division of Special Pathogen and Transplant Products

Subject: **Request for Clinical Site Inspections**
NDA 22-027
Schering Corporation
Noxafil (posaconazole) Oral Suspension

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Brosgart, Carol L., MD East Bay AIDS Center 3031 Telegraph Avenue Berkeley, CA 94705	C96-209	N = 30	Treatment of Oropharyngeal Candidiasis (OPC) in HIV-positive patients
Brosgart, Carol L., MD Same as above	C97-330	N = 3	Treatment of Azole Refractory Candidiasis in HIV-Infected Subjects
Susan Jacobson, M.D. Alta Bates Medical Center East Bay AIDS Center 2850 Telegraph Avenue, Suite 110 Berkeley, CA 94705	C97-331	N = 15	Treatment of Oropharyngeal Candidiasis (OPC) in HIV-positive patients
Susan Jacobson, MD (replaced at some point in the study by Claire Borkert, MD) Same as above	P00298	N = 7	Treatment of HIV-Infected Patients With Azole-Refractory Candidiasis

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Susan Jacobson, M.D. Same as above	C97-330	N = 3	Treatment of Azole Refractory Candidiasis in HIV-Infected Subjects
Daniel J. Skiest, M.D. The University of Texas Southwestern Medical Center 5323 Harry Hines Blvd. Dallas, Texas 75235-9113	C96-209	N = 9	Treatment of Oropharyngeal Candidiasis (OPC) in HIV-positive patients
Daniel J. Skiest, M.D. Same as above	C97-331	N = 8	Treatment of Oropharyngeal Candidiasis (OPC) in HIV-positive patients
Daniel J. Skiest, M.D. Same as above	P00298	N = 6	Treatment of HIV-Infected Patients With Azole-Refractory Candidiasis
Daniel J. Skiest, M.D. Parkland HIV/AIDS Clinic 1936 Amelia Court Dallas, TX 75235	C97-330 (11)	N < 10	Treatment of Azole Refractory Candidiasis in HIV-Infected Subjects

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by August 25, 2006. The PDUFA due date for this application is October 21, 2006.

Should you require any additional information or if there are concerns with meeting the goal inspection date, please contact Kristen Miller.

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/s/

Kristen Miller
7/20/2006 01:53:49 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
DA 22-027	Efficacy Supplement Type SE- N/A	Supplement Number- N/A	
Drug: Noxafil (posaconazole) Oral Suspension		Applicant: Schering Corporation	
RPM: Kristen Miller		HFD- 590	Phone # 301-796-0762

Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s): N/A

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	Type 6
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	October 20, 2006
Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 3006318
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	(X) 5/31/06 N/A (regarding remaining 3-year exclusivity)
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	(X) Filing Review: 5/31/06

General Information	
❖ Actions	
• Proposed action	(X) AP
• Previous actions (specify type and date for each action taken)	NDA 22-003 = AP on 9/15/06
• Status of advertising (approvals only)	(X)Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X- 10/19/06
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X- Consults DDMAC Review: 6/20/06 DMETS Review: 5/23/06 DMETS name consult- 8/25/06 DMETS name review- 8/30/06 DSRCS PPI review- 10/13/06 DDMAC Review: 10/24/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X- Voriconazole (5/19/06), Fluconazole (10/7/04), Itraconazole (9/24/03)
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X- 12/21/06 and 6/16/06
• Reviews	See DMETS reviews under labeling
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	2/8/06 (Acknowledge letter) 3/2/06 (Filing letter- issues noted) 3/21/06 (Review update letter) 4/24/06 (statistical request fax) 4/28/06, 5/15/06, 5/17/06, 5/23/06 (clinical info request faxes) 5/23/06, 6/5/06, 6/14/06 (PK request fax) 5/30/06, 8/30/06 (Label comments)
❖ Memoranda and Telecons	X- Admin split MEMO (see prophylaxis package)
❖ Minutes of Meetings	

• EOP2 meeting (indicate date)	X- 12/13/00 (Schering's minutes)
• Pre-NDA meeting (indicate date)	X- 10/25/05
• Pre-Approval Safety Conference (indicate date; approvals only)	X- 6/9/06
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X- 10/20/06
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X- 10/17/06
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	X - 9/13/06;Team Leader-10/18/06
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Clinical Review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X – 5/30/06
❖ Statistical review(s) *(indicate date for each review)*	X- 9/26/06
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X- 6/20/06, Addendum: 10/20/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X- 7/20/06 (requested) X – 9/12/06 (inspection summary)
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	X- 6/21/06
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X – 6/21/06
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: 5/31/06 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X- 6/20/06
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	X- 6/2/05 (for

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: **August 30, 2006 / (sent October 24, 2006)**

To: **Kristen Miller, PharmD**
Division of Special Pathogen and Transplant Products

From: Suzanne Berkman, PharmD
Division of Drug Marketing, Advertising, and Communications

Subject: **Drug: Noxafil (posaconazole) PPI**
NDA: 22-003

PPI

Currently, the FDA does not have a guidance or standard template for PPIs. The CFR applies to medication guides only. We recommend referring to DSRCS for their review of this proposed PPI for comments on formatting, order of presentation, consistency, and readability. These recommendations reflect my own experience in reviewing a number of PPIs.

I have revised the current PPI and you can track my changes under "final showing markup" in Word. Many of the revisions involve more patient-friendly language. The average consumer reads at an eighth grade level. I have also removed a couple statements that sound too promotional in nature.

APPEARS THIS WAY
ON ORIGINAL

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_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Suzanne Berkman
10/24/2006 01:06:49 PM
DDMAC REVIEWER

MEMORANDUM

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

DATE: October 13, 2006

TO: Renata Albrecht, M.D., Director
Division of Special Pathogen and Transplant Products

VIA: Kristen Miller, Regulatory Project Manager
Division of Special Pathogen and Transplant Products

FROM: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for Noxafil (posaconazole oral suspension), NDA 22-003 and NDA 22-027

Background and Summary

Noxafil was granted priority review status for NDA 22-033, and received approval on September 15, 2006. Noxafil is indicated for "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 hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy."

DSRCS has been consulted to review a proposed Patient Package Insert (PPI) submitted by the sponsor on August 1, 2006. We subsequently learned that the review division is also reviewing NOXAFIL under NDA 22-027 for a proposed indication in oropharyngeal candidiasis including infections that are refractory to itraconzaole and fluconazole. We have been asked to review this combined proposed PPI which reflects both the approved indication under NDA 22-003 and the proposed new indication under NDA 22-027.

See the attached patient labeling (PPI) for our recommended revisions to the draft combined PPI submitted for Noxafil (posaconazole oral suspension) under the above referenced NDAs. The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. We have simplified the wording where possible, made it consistent with the Professional Information (PI) and removed unnecessary information. We have also put this PPI in the patient-friendly format (specified in 21 CFR 208.20) that we are recommending for all FDA approved patient labeling, although this format is not required for

voluntary PPIs. These recommended changes are consistent with current research to improve risk communication to a lower literacy audience.

These revisions are based on the currently approved PI. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments and Recommendations

1. A PPI for Noxafil is voluntary. Except where drug products are dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that patients will receive the PPI. The Sponsor should state their mechanism for intended distribution of the PPI to patients.
2. The draft combined PPI submitted by the sponsor has a Flesch Kinkaid grade level of 7.7, and a Flesch Reading Ease score of 60.9. To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable. However, we have added bullets, boxes and bolding throughout the revised draft PPI to draw the patient's attention to critical information, and to enhance understanding and safe use of NOXAFIL, as well as used a shortened 2-column format.
3. We have addressed the clinical reviewer's concerns regarding prominence of important safety information in the PPI by placing information about serious adverse events and important drug interaction up front in a box under the section called, "What is the most important information I should know about NOXAFIL?" This information is then referenced in the following sections: "Who should not take NOXAFIL," What should I tell my doctor before taking NOXAFIL," and "What are the possible side effects of NOXAFIL."
4. We reviewed the treatment-related adverse events in the PI for all events occurring with a frequency of 3% or greater, and modified the common side effects list in the PPI accordingly.

Comments to the review division are ***bolded, underlined and italicized***. Attached to this memo, we are providing to the review division a marked-up and clean copy of the revised PPI in Word. We recommend using the clean copy as the working document.

Please call us if you have any questions.

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X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Sharon Mills
10/13/2006 05:10:08 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/13/2006 10:05:50 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM	**Division of Medication Errors and Technical Support (DMETS)** **Office of Surveillance and Epidemiology** **WO22, Mail Stop 4447** **Center for Drug Evaluation and Research**

TO: Renata Albrect, MD
Division of Special Pathogens and Transplant Products (HFD-590)

THROUGH: Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Alina Mahmud, R.Ph, MS, Team Leader
Division of Medication Errors and Technical Support

DATE: August 29, 2006

SUBJECT: **DMETS PROPRIETARY NAME REVIEW**
Drug: Noxafil (Posaconazole Oral Suspension) 200 mg/5 mL
Sponsor: Schering Corporation
BLA#: NDA 22-003, 22-027

OSE PROJECT #: 2006-90

This consult was written in response to an August 25, 2006 request from the Division of Special Pathogens and Transplant Products (HFD-590) for a re-assessment of the proprietary name Noxafil. DMETS previously reviewed the proposed proprietary name, Noxafil, on March 23, 2006 and December 12, 2004 (OSE consults #04-0028 and 06-0028-1, respectively) and did not recommend the use of the proprietary name. DMETS was concerned that Noxafil would be confused with the currently marketed drug products Lorabid, Mexitil Amoxil, and Minoxadil. Although the sponsor submitted a rebuttal in defense of the name Noxafil, DMETS was not convinced that the potential for confusion is minimal.

DMETS continues to object to the use of the proprietary name Noxafil. Since the sponsor has not submitted additional information to support the use of the proprietary name Noxafil, and the Division has decided to allow the use of the proposed name, DMETS has not conducted another proprietary name review.

We would be willing to meet with the Division for further discussion. If you have further questions or need clarification, please contact Diane Smith, Project Manager, at 301-796-0538.

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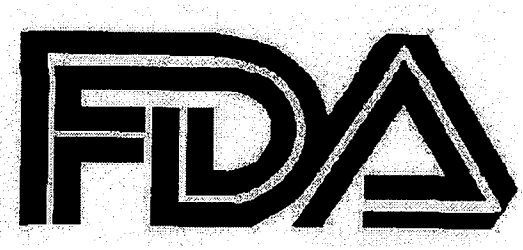
/s/

Alina Mahmud
8/30/2006 03:21:16 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/30/2006 03:25:03 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/30/2006 03:31:12 PM
DRUG SAFETY OFFICE REVIEWER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 30, 2006

To: Todd Paporello, Pharm.D.	**From:** Kristen Miller, Pharm.D.
Company: Schering	Division of Special Pathogen and Transplant Products
Fax Number: 908-740-6500	**Fax Number:** 301-796-9882
Phone Number: 908-740-4252	**Phone Number:** 301-796-0762

Subject: OPC Labeling NDA 22-027

Total no. of pages including cover: 10

Comments: Concur:

Regina Alivisatos, M.D.	Medical Officer
Leonard Sacks, M.D.	Medical Team Leader
Karen Higgins, Sc.D.	Statistics Team Leader
Cheryl Dixon, Ph.D.	Statistics Reviewer
Shukal Bala, Ph.D.	Microbiology Team Leader
Kalavati Suvarna, Ph.D.	Microbiology Reviewer

Document to be mailed: ☐ YES ☑ NO

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Please refer to your new drug application (NDA) 22-027 for Noxafil® (posaconazole) Oral Suspension submitted on December 22, 2005. Please see attached draft labeling for the **INDICATIONS, CLINICAL STUDIES** and **ADVERSE EVENTS** sections of the label that pertain to OPC. Please note that the Review Team would like to proceed with labeling negotiations for the OPC sections of the label separately from the prophylaxis label. Any edits should be made only to these sections and NOT on the master label for the present time.

This draft was composed taking into account the prophylaxis labeling. The MITT population as originally defined is included in the efficacy tables. However, the cutoff value of 0 CFU was used for assessing mycological response. Your analysis of sustained mycological eradication at 4 weeks post-treatment was not included as it was not performed in the MITT population and it is our position that reporting relapse at the 4 week post treatment visit is more clinically meaningful.

The denominator in the refractory section was obtained by applying a strict definition of refractory disease as described in the text. This led to the inclusion of only subjects from one trial. If there are any questions about how any of the denominators were obtained we will be happy to discuss.

In the **ADVERSE EVENTS** section, the table of treatment related AEs was omitted as per current guidance. We included a table of all treatment emergent AEs occurring in $\geq$10% as well as less frequent AEs of clinical significance.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

_____

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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/s/

Kristen Miller
8/30/2006 03:37:42 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 6, 2006
APPLICATION: NDA 22-003
NDA 22-027
DRUG NAME: Noxafil® (posaconazole) Oral Suspension
TYPE OF MEETING: Pre-Approval Safety Conference

ATTENDEES:

Mark Goldberger, M.D., MPH, Director [Office of Antimicrobial Products (OAP)]
David Roeder, M.S., Associate Director, Regulatory Affairs (OAP)
Renata Albrecht, M.D. Division Director [Division of Special Pathogen and Transplant Products (DSPTP)]
Rosemary Johann-Liang, M.D. Deputy Director [Office of Surveillance and Epidemiology (OSE)/Division of Drug Risk Evaluation (DDRE)]
Melissa Truffa, R.Ph., Safety Evaluator Team Leader (OSE/DDRE)
Jenna Lyndly, Pharm.D., Project Manager (OSE/DDRE)
Todd Bridges, Pharm.D., Safety Evaluator, [OSE/Division of Medication Errors and Technical Support (DMETS)]
Sammie Beam, Pharm.D. Regulatory Health Project Manager (OSE/DDRE)
Leonard Sacks, M.D. Medical Team Leader (DSPTP)
Maureen Tierney, M.D., Medical Reviewer (DSPTP)
Regina Alivisatos, M.D., Medical Reviewer (DSPTP)
Karen Higgins, Sc.D., Statistics Team Leader (Division of Biometrics III)
Cheryl Dixon, Ph.D., Statistics Reviewer (Division of Biometrics IV)
Jyoti Zalkikar, Ph.D., Statistics Reviewer (Division of Biometrics IV)
William Taylor, Ph.D. Pharmacology Toxicology Team Leader (DSPTP)
Owen McMaster, Ph.D. Pharmacology Toxicology Reviewer (DSPTP)
Mark Seggel, Ph.D. Chemistry Reviewer (Office of New Drug Quality Assessment)
Philip Colangelo, Ph.D. Clinical Pharmacology Team Leader (OCP/DCP4)
Seong Jang, Ph.D. Clinical Pharmacology Reviewer (OCP/DCP4)
Kalavati Suvarna, Ph.D., Microbiology Reviewer (DSPTP)
Shukal Bala, Ph.D., Microbiology Team Leader (DSPTP)
Kristen Miller, Pharm.D., Regulatory Project Manager (DSPTP)

MEETING OBJECTIVES:

The purpose of the PSC is to:

- Ensure the Office of Surveillance and Epidemiology's (OSE) Division of Drug Risk Evaluation (DDRE) is aware of potential postmarketing safety problems with posaconazole.
- Consider the need for any special postmarketing analyses/safety studies or evaluations to be agreed to by Schering prior to approval.
- Determine if there is any specific information or feedback that the Division would like from OSE.

BACKGROUND:

On December 21, 2005, Schering submitted NDA 22-003 for Noxafil® (posaconazole) Oral Suspension, 200mg/5mL. This application was split for our administrative purposes and assigned a second NDA number, 22-027. NDA 22-003 was granted a priority review for the indication of prophylaxis of invasive fungal infections, and NDA 22-027 was granted a standard review for the indication of treatment of oropharyngeal candidiasis. On June 22, 2006, NDA 22-003 will be approved for the indication of prophylaxis of invasive *Aspergillus* and *Candida* infections.

DISCUSSION POINTS:

Following introductions, a summary of the posaconazole safety for the prophylaxis of invasive fungal infections (IFI) was provided. Posaconazole is a relatively well tolerated azole with some of the same safety concerns as other members of the azole class and some possibly unique safety issues. The following potential safety concerns were discussed:

Hepatic Effects
The Division noted that an increase in hepatic adverse events including elevation in liver function tests and rare cases of severe liver injury have been seen in patients with severe underlying co-morbidity. Including this in the WARNING or PRECAUTION section of the labeling is recommended. DDRE noted that if posaconazole will be used in an outpatient setting, monitoring of liver function tests during the course of posaconazole therapy may be difficult; however, these patients may be less at risk as patients may not have as severe co-morbidities.

Drug Interactions
Posaconazole is an inhibitor of CYP3A4. Drug interactions have been noted with posaconazole and cyclosporine which can lead to severe, even fatal, cyclosporine toxicity (one death in the prophylaxis study). Additionally, interactions have been seen with tacrolimus. The Review Team plans to include the cyclosporine interaction and potentially fatal toxicity information in the WARNINGS section. DDRE asked if other azoles have similar interactions and if posaconazole would be the only label to contain wording regarding the fatalities with cyclosporine. The Review Team agreed that this may be the only product with such wording, and verified that other azoles have similar interactions with cyclosporine.

> **Addendum:** The Review Team consulted OSE to review the AERS database for any serious and/or fatal drug interactions in patients taking other azoles concomitantly with cyclosporine, tacrolimus, or sirolimus.

Cardiotoxicity
A thorough QT study was conducted and patients receiving prophylaxis with posaconazole and fluconazole had similar rates of increase of >60msec of QTc from baseline and QTc over 500 msec. Similar events were not recorded in healthy subjects receiving posaconazole. There was one case of torsades de pointes in patients with severe electrolyte abnormalities receiving prophylaxis with posaconazole. Additionally, a mild increase in incidence of significant hypokalemia (13%) was seen in patients receiving posaconazole compared to patients receiving fluconazole (10%). These events will be included in the PRECAUTIONS section of the labeling.

Pulmonary Embolus
There was an increase in the number of patients with pulmonary emboli in the post stem cell transplant patients with graft versus host disease (GVHD) who received posaconazole in comparison to fluconazole (6 patients versus 0 patients). These events will be included in the ADVERSE REACTIONS section of the labeling. A post-marketing commitment may also be added to monitor the incidence of pulmonary emboli.

Blood Dyscrasias
Mild increases in hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) (and overall thrombocytopenia) were seen in the post stem cell transplant patients with GVHD who received posaconazole in comparison to fluconazole. These events will be included in the ADVERSE REACTIONS section of the labeling. A post-marketing commitment may also be added to monitor the incidence of TTP and HUS.

Neurophospholipidosis
DDRE asked for an update on neurophospholipidosis seen in animal studies. The Review Team stated that phospholipidosis has been seen in fluconazole and itraconazole, but that neurophospholipidosis has only been found in studies with posaconazole.
Neurophospholipidosis was seen after approximately three months of posaconazole dosing in dogs, but no changes were seen in functional testing. Additionally, no neurophospholipidosis or functional changes were seen in monkeys or human studies. DDRE asked if specific imaging or clinical neurotoxicity assessments were systematically performed in human studies. The Review Team stated that although specific monitoring was not performed in any human studies to date, there were no differences in the incidence of neurological adverse events between posaconazole and comparator arms of the human studies. DDRE stated that neurotoxicity will need to be closely monitored after posaconazole is on the market.

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/s/

Mark Goldberger
8/8/2006 09:52:20 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

****Pre-Decisional Agency Information****

Date: June 20, 2006

To: Kristen Miller, Project Manager
Division of Special Pathogens and Transplant Products

From: Sheila Ryan, Pharm.D.
Division of Drug Marketing, Advertising, and Communications

Subject: Noxafil® (posaconazole) Oral Suspension
NDA 22-003

DDMAC has reviewed the proposed product labeling (PI) for Noxafil and we offer the following comments. Please feel free to contact me with any questions or clarifications.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

Distribution

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/s/

Sheila Ryan
6/20/2006 08:49:32 AM
DDMAC REVIEWER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 14, 2006

To: Todd Paporello, Pharm.D.	**From:** Kristen Miller, Pharm.D.
Company: Schering	Division of Special Pathogen and Transplant Products
Fax Number: 908-740-6500	**Fax Number:** 301-796-9882
Phone Number: 908-740-4252	**Phone Number:** 301-796-0762

Subject: Comments and requests regarding NDAs 22-003

Total no. of pages including cover:

Comments: Concur:

Maureen Tierney, M.D.	Medical Officer
Leonard Sacks, M.D.	Medical Team Leader
Jyoti Zalkikar, Ph.D.	Statistics Reviewer
Seong Jang, Ph.D.	Clinical Pharmacologist Reviewer
Philip Colangelo, PhD, PharmD	Clinical Pharmacologist Team Leader

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NDA 22-003

Please refer to your new drug application (NDA) 22-003 for Noxafil® (posaconazole) Oral Suspension submitted on December 22, 2005. Please also refer to our teleconference scheduled for June 16, 2006. In preparation for this teleconference, the Review Team has the following comments:

As you are aware from our May 26, 2006 teleconference, we have determined from the data collected in studies C98-316 and P01899 that there was a very broad range of posaconazole concentrations achieved in patients who took the proposed dose of 200 mg po TID for the prophylaxis of invasive fungal infections (IFIs). The patient data, including posaconazole plasma concentrations, clinical outcomes and specifically the incidence of IFIs were carefully reviewed. Attached is a summary of all of these analyses which is more extensive than the summary supplied to you on May 26, 2006.

As you can see from these analyses, the data from these two clinical studies show a strong relationship between a higher incidence of clinical failure and lower plasma exposure to posaconazole. As mentioned in the June 5, 2006 facsimile, we continue to be concerned that the low success rates may be due, in part, to the corresponding low posaconazole plasma concentrations. Although other factors may also account for this finding, there is, for example, no convincing evidence that baseline risk factors alone can identify the patients who attained low plasma exposure to posaconazole.

The Review Team feels that although this finding does not preclude approval of posaconazole at this time, a better understanding of why certain patients achieve such low levels and how they should be managed is important to pursue. Consequently, during our June 16, 2006 teleconference, we would like to discuss with you how to further study this issue. Options could include a post-marketing study commitment to look at therapeutic drug monitoring using a scheme such as that outlined on page 6 of the attachment, or a drug/exposure response study in the treatment of certain invasive fungal infections, particularly *Aspergillus*.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

_____

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

Summary of exposure-response analysis and potential dose recommendation based on the exposure-response relationship

Exposure-response relationship-Effectiveness

The exposure-response analyses revealed a strong relationship between a higher incidence of Clinical Failure and lower plasma exposure to POS, suggesting that ensuring high plasma exposure to POS appears to be needed especially for patients whose steady state average concentration (C_{avg}) is low (See Figure 1). Table 1 shows the Clinical Failure rate and Proven/Probable IFIs in the All Treated population during the Primary Time Period for 4 quartiles of POS C_{avg}.

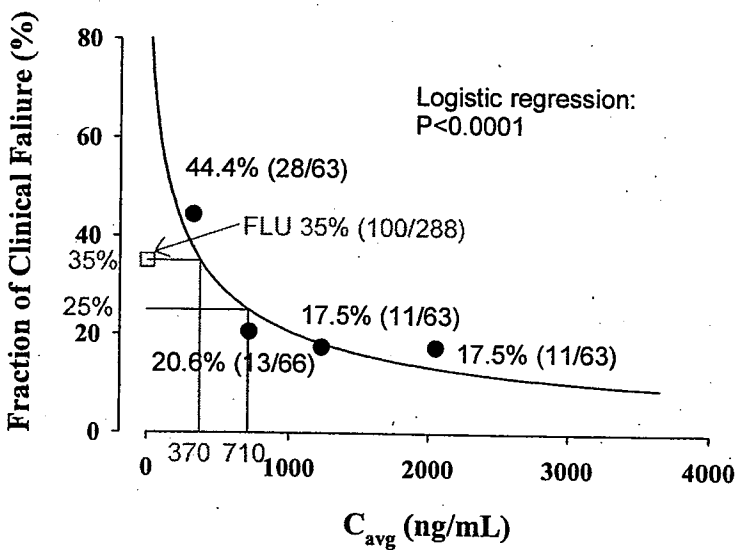


Figure 1. POS exposure-response relationship for patients in the All Treated population during the Primary Time Period (N=252) (Study C98-316). Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 quartiles of C_{avg} (closed circles) are plotted to assess the goodness-of-fit. The response rate for patients treated with fluconazole (FLU, open square) is plotted as a reference. The blue lines showed that 710 ng/mL of C_{avg} is required to achieve 25% Clinical Failure rate. The red lines showed that 370 ng/mL of C_{avg} is required to achieve 35% Clinical Failure rate.

Table 1. Incidence of Clinical Failure in the All Treated population during the Primary Time Period in 4 quartiles of POS C_{avg} (Study C98-316).

Quartiles	Q1	Q2	Q3	Q4
C_{avg} (ng/mL)	**21.5-557**	**557-915**	**915-1563**	**1563-3650**
Clinical Failure	**44.4% (28/63)**	**20.6% (13/63)**	**17.5% (11/63)**	**17.5% (11/63)**
Proven/probable IFI	4.76% (3/63)	4.76 % (3/63)	1.59% (1/63)	3.17% (2/63)
Empirical use of Sys. Antifungal [a]	17.5% (11/63)	3.17% (2/63)	6.35% (4/63)	4.76% (3/63)
Death	34.9% (22/63)	20.6% (13/63)	17.5% (11/63)	11.1% (7/63)
Discontinuation [b]	23.8% (15/63)	14.3% (9/63)	9.52% (6/63)	9.52% (6/63)

There is some overlap in the rows.
[a]: Use of systemic antifungal agents in addition to study drug more than 5 days, from all causes
[b]: Discontinuation due to any reason

Dose recommendation based on the exposure-response relationship

There are no patient demographic covariates (or combination of those covariates) that can successfully identify the patients who will attain low plasma concentrations of POS. Therefore, measuring plasma concentrations of POS is considered by this reviewer to be the most reliable way to identify those patients who will attain low plasma concentrations of POS.

Based on the relationship between C_{avg} of POS and Clinical Failure (See Figure 1), a Clinical Failure rate of <25% is considered to be acceptable by the reviewing medical officer as a target clinical outcome that should be achieved with POS and C_{avg} should be greater than 700 ng/mL to achieve this target outcome. Thus, 700 ng/mL is the lower threshold value for C_{avg} to determine if the POS dosage needs to be increased for a given patient. Subsequently, the concentration on Day 2 which would result in a C_{avg} of 700 ng/ml at steady state was calculated using an accumulation factor of 8 obtained from a multiple dose-escalating PK study (Study I96089). Based on this, a concentration of 350 ng/mL measured at 3 to 5 hours post dose on Day 2 is recommended as a cutoff plasma concentration of POS to determine if the POS dosage needs to be increased for a given patient.

The threshold concentration of 700 ng/mL as C_{avg} also appears appropriate in terms of the incidence of Proven/Probable IFIs, because the incidence of Proven/Probable IFIs also tended to be greater for patients whose C_{avg} was ≤700 ng/mL compared with patients whose C_{avg} was >700 ng/mL. Tables 2 and 3 shows the incidence of Prove/Probable IFIs between group of patients whose C_{avg} was ≤700 ng/mL and group of patients whose C_{avg} was >700 ng/mL in Study C98316 and P01899, respectively.

Table 2. Incidence of Proven/Probable IFIs between those patients whose POS C_{avg} was ≤700 ng/mL and those patients whose POS C_{avg} was >700 ng/mL (Study C98316).

C_{avg} (ng/mL)	≤700 ng/mL (N=92)	>700 ng/mL (N=160)
Incidence of Prove/Probable IFIs	6.52% (6/92)	1.88% (3/160)
Incidence of Aspergillosis	4.35% (4/92)	0.63% (1/160)

Table 3. Incidence of Proven/Probable IFIs between those patients whose C_{avg} was ≤700 ng/mL and those patients whose C_{avg} was >700 ng/mL (Study P01899).

C_{avg} (ng/mL)	≤700 ng/mL (N=155)	>700 ng/mL (N=60)
Incidence of Prove/Probable IFIs	3.87% (6/155)	0% (0/60)

Four clinical pharmacology studies (i.e., single and multiple dose escalating studies and food effect studies following 200 mg and 400 mg of POS) support that the increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

When dose is adjusted from 200 mg TID to 400 mg TID, based on the threshold C_{avg} of 700 ng/mL, the percent of patients whose C_{avg} is ≤700 ng/mL would be decreased from 37% (92/252) to 14% (35/252). The Clinical Failure rate for patients whose C_{avg} was ≤700 ng/mL (i.e., with 200 mg TID) would be reduced from 37% (34/92) to 25% (23/92) (Table 4).

Table 4. Percent of patients whose C_{avg} is ≤700 ng/mL and Clinical Failure rate as a function of POS dosing regimen

C_{avg} ≤700 ng/mL	200 mg TID	400 mg TID (projection)
% of patients whose C_{avg} is ≤700 ng/mL	37% (92/252)	14% (35/252)
Clinical Failure rate in patients whose C_{avg} was ≤700 ng/mL	37% (34/92)	25% (23/92)

For patients whose plasma concentrations of POS cannot be high enough to ensure desirable clinical outcomes with 400 mg TID, other antifungal treatment for prophylaxis of IFIs may be needed. Thus, it is recommended to use other antifungal treatment instead of POS for patients who receive 400 mg TID and if plasma concentrations of POS after Day 7 (presumed steady state) are ≤700 ng/mL.

In summary, the exposure-response analysis showed:

(a) The exposure-response relationship for POS effectiveness for the prophylaxis against IFIs was not significantly confounded with any patient demographic covariates

(b) POS concentration of 350 ng/mL determined at 3 to 5 hours post dose on Day 2 after the beginning of POS treatment would result in a steady-state C_{avg} of 700 ng/mL and subsequently result in the incidence of Clinical Failure of

<25%. Plasma concentration monitoring of POS may be used as a tool to identify those patients who will have lower than desired plasma exposure.

(c) The increase of POS dose from 200 mg TID to 400 mg TID is most likely to result in an increase in plasma exposure to POS by at least 2 fold when POS is given either with food or under fasting conditions.

Collectively, the following dose administration and plasma concentration monitoring scheme is recommended by this reviewer.

Initial dose: 200 mg TID for all patients

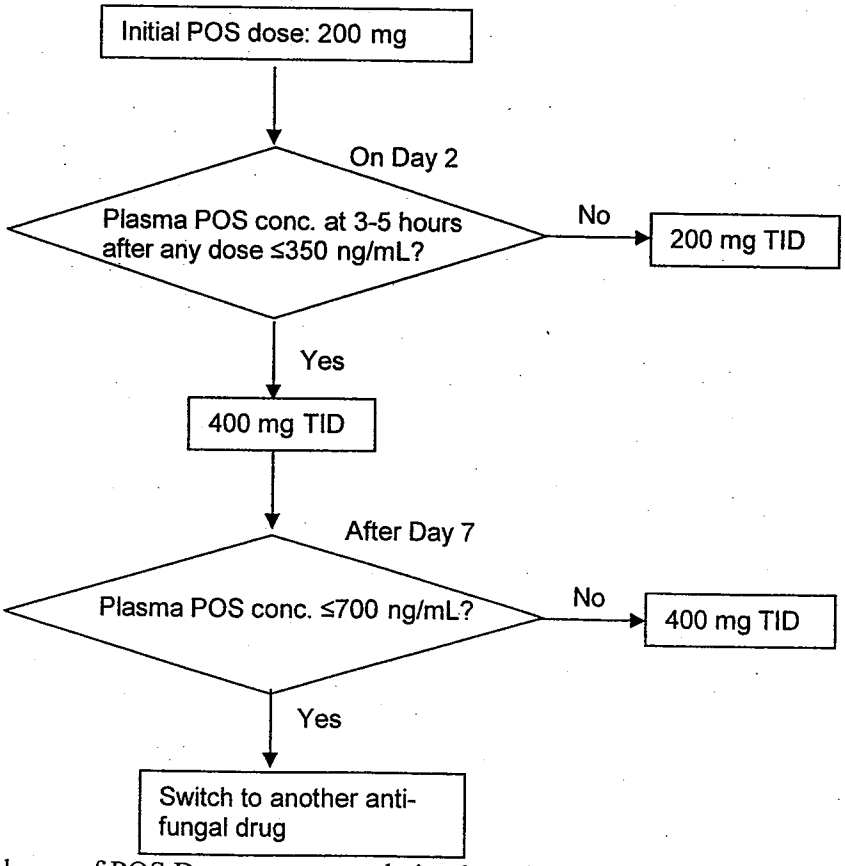
Monitoring of plasma concentration(s) of POS on Day 2:

Plasma samples should be collected at 3 to 5 hours after any dose on Day 2.

(a) If plasma concentration(s) of POS is ≤350 ng/mL, then give 400 mg TID
(b) If plasma concentration(s) of POS is >350 ng/mL, then give 200 mg TID

Monitoring of plasma concentration(s) of POS after Day 7 for patients who received 400 mg TID:

(a) If plasma concentration(s) of POS is >700 ng/mL, then give 400 mg TID
(b) If plasma concentration(s) of POS is ≤700 ng/mL, then switch to another anti-fungal drug



Scheme of POS Dose recommendation based on plasma concentrations of POS

Exposure-response relationship-Safety

The most common treatment-related (Possible and Probable) treatment-emergent adverse events were nausea, vomiting, diarrhea, hypokalemia, rash and elevations in hepatic enzymes (SGOT and SGPT increase). For exposure-response relationship regarding safety, data from Study C98316 and P01899 were pooled. Although the incidence of most treatment-related adverse events tended to be lower in the first quartile of C_{avg} compared with the fourth quartile of C_{avg}, the incidence rates of adverse events were not significantly dependent on plasma drug concentration (Table 5).

Table 5. Incidence of treatment-emergent and drug-related (Possible and Probable) AEs (%) in the All Treated population in 4 quartiles of average plasma concentration POS (C_{avg}) (N=450; Studies C98-316 and P01988). Datasets from Study C98-316 and P01899 were pooled for these analyses.

	1st Q (n=119)	2nd Q (N=121)	3rd Q (N=120)	4th Q (N=120)	P value[b]
C_{avg} (ng/mL)[a]	205±105 [2.51-355]	498±77.1 [355-626]	835±138 [626-1118]	1751±538 [1118-3650]	
Diarrhea	3.36%	4.96%	8.33%	6.67%	0.4378
Nausea	7.56%	6.61%	10%	12.5%	0.3746
Vomiting	3.36%	4.96%	7.5%	6.67%	0.4639
Discontinuation	8.4%	7.44%	14.2%	17.5%	0.0595
Bilirubinemia	1.68%	3.31%	4.17%	3.33%	0.4787
SGOT increased	1.68%	2.48%	4.17%	3.33%	0.4016
SGPT increased	1.68%	3.31%	5%	3.33%	0.4911
Hepatic enz. increased	1.68%	3.31%	4.17%	3.33%	0.4787
Hypokalemia	0.84%	1.65%	4.17%	2.5%	0.4818
Rash	0.84%	1.65%	4.17%	3.33%	0.1739

[a]: Mean±SD [range]

[b]: Logistic regression for the relationship between the incidence of treatment-related adverse events and C_{avg}

There would be expected to be no additional safety findings with 400 mg TID for those patients whose C_{avg} was ≤700 ng/mL (i.e., those who receive 200 mg TID initially). Based on the dose-proportional PK of POS, following 400 mg TID administration to patients whose C_{avg} was ≤700 ng/mL (i.e., those who receive 200 mg TID initially), C_{avg} would not be expected to be greater than 3650 ng/mL, which is the highest C_{avg} observed in patients treated with 200 mg TID in Study C98316.

Appendix

Table A1. Incidence of Clinical Failure and Proven/Probable IFIs in the All Treated population during the Oral Treatment Phase in 4 concentration quartiles of POS (Study P01899).

C_{avg} (ng/mL)	Clinical Failure	Proven/probable IFI
89.65-322	54.7% (29/53)	3.77% (2/53)
322-490	37.0% (20/54)	1.85 % (1/54)
490-733.5	46.3% (25/54)	5.56% (3/54)
733.5-2200	27.8% (15/54)	0% (0/54)

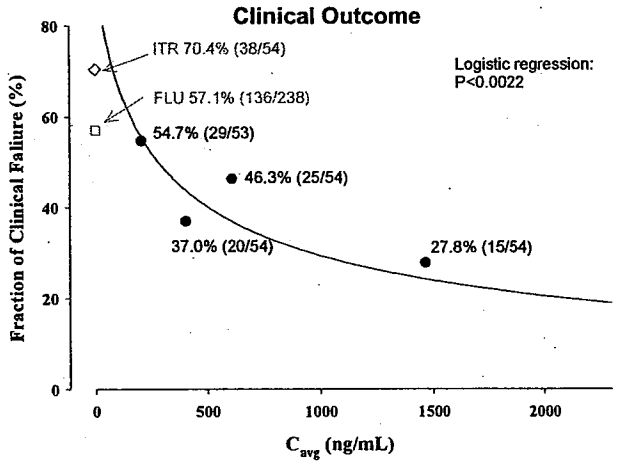


Figure A1. POS exposure-response relationship for patients in All Treated population during the Oral Treatment Phase (n=215) (Study P01899). Logistic regression was performed using natural log of average concentrations per patient ($\log(C_{avg})$) as a continuous variable and the Clinical Failure as a binary variable (yes or no). The solid line represents the regression fit. Subsequent to the logistic regression, the response rates in each of the 4 concentration quartiles (closed circles) are plotted to assess the goodness-of-fit. The response rates in patients treated with fluconazole (FLU, open square) and itraconazole (ITZ, open diamond) are plotted as references.

Table A2. Calculated plasma concentrations of POS before C_{avg} reaches 700 ng/mL at Day 7 (presumed at steady state) following oral administration of POS 200 mg TID.

Day	No. of Dose	Plasma concentration of POS (ng/mL)
1	1	67
	2	186
	3	238
2	4	286
	5	331
	6	371
3	7	408
	8	442
	9	474
4	10	503
	11	529
	12	553
5	13	576
	14	596
	15	615
6	16	632
	17	648
	18	663
7	19	676
	20	689
	21	700

For the calculation, 7.6±2.8 of accumulation ratio ($R_{0\text{-}12h}$) obtained following oral administration of POS 200 mg BID for 14 days (Study I96089) were used.

Table A3. Pharmacokinetic parameters (Mean±SD [range]) of POS tablets on Day 14 after oral (Q12 hr) administration of POS tablets for 14 days (n=9/Dose) (Study I96-089)

	200 mg BID	400 mg BID	Fold Difference
C_{max} (ng/mL)	1753±466 [1020-2230]	4150±816 [2920-5710]	2.37
AUC_{0-12} (ng·hr/mL)	16801±4319 [8929-21960]	39206±8020 [24475-47985]	2.33

Table A4. Pharmacokinetic parameters (Mean±SD [range]) of POS following single oral administration of POS tablets to healthy male volunteers (n=6 for each dose). (Study I95-098)

	200 mg	400 mg	Fold Difference
C_{max} (ng/mL)	332±70.8 [273-470]	611±190 [424-964]	1.84
AUC_{inf} (ng·hr/mL)	10896±3411 [5650-14634]	20264±6781 [12716-29387]	1.86

Table A5. Pharmacokinetic parameters (Mean±SD [range]) of POS (n=20) after a single oral administration of 400 mg oral suspension after a 10-hr fast or a high-fat breakfast (Study I96099)

	Suspension (fasted)	Suspension (high-fat meal)	Fold Difference
C_{max} (ng/mL)	132±65.8 [45.7-267]	512±176 [241-1016]	3.88
AUC_{inf} (ng·hr/mL)	4179±1285 [2705-7269]	13885±5655 [7854-34824]	3.3

Table A6. Pharmacokinetic parameters (Mean (CV%)) of POS (n=20) after a single oral administration of 200 mg oral capsule after a 10-hr fast or a high-fat breakfast (Study I95099)

	Capsules (fasted)	Capsules (high-fat meal)	Fold Difference
C_{max} (ng/mL)	102.3 (39%)	531.4 (32%)	5.2
AUC_{inf} (ng·hr/mL)	3588 (37%)	14293 (38%)	3.98

Table A7. POS C_{avg} in patients who has Proven/Probable IFIs (Study C98316)

Subject ID	C_{avg} (ng/mL)	Quartile	Pathogen
I004000048	99	Q1	Aspergillosis
I004000049	158	Q1	Aspergillosis
I004000050	319	Q1	Candidiasis
I004000051	565	Q2	Aspergillosis
I004000052	681	Q2	Aspergillosis
I004000053	691	Q2	Other Fungi
I004000054	1562	Q3	Aspergillosis
I004000055	2080	Q4	Candidiasis
I004000056	2190	Q4	Other fungi

Table A8. POS C_{avg} in patients who had Proven/Probable IFIs (Study P01899)

Subject ID	C_{avg} (ng/mL)	Quartile	Pathogen
0054001468	254	Q1	Aspergillosis
0010001371	294	Q1	Other Fungi
0015001239	417	Q2	Aspergillosis
0015001415	491	Q3	Candidiasis
0057001492	606	Q3	Candidiasis
0002001271	629	Q3	Other Fungi

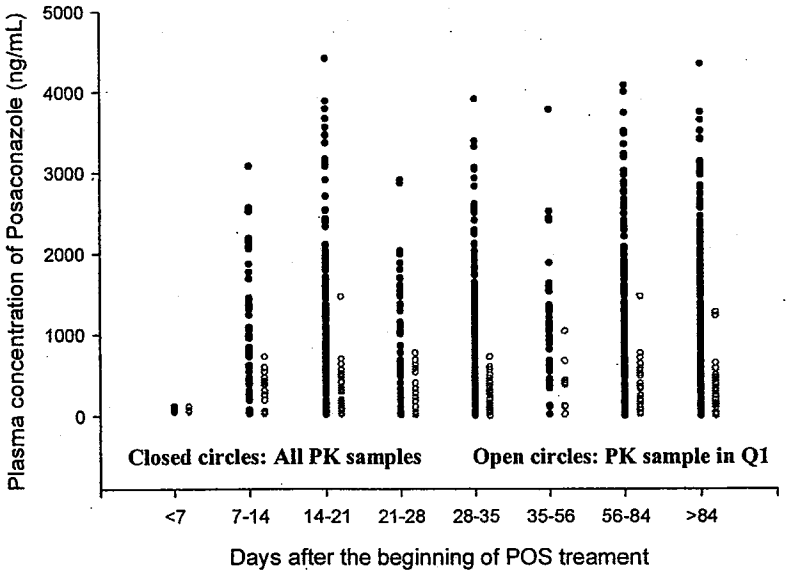


Figure A2. Plasma concentrations of POS (PK sample number=870) in all patients (n=252) as a function of time (days) after the beginning of POS treatment. (Study C98316)

Effect of risk factors that the sponsor determined on exposure-response relationship of posaconazole

A sub population (n=51) that the sponsor chose:

Acute GVHDBDID, male and CMV positive (A-M-C)

Based on new dataset (excluding plasma samples collected at more than 24 hr after last dose), 6 patients did not have C_{avg} data and 46% of patients belong to Q1.

A sub population excluding this higher risk population (i.e., Not A-M-C; N=291-51=240):

Among this group, C_{avg} values are available in 207 patients.

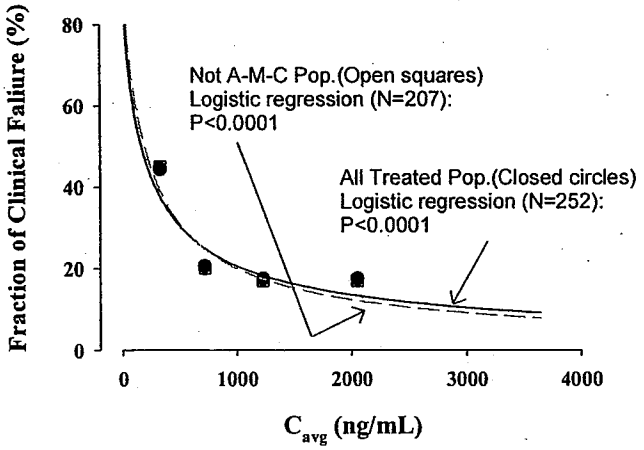
Clinical failure rate in 4 quartiles of C_{avg} in A-M-C (N=45) vs. Not A-M-C (N=207)

	Q1 (N=63)	Q2 (N=63)	Q3 (N=63)	Q4 (N=63)
A-M-C (N=45)	43%(9/21)	25% (3/12)	22% (2/9)	33% (1/3)
Not A-M-C (N=207)	45% (19/42)	20% (10/51)	17% (9/54)	17% (10/60)
Total (N=252)	44.4% (28/63)	20.6% (13/63)	17.5% (11/63)	17.5% (11/63)

Clinical failure rate in Q1 vs. Q2-Q4 of C_{avg} in A-M-C (N=45) vs. Not A-M-C (N=207)

	Q1 (N=63)	Q2-Q4 (N=189)
A-M-C (N=45)	43% (9/21)	25% (6/24)
Not A-M-C (N=207)	45% (19/42)	18% (29/165)
Total (N=252)	44.4% (28/63)	19% (35/189)

Logistic regression for Clinical Failure vs. C_{avg} in this sub population



Within a higher risk group, Clinical Failure rate was greater in Q1 compared with Q2-Q4, indicating that low plasma exposure to posaconazole is a major determinant for Clinical Outcome of posaconazole for the prophylaxis of IFIs (i.e., The exposure response relationship was not confounded with these risk factors)

The same results obtained from another sub population (N=33).

Acute GVHDBDID, male, CMV positive and baseline Cort ≥ 1 (A-M-C-C)

Based on new dataset (excluding plasma samples collected at more than 24 hr after last dose), 6 patients did not have C_{avg} data and 57% of patients belong to Q1.

A sub population excluding this higher risk population (i.e., Not A-M-C-C; N=291-33=258):

Among this group, C_{avg} values are available in 224 patients.

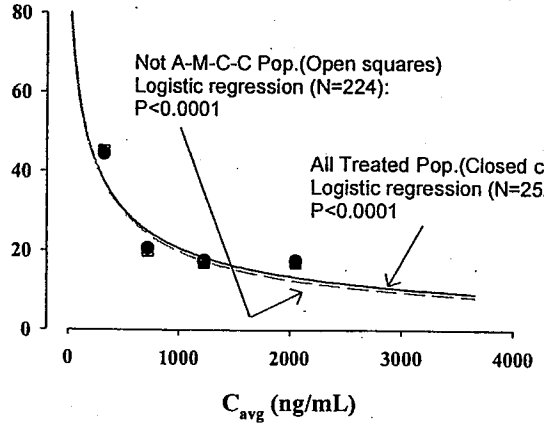
Clinical failure rate in 4 quartiles of C_{avg} in A-M-C (N=28) vs. Not A-M-C-C (N=224)

	Q1 (N=63)	Q2 (N=63)	Q3 (N=63)	Q4 (N=63)
A-M-C-C (N=28)	50% (8/16)	43% (3/7)	33.3% (1/3)	0% (0/2)
Not A-M-C-C (N=224)	43% (20/47)	18% (10/56)	17% (10/60)	18% (11/63)
Total (N=252)	44.4% (28/63)	20.6% (13/63)	17.5% (11/63)	17.5% (11/63)

Clinical failure rate in Q1 vs. Q2-Q4 of C_{avg} in A-M-C (N=45) vs. Not A-M-C (N=207)

	Q1 (N=63)	Q2-Q4 (N=189)
A-M-C (N=28)	50% (8/16)	33% (4/12)
Not A-M-C (N=224)	43% (20/47)	18% (31/177)
Total (N=252)	44.4% (28/63)	19% (35/189)

Logistic regression for Clinical Failure vs. C_{avg} in this sub population



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/s/

Kristen Miller
6/14/2006 12:43:39 PM
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Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 5, 2006

To: Todd Paporello, Pharm.D.	**From:** Kristen Miller, Pharm.D.
Company: Schering	Division of Special Pathogen and Transplant Products
Fax Number: 908-740-6500	**Fax Number:** 301-796-9882
Phone Number: 908-740-4252	**Phone Number:** 301-796-0762

Subject: Comments and requests regarding NDAs 22-003 and 22-027

Total no. of pages including cover: 3

Comments: Concur:

Maureen Tierney, M.D.	Medical Officer
Leonard Sacks, M.D.	Medical Team Leader
Karen Higgins, Sc.D.	Statistics Team Leader
Seong Jang, Ph.D.	Clinical Pharmacologist Reviewer
Philip Colangelo, PhD, PharmD	Clinical Pharmacologist Team Leader

Document to be mailed: ☐ YES ☑ NO

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Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil® (posaconazole) Oral Suspension submitted on December 22, 2005. The Review Team has the following comments and requests:

We have more closely reviewed your submission that was discussed during the teleconference on Friday, May 26, 2006. Though the risk factors that you determined (GVHD, gender, and CMV status) do point to a group of posaconazole patients that have lower failure rate than similar fluconazole patients, they do not provide a reliable prediction for the occurrence of low posaconazole levels and, therefore, do not provide an adequate fluconazole group for comparison. In fact, the exposure-response (E-R) relationships are similar between the subgroup that you determined to be at high risk to the subgroup that excludes these patients, indicating that the E-R relationship was not confounded by these risk factors.

As we discussed in the meeting on Friday, May 26, there are other risk factors that may be considered when trying to more accurately model the development of low posaconazole levels (these are listed below); however, as we looked more closely at potential models, we were unable to come up with an adequate model and are concerned that you will also not be able to come up with one. Therefore, it is up to you whether or not to continue to model the baseline risk factors. Please be aware that absent convincing evidence that baseline risk factors alone can explain the low posaconazole levels, which could then be used to define an adequate fluconazole group for comparison, we continue to be concerned that the low posaconazole levels are causing, at least in part, the low success rates in these subjects. Please consider how this can be addressed in labeling.

Risk factors include body irradiation (BODYIRRD), central venous catheter at baseline (CATHCDBS), risk with donor (DONORCD), GVHD grade 3/4 (GVHDBS), baseline aspergillus antigen (MAXASPAG), neutropenia at baseline (NEUTPTBS), oral swish for yeast (ORALYTBS), ECOG status at baseline (PRFRSTBS), race (RACE), and time from transplant to baseline (TRANDAY).

Additionally, please do separate analyses of the following:

- levels versus diarrhea
- acute graft versus host disease (GVHD) Grades 3 and 4 separate from Grade 2.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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/s/

Kristen Miller
6/5/2006 04:31:33 PM
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Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 30, 2006

To: Todd Paporello, Pharm.D.	**From:** Kristen Miller, Pharm.D.
Company: Schering	Division of Special Pathogen and Transplant Products
Fax Number: 908-740-6500	**Fax Number:** 301-796-9882
Phone Number: 908-740-4252	**Phone Number:** 301-796-0762

Subject: Labeling comments regarding NDAs 22-003 and 22-027

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☑ NO

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Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil® (posaconazole) Oral Suspension submitted on December 22, 2005. The Division of

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FACSIMILE TRANSMITTAL SHEET

DATE: May 23, 2006

To: Todd Paporello, Pharm.D.	**From:** Kristen Miller, Pharm.D.
Company: Schering	Division of Special Pathogen and Transplant Products
Fax Number: 908-740-6500	**Fax Number:** 301-796-9882
Phone Number: 908-740-4252	**Phone Number:** 301-796-0762

Subject: PK request regarding NDAs 22-003 and 22-027

Total no. of pages including cover:

Comments: Concur:

Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader
Seong Jang, Ph.D.	Clinical Pharmacology Reviewer
Leonard Sacks, M.D.	Clinical Team Leader
Maureen Tierney, M.D.	Medical Officer
Karen Higgins, Sc.D.	Statistics Team Leader
Jyoti Zalkikar, Ph.D.	Statistics Reviewer

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Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil® (posaconazole) Oral Suspension submitted on December 21, 2005. In the process of completing their review, our clinical pharmacologists, Dr. Jang and Dr. Colangelo have determined that there is a impressive difference in the clinical outcome and incidence of proven/probable IFI in the lowest quartile of patients (based on posaconazole levels) as opposed to the three higher quartiles of posaconazole patients or to the comparator in Study 98-316.

Dr. Jang composed the following questions along with the accompanying report. We are requesting the telecon scheduled for this Friday, May 26, 2006 in order to discuss this finding. We are hoping that you will be able to help us answer the questions below. Also attached are the datasets Dr. Jang used to examine this information.

1. Is the exposure-response relationship confounded by any other factors (for example food intake, disease severity, treatment period, baseline factors, etc.)?

2. Are there other outcome measures that show a similar pattern to that seen for Clinical Failure and Proven/Probable (PP) invasive fungal infections (IFIs) during the Primary Time Period?

3. Can you define four comparable comparator groups for the four posaconazole-exposure groups using baseline data including disease severity so that the efficacy of posaconazole of these groups can be considered relative to the control? This will help us determine if it is possibly the levels of posaconazole obtained in these groups or mainly the baseline variables that are causing the lower efficacy (i.e., higher incidence of clinical failure and P/P IFIs) compared with higher exposure group?

4. Is there any way to sort out the patients who will be exposed to low plasma levels of posaconazole? Is there any way to check to the baseline disease severity or the ability for food intake? Should plasma levels of posaconazole be measured during the first one or two weeks after the beginning of the treatment?

5. What can be done to the low exposure group of patients to improve efficacy?

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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FACSIMILE TRANSMITTAL SHEET

DATE: May 23, 2006

To: Todd Paporello, Pharm.D.	**From:** Kristen Miller, Pharm.D.
Company: Schering	Division of Special Pathogen and Transplant Products
Fax Number: 908-740-6500	**Fax Number:** 301-796-9882
Phone Number: 908-740-4252	**Phone Number:** 301-796-0762

Subject: Micro regarding annotated labeling (NDAs 22-003 and 22-027)

Total no. of pages including cover: 3

Comments: Concur:

Shukal Bala, Ph.D. — Microbiology Team Leader
Kalavati Suvarna, Ph.D. — Microbiology Reviewer

Document to be mailed: ☐ YES ☑ NO

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Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil ® (posaconazole) Oral Suspension submitted on December 22, 2005. Please also refer to your

May 8 and 16, 2006 submissions providing annotated labeling for the MICROBIOLOGY section. The Review Team has the following request:

> Your May 8 and 16, 2006 submissions provide annotated labeling for the MICROBIOLOGY/Mechanism of Action and Activity in vitro and in vivo subsections of the labeling. Please provide us with annotations to the actual study reports or publications for the remaining subsections (Drug Resistance and Antifungal Drug Combinations).

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

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Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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/s/

Kristen Miller
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Office of Surveillance and Epidemiology

MEMO

To: Renata Albrecht, MD
Director, Division of Special Pathogens and Transplant Products (HFD-590)

Through: Linda Y. Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

From: Todd D. Bridges, RPh
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety

Date: March 27, 2006

Re: ODS Consult 04-0028-2, Noxafil (Posaconazole Oral Suspension), 40 mg/mL;
NDAs: 22-003 and 22-027.

This memorandum is in response to a March 9, 2006 request from the Division of Special Pathogens and Transplant Products for a review of the container label, carton and insert labeling of Noxafil Oral Suspension.

In the review of the labels and labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

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Todd Bridges
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DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
5/23/2006 01:56:58 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/23/2006 04:10:01 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/23/2006 04:20:07 PM
DRUG SAFETY OFFICE REVIEWER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 17, 2006

To: Todd Paporello, Pharm.D.	**From:** Kristen Miller, Pharm.D.
Company: Schering	Division of Special Pathogen and Transplant Products
Fax Number: 908-740-6500	**Fax Number:** 301-796-9882
Phone Number: 908-740-4252	**Phone Number:** 301-796-0762

Subject: Request regarding NDAs 22-003 and 22-027

Total no. of pages including cover: 3

Comments: Concur:

Maureen Tierney, M.D.	Medical Officer
Karen Higgins, Sc.D.	Statistics Team Leader

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_____

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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/s/

Kristen Miller
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FACSIMILE TRANSMITTAL SHEET

DATE: May 15, 2006

To: Todd Paporello, Pharm.D.	**From:** Kristen Miller, Pharm.D.
Company: Schering	Division of Special Pathogen and Transplant Products
Fax Number: 908-740-6500	**Fax Number:** 301-796-9882
Phone Number: 908-740-4252	**Phone Number:** 301-796-0762

Subject: Request regarding NDAs 22-003 and 22-027

Total no. of pages including cover: 3

Comments: Concur:

Maureen Tierney, M.D.	Medical Officer
Karen Higgins, Sc.D.	Statistics Team Leader

Document to be mailed: ☐ YES ☑ NO

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Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil ® (posaconazole) Oral Suspension submitted on December 22, 2005. The Review Team has the following requests and questions:

1. The clinical outcome tables G.3, G.3.1a, and I.3.1aa have different clinical outcomes than in the study report. Please explain the difference and list the categories of which patients are now considered failures.

2. In every table separating out the POS/ITRA results, the results comparing POS to FLU should only compare POS at the FLU sites to FLU. We can figure those results appropriately for the tables but please provide ASAP the Time to IFI and Time to Death for the POS/FLU at the FLU sites only.

3. Is the Clinical Outcome for the Oral treatment Phase or the for the Day 100 phase? Could you please provide the Clinical Outcome for both?

4. For Study C98-316, please provide the same analysis with the same definition of clinical failure used for tables G.3, etc. for Study PO1899. For Study PO1899, please provide a similar background for these outcomes as requested in Question 1 above.

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_____

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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Kristen Miller
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FACSIMILE TRANSMITTAL SHEET

DATE: April 28, 2006

To: Todd Paporello, Pharm.D.	**From:** Kristen Miller, Pharm.D.
Company: Schering Corporation	Division of Special Pathogen and Transplant Products
Fax Number: 908-740-6500	**Fax Number:** 301-796-9882
Phone Number: 908-740-4252	**Phone Number:** 301-796-0762

Subject: Request regarding NDAs 22-003 and 22-027

Total no. of pages including cover: 4

Concurrence:

Maureen Tierney, M.D.	Medical Officer
Kalavati Suvarna, Ph.D.	Microbiology Reviewer

Document to be mailed: ☐ YES ☑ NO

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Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil ® (posaconazole) Oral Suspension submitted on December 22, 2005. The Review Team requests that you provide responses for the information requests (listed below) by Monday, May 8, 2006.

Clinical

1. As was requested for study C/I98-316, we request an analysis of clinical failure as a composite end-point of proven/probable IFIs and for empiric use of antifungal agents, deaths, and early discontinuations (including AEs) for all treated subjects during the primary time period.
   In addition, we request a similar failure/success analysis while on treatment for POSACONAZOLE VS FLUCONAZOLE VS ITRACONAZOLE for study P01899 during the primary time period.

2. In the aforementioned analyses provided for C/I98-316, the following table was provided as an adjunct to Table G.3.3

   Table G.3.3.1.Treatment Failure During Primary Time Period by Criteria Met and by Treatment Group

	IFI	Empiric use of AF	Discontinued Treatment
Posaconazole	15	25	89
Fluconazole	27	29	97

   Does the "Discontinued Treatment" column include death? Did the clinical failure for tables G.3.3 and G.3.4. include death?

3. In study P01899, almost of all the analyses are presented as POSACONAZOLE VS FLU/ITRA. We request that you provide the major analyses listed below for POSACONAZOLE VS FLUCONAZOLE VS ITRACONAZOLE.

   - Incidence of IFI in the Oral Treatment Phase and at 100 days, both total and broken down by organism
   - IFI broken down by Proven/Probable, total and by organism
   - Deaths (All Cause especially)
   - Time to Death
   - Time to IFI

4. For the Centers where itraconazole was the standard azole, we request the above analyses for Posaconazole versus Itraconazole at those sites, individually and pooled.

Microbiology

1. In studies C/I98-316 and P01899, the presence of Aspergillus antigen in serum and BAL samples was tested using the —— Aspergillus EIA test manufactured by —— ———— aboratory. The test kit manufactured by —— ———— is not approved in the US. Please provide the following information for our review:

   (a) the performance characteristics of the test, and
   (b) the basis for an optical density index of ≥ 0.5 as the threshold for categorizing the test as positive

2. Please provide details of the microbiological criteria used to determine probable infections in the patients listed below:

Study C/I98-316
C012000014
C025000034
I 028000785
C009000341
I004000048
Study P01899
0125001109

3. The microbiology section of the draft product labeling (PI) includes annotations to summary sections in module 2 of the submission. Please provide the microbiology section of the draft PI with annotations to the actual study reports or publications.

Please feel free to contact me at 301-796-0762 if you have any questions.

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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/s/

Brenda Marques
4/28/2006 03:04:19 PM
On behalf of Kristen Miller

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: April 24, 2006

To: Todd Paporello, Pharm.D.	**From:** Kristen Miller, Pharm.D.
Company: Schering	Division of Special Pathogen and Transplant Products
Fax Number: 908-740-6500	**Fax Number:** 301-796-9882
Phone Number: 908-740-4252	**Phone Number:** 301-796-0762

Subject: Request regarding Non-inferiority Margins

Total no. of pages including cover: 3

Comments: Concur:
Karen Higgins Sc.D. Statistics Team Leader

Document to be mailed: ☐ YES ☑ NO

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Please refer to your new drug applications (NDAs) 22-003 and 22-027 for Noxafil ® (posaconazole) Oral Suspension submitted on December 22, 2005. The Review Team has the following request:

We have been unable to find any discussion as to the appropriateness of the pre-specified non-inferiority margins used in your phase 3 studies. Please provide a discussion of why posaconazole should be considered effective from the results of these studies including a justification for your choice of non-inferiority margins for each study or direct us to its location in the submission.

As discussed in the ICH guidance documents "E9 Statistical Principles for Clinical Trials" and "E10 Choice of Control Group and Related Issues in Clinical Trials" (located at www.fda.gov/cder/guidance/index.htm) a non-inferiority margin should be defined as "the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator." It "cannot be greater than the *smallest effect size that the active drug would be reliably expected to have* compared with placebo in the setting of the planned trial." Furthermore, 21CFR314.126(b)(2)(iv) states the following:

> If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-796-0762 if you have any questions.

Kristen Miller, Pharm.D.
Regulatory Health Project Manager

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/s/

Kristen Miller
4/24/2006 01:13:34 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-003
NDA 22-027

Schering Corporation
Attention: Todd Paporello, Pharm.D.
Regulatory Affairs Manager, Global Regulatory Affairs
2000 Galloping Hill Roads
Kenilworth, NJ 07033

Dear Dr. Paporello:

Please refer to your February 23, 2006 correspondence requesting a meeting to discuss the status of the ongoing NDA reviews for Noxafil ® (posaconazole) Oral Suspension (NDAs 22-003 and 22-027), in accordance with 21 CFR 314.102(c).

The following are the Division's responses to the questions submitted for the proposed meeting. If our responses are clear to you and you determine that further discussion is not required, you have the option of canceling the teleconference scheduled for March 27, 2006. Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.

1. Is the Division on target for a June 22, 2006 Action Date for NDA 22-003 (prophylaxis) and an October 20, 2006 Action Date for NDA 22-027 (OPC)? Has the Division identified any barriers to achieving this target? If so, please elaborate.

   The Division is currently on target for a June 22, 2006 action date for NDA 22-003 (for prophylaxis) and an October 20, 2006 action date for NDA 22-027 (OPC). No barriers to achieving these targets have been identified to date. The reviews, however, have not been finalized and unforeseen issues may arise that require further discussion or data as the review progresses.

2. Does the Division continue to believe that an Advisory Committee Meeting will not be necessary in order to approve posaconazole for the prophylaxis and OPC indications?

   Currently, no issues have arisen that would lead the Division to believe that an Advisory Committee Meeting is necessary to discuss the data submitted for either application. However, full review of the applications is needed to definitively state that an Advisory Committee Meeting will not be necessary in order to approve posaconazole for the prophylaxis and OPC indications.

3. Does the Division have any outstanding requests for NDAs 22-003 and/or 22-027 that have not been addressed by Schering? If so, please elaborate.

   We acknowledge that you are compiling responses to the clinical pharmacology requests outlined in the March 2, 2006 letter and plan to submit them to the Division within the next week. There are no additional outstanding requests at this time.

4. In reference to the NDA Filing Letter received on March 2, 2006 for NDAs 22-003 and 22-027, the Division indicated that the potential review issues identified were not required prior to approval but that the absence of the information may require the labeling to be modified. Please elaborate on the modifications envisioned by the Division.

   At this point in the review, the Review Team is not able to elaborate on any envisioned labeling modifications. In the absence of requested pharmacokinetic study results, the labeling would be modified to reflect to reflect the lack of data; however, reviews need to be finalized and further internal discussion among disciplines is necessary prior to labeling negotiations with you.

5. Please speculate when labeling negotiations may commence for NDA 22-003 and 22-027.

   Labeling negotiations are anticipated to begin in mid-May for NDA 22-003. Labeling negotiations for NDA 22-027 are anticipated to begin mid-September.

6. Is there anything else that Schering can do for the Division to aid in the review process of NDA 22-003 and 22-027?

   Although there are currently no specific actions that Schering can take to aid the Review Team in the review process, the Division appreciates the open lines of communication and will contact Schering with any future requests.

If you have any questions, please call Kristen Miller, Pharm.D., 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

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/s/

Kristen Miller
3/20/2006 05:45:26 PM
CSO

Renata Albrecht
3/21/2006 08:25:17 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): **Office of Medical Policy- Division of Drug Marketing, Advertising, and Communications**			FROM: **Division of Special Pathogen and Transplant Products Kristen Miller, Regulatory Project Manager (301) 796-0762**	
DATE **March 9, 2006**	IND NO. **N/A**	NDA NO. **22-003/ 22-027**	TYPE OF DOCUMENT **N-000 Original NDA**	DATE OF DOCUMENT **December 21, 2005**
NAME OF DRUG **Noxafil (posaconazole)**	PRIORITY CONSIDERATION **22-003 (Priority) 22-027 (Standard)**		CLASSIFICATION OF DRUG **7030410 (Antifungal)**	DESIRED COMPLETION DATE **May 22, 2006**

NAME OF FIRM: **Schering Corporation**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION ☐ BIOAVAILABILTY STUDIES ☐ PHASE IV STUDIES	☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Request for review of sponsor's proposed labeling (PI) and labels for posaconazole. This application was submitted electronically and is available at \\Cdsesub1\n22003\N_000\2005-12-21\m1\us\114-label\1141-draft-label. Schering submitted NDA 22-003 and we split this for our administrative purposes and a second NDA number, 22-027 was assigned. NDA 22-003 was granted a priority review for the indication of prophylaxis of invasive fungal infections, and NDA 22-027 was granted a standard review for the indication of treatment of oropharyngeal candidiasis.

Please let me know if you have any questions (millerk@cder.fda.gov or 301- 796-0762).

SIGNATURE OF REQUESTER Kristen Miller, March 9, 2006	METHOD OF DELIVERY (Check one) ■ E-MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Kristen Miller
3/9/2006 02:18:00 PM

MEMORANDUM

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

Date: March 9, 2006
To: NDAs 22-003 and 22-027/ Schering-Plough
From: Kristen Miller, Pharm.D.
Subject: Administrative split of NDA 22-003

On December 21, 2005, Schering submitted a new drug application (NDA) for Noxafil® (posaconazole) Oral Suspension, 200mg/5mL. This application contained two indications: prophylaxis of invasive fungal infections and treatment of oropharyngeal candidiasis. NDA 22-003 was split for our administrative purposes and a second NDA number, 22-027 was assigned. NDA 22-003 was granted a priority review for the indication of prophylaxis of invasive fungal infections, and NDA 22-027 was granted a standard review for the indication of treatment of oropharyngeal candidiasis. Schering was notified of this split in the February 8, 2006, acknowledgement letter.

MEMORANDUM

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/s/ .

Kristen Miller
3/9/2006 03:27:37 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-003 & 22-027 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: Noxafil
Established Name: posaconazole
Strengths: 200mg/ 5mL Oral Suspension

Applicant: Schering Corporation
Agent for Applicant:

Date of Application: December 21, 2005
Date of Receipt: December 22, 2005
Date clock started after UN: N/A
Date of Filing Meeting: February 6, 2006
Filing Date: February 20, 2006
Action Goal Date (optional): User Fee Goal Date: 22-003: June 22, 2006 22-027: October 22, 2006

Indication(s) requested: 22-003: Prophylaxis of invasive fungal infections
22-027: Treatment of oropharyngeal candidiasis

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ 22-027 P ☒ 22-003
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication*

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? All forms and certifications.

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  ***NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☐
  Requested: 3/6/06 ☒ NO
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 51,662

- End-of-Phase 2 Meeting(s)? Date(s) December 13, 2000 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) October 25, 2005 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 6, 2006

BACKGROUND:
Schering Plough Research Institute (SPRI) submitted IND 51,662 for SCH56592 (posaconazole) oral suspension on October 4, 1996. A further development meeting was held on December 13, 2000.

On October 25, 2005, a pre-NDA meeting was held for the indications treatment of oropharyngeal candidiasis and the prophylaxis of invasive fungal infections. On December 21, 2005, Schering submitted NDA 22-003 for Noxafil® (posaconazole) Oral Suspension, 200mg/5mL. This application was split for our administrative purposes and assigned a second NDA number, 22-027. NDA 22-003 was granted a priority review for the indication of prophylaxis of invasive fungal infections, and NDA 22-027 was granted a standard review for the indication of treatment of oropharyngeal candidiasis.

ATTENDEES:

Mark Goldberger, M.D., M.P.H.
Renata Albrecht, M.D.
Leonard Sacks, M.D.,
Maureen Tierney, M.D.
Regina Alivisatos, M.D.
Elizabeth O'Shaughnessy, M.D.
Karen Higgins, Sc.D.
Jyoti Zalkikar, Ph.D.
Cheryl Dixon, Ph.D
William Taylor, Ph.D.
Owen McMaster, Ph.D.
Mark Seggel, Ph.D.
Rapti Madurawe, Ph.D.
Philip Colangelo, Pharm.D., Ph.D.
Seong Jang, Ph.D

Shukal Bala, Ph.D.
Kalavati Suvarna, Ph.D.
Diana Willard
Kristen Miller, Pharm.D.

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline	**Reviewer**
Medical:	Maureen Tierney, M.D. Regina Alivisatos, M.D.
Statistical:	Jyoti Zalkikar, Ph.D. Cheryl Dixon, Ph.D
Pharmacology:	Owen McMaster, Ph.D.
Chemistry:	Mark Seggel, Ph.D.
Biopharmaceutical:	Seong Jang, Ph.D. Dakshina Chilukuri, Ph.D.
Microbiology, clinical:	Kalavati Suvarna, Ph.D. Lynn Steele-Moore
DSI:	Karen Storms
Regulatory Project Management:	Kristen Miller, Pharm.D.
Other Consults:	DMETS, DDMAC

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List:

We also request that you submit the following datasets to support the population PK analysis in Study P01899:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line.

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Sent to Schering on March 2, 2006.

Kristen Miller, Pharm.D.
Regulatory Project Manager, HFD-590

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/s/

Kristen Miller
3/6/2006 03:38:04 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-003
NDA 22-027

Schering Corporation
Attention: Todd Paporello, Pharm.D.
Regulatory Affairs Manager, Global Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Paporello:

Please refer to your December 21, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Noxafil® (posaconazole) Oral Suspension, 200mg/5mL. As stated in the February 8, 2006, acknowledgement letter, NDA 22-003 was split for our administrative purposes and a second NDA number, 22-027 was assigned. NDA 22-003 was granted a priority review for the indication of prophylaxis of invasive fungal infections, and NDA 22-027 was granted a standard review for the indication of treatment of oropharyngeal candidiasis.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications have been filed under section 505(b) of the Act on February 20, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

2. We also request that you submit the following datasets to support the population PK analysis in Study P01899:

   a. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

   b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

      For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of these applications and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the applications.

If you have any questions, please call Kristen Miller, Pharm.D., 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

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/s/

Renata Albrecht
3/2/2006 08:50:43 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-003
NDA 22-027

NDA ACKNOWLEDGMENT

Schering Corporation
Attention: Todd Paporello, Pharm. D., MBA
Associate Director & Liaison
2000 Galloping Hill Rd
Kenilworth, New Jersey 07033

Dear Dr. Paporello:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for posaconazole oral suspension, 40 mg/mL.

Please note that this application was split for our administrative purposes and assigned a second NDA number, 22-027. Once a final action is taken on these applications, the NDA number that is approved second will be retired and all future correspondence should refer to the NDA approved first.

Our Reference Number	NDA 22-003	NDA 22-027
Date of Application	December 21, 2005	December 21, 2005
Date of Receipt	December 22, 2005	December 22, 2005
Indication	Prophylaxis of invasive fungal infections	Treatment of oropharyngeal candidiasis
Review Priority Classification	Priority (P)	Standard (S)

Unless we notify you within 60 days of the receipt date that these applications are not sufficiently complete to permit a substantive review, we will file the applications on February 20, 2006 in accordance with 21 CFR 314.101(a). If we file the applications, the user fee goal date will be June 22, 2006 for NDA 22-003 and October 22, 2006 for NDA 22-027.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the reviews but not on the ultimate approvability of the applications. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted for the pediatric study requirement for these indications during the October 25, 2005 pre-NDA meeting for posaconazole.

Please cite the NDA numbers listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Division of Special Pathogen and Transplant Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me, at (301) 796-0762.

Sincerely,

{See appended electronic signature page}

Kristen Miller, Pharm.D.
Regulatory Health Project Manager
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Kristen Miller
2/8/2006 01:50:17 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Attn: Todd Paporello, Pharm.D., MBA

2. TELEPHONE NUMBER *(Include Area Code)*
(908) 740-4252

3. PRODUCT NAME
NOXAFIL (Posaconazole) Oral Suspesion

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
22-003

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☒ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
3006318

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
		12/21/2005

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,662

Schering Corporation
Attention: Todd Paporello, Pharm.D.
Regulatory Affairs Manager, Global Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Paporello:

Please refer to the meeting between representatives of your firm and the FDA on October 25, 2005. The purpose of the meeting was to discuss the planned December 2005 filing of your NDA for posaconazole for the prevention of invasive fungal infections (IFI) and the treatment of oropharyngeal candidiasis (OPC), refractory oropharyngeal candidiasis (rOPC)

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Kristen Miller, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Mark Goldberger, M.D., M.P.H
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

4 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Mark Goldberger
11/22/2005 04:45:31 PM

Executive CAC
Date of Meeting: May 31, 2005

Committee: Abby Jacobs, Ph.D., HFD-024, Acting Chair
Jim Farrelly, Ph.D., HFD-530, Alternative Member
Jeri El Hage, Ph.D., HFD-510, Alternate Member
Terry S Peters DVM, HFD-520, representing Robert Osterberg, Acting Team Leader, HFD-590
Owen McMaster, Ph.D., HFD-590, Presenting Reviewer

Author of Draft: Owen McMaster

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

Drug name Posaconazole
Sponsor: Schering

Posaconazole is a triazole antifungal currently being developed by Schering Corporation for the treatment of invasive fungal infections.

Since Posaconazole is being developed as an oral suspension, carcinogenicity studies were conducted in mice and rats using a dietary admixture.

Mouse Carcinogenicity Study:
A carcinogenicity study was initiated in mice in October, 1997, based on a design approved by the Executive CAC. Mice were initially dosed at 10, 30 and 60 mg/kg/day. After 5 weeks, the 60 mg/kg dose was increased to 90 mg/kg. By week 24 dosing was stopped in the high dose group because of high mortality in that group (10 % mortality in males and 8 % mortality in females). There were neither dose-related nor toxicologically significant increases in any tumor type in this study.

Rat Carcinogenicity Study:
A carcinogenicity study was initiated in Crl:CD®(SD)BRVAP/Plus rats in November , 1997 based on a design approved by the Executive CAC. Male rats were dosed at 5, 10 and 30 mg/kg/day, while female rats received 5, 10 or 20 mg/kg/day. The animals were 25% diet-restricted. The following mortality and neoplastic findings were recorded:

Mortality (%) Prior to Study Termination for Rats Treated with Posaconazole

Dose (mg/kg/d)	0	0	5	10	20	30
Males	30	30	60	66		91
Females	20	28	20	28	68	

Neoplastic Findings in Rats Treated for up to 104 Weeks in the Diet with Posaconazole

	Males					Females				
Dose (mg/kg/d)	**0**	**0**	**5**	**10**	**30**	**0**	**0**	**5**	**10**	**20**
Adrenal pheochromocytoma-										
Benign	7	9	5	12	18	4	5	3	4	17
Malignant	1	1	-	-	1	1	-	-	3	2
Adrenal cortical adenoma	1	5	2	2	12	5	5	1	5	22
Adrenal cortical carcinoma	-	-	-	-	1	-	-	-	3	1

Adrenal cortical toxicity and neoplasms were found in this study in a dose-related fashion.

Executive CAC Recommendations and Conclusions:

Mice:

Based on the excessive, early mortality in this high dose group in the carcinogenicity study and the 100 % mortality at 120 mg/kg in a three week study, the exec-CAC concurred that 60/90 mg/kg dose regimen had exceeded the MTD. The Committee considered this study to be acceptable. The committee concurred that there were no drug-related neoplasms.

Rats:

The CAC concurred that since the study design had prior concurrence from the CAC, the study was acceptable. However, based on the mortality data obtained during the carcinogenicity study, the CAC concluded that the high doses (30 mg/kg in the males and 20 mg/kg for the females) had exceeded the MTD's. The committee noted that the statistically significant increased incidences of adrenal pheochromocytomas and adrenal cortical neoplasms only occurred at doses that exceeded the MTD.

Abigail Jacobs, Ph.D.
Chair, Executive CAC

cc:\

HFD590/Division File, HFD-590
OsterbergR, HFD-590
McMasterO, HFD-590
PetersT, HFD-520
MillerK, HFD-590
ASeifried, HFD-024

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/s/

Abby Jacobs
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