CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205053Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205053 SUPPL # HFD #

Trade Name Noxafil Delayed-Release Tablets

Generic Name Posaconazole

Applicant Name Merck Sharp & Dohme Corp.

Approval Date, If Known 11-25-13

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 X 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 X

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.

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:

d) Did the applicant request exclusivity?

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YES X NO ☐

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

3

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

YES ☐ NO X

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?

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 X

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 X NO ☐

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

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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)

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is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO X

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?

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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?

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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: Alison Rodgers
Title: Regulatory Project Manager
Date: November 7, 2013

Name of Office/Division Director signing form: Katherine Laessig, MD
Title: Deputy Director, Division of Anti-Infective Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

Reference ID: 3412574

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

/s/

ALISON K RODGERS
11/25/2013

KATHERINE A LAESSIG
11/25/2013

Posaconazole Tablet Original Marketing Application
Debarment Certification

The applicant cited on the Form FDA 356h included with this submission 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.

Barbara Gunther

7-JAN-2013

Barbara Gunther, MA, MBA
Associate Director & Liaison
Global Regulatory Affairs

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205053	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: NOXAFIL Established/Proper Name: Posaconazole Dosage Form: Delayed-Release Tablets		Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):
RPM: Alison Rodgers		Division: Anti-Infective Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: X 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):
Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is November 25, 2013	X AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	X None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only): 3 – New Dosage Form

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes X No
• Press Office notified of action (by OEP)	☐ Yes X No
• Indicate what types (if any) of information dissemination are anticipated	X None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic 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.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: 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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric 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.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	**X** Verified ☐ Not applicable because drug is an old antibiotic.
• 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).	☐ No paragraph III certification Date patent will expire
• [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 section below (*Summary Reviews*)).*	☐ 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? ☐ Yes ☐ No

  (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).*

  (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)? ☐ Yes ☐ No

  *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 the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (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 (b)(2) 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)? ☐ Yes ☐ No

  *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 section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) 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 (b)(2) 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 section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	X Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval; 11-25-13
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	11-21-13
• Original applicant-proposed labeling	1-25-13
• Example of class labeling, if applicable	N/A

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide X Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	11-18-13
• Original applicant-proposed labeling	1-25-13
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	10-2-13
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A – Product name previously approved.
❖ Labeling reviews *(indicate dates of reviews and meetings)*	X RPM 4-16-13 X DMEPA 9-27-13 X DMPP/PLT (DRISK) 10-17-13 X ODPD (DDMAC) 10-21-13 X SEALD 11-19-13 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	4-26-13 X Not a (b)(2) X Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included 11-25-13
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes X No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 10-2-13 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	X Verified, statement is acceptable

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	10-8-13; 9-20-13; 9-10-13; 8-29-13; 8-28-13; 8-8-13; 7-22-13; 6-6-13; 4-16-13; 4-9-13; 3-27-13; 3-4-13; 2-20-13; 2-15-13
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	X No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	X N/A
• Pre-NDA/BLA meeting *(indicate date of mtg)*	X No mtg; Mtg cancelled by sponsor upon receipt of Division's responses to briefing package questions.
• EOP2 meeting *(indicate date of mtg)*	X No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	X None
Division Director Summary Review *(indicate date for each review)*	11-25-13
Cross-Discipline Team Leader Review *(indicate date for each review)*	11-4-13
PMR/PMC Development Templates *(indicate total number)*	2 templates; 11-25-13
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	X See concurrence on clinical review.
• Clinical review(s) *(indicate date for each review)*	11-7-13
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See page 11 of clinical review.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	X Not applicable
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	X None

[6] Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	X None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	X None See concurrence on Clinical Microbiology review
Clinical Microbiology Review(s) *(indicate date for each review)*	10-29-13; 3-12-13
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	X None
Statistical Team Leader Review(s) *(indicate date for each review)*	X None See concurrence on filing review
Statistical Review(s) *(indicate date for each review)*	03-04-13
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	X None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	See Cross-Discipline Team Leader Memo dated 11-04-13
Clinical Pharmacology review(s) *(indicate date for each review)*	10-17-13
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	11-06-13
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	X None
• Supervisory Review(s) *(indicate date for each review)*	X None See concurrence on Pharm/Tox review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	10-09-13; 3-19-13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
❖ ECAC/CAC report/memo of meeting	X None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	X None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	X None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	X None See concurrence on Product Quality Review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	10-25-13; 9-23-13 (Biopharmaceutics); 3-25-13
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	X Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See page 108 of Product Quality Review dated 10-25-13
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
X NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 10-4-13 **X** Acceptable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: Acceptable Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	X Not needed (per review) See page 105 Product Quality Review dated 10-25-13

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

PeRC PREA Subcommittee Meeting Minutes
October 2, 2013

PeRC Members Attending:
Lynne Yao
Hari Cheryl Sachs
Karen Davis-Bruno
Tom Smith
Andrew Mulberg (b) (4)
Wiley Chambers
Donna Katz
Robert "Skip" Nelson
Shrikant Pagay
Lily Mulugeta
Andrew Mosholder
Kevin Krudys
Barbara Buch
Susan McCune
Daiva Shetty
Martha Nguyen
Peter Starke
Ruthianna Davi
Gregory Reaman
Jane Inglese
William Rodriguez
George Greeley
Coleen LoCicero
Robert "Skip" Nelson
Rachel Witten
Maura O'Leary

Guests Attending:
Nichella Simms (PMHS)
Erica Radden (PMHS)
Courtney Suggs (OCP)
Donna Snyder (PMHS)
Dionna Green (OCP)
Alison Rodgers (DAIP)
Jian Wang (OCP)
Elizabeth Kilgore (DAAAP)
Aisar Atrakdei (DPP)
Hao Zhu (OCP)
Amy Taylor (PMHS)
GT Wharton (OPT)
Gilbert Burckart (OCP)
Robert Levin (DPP)
Owen McMaster (DAIP)
Ronald L. Ariagno (OPT/PMHS)
Ellen Fields (DAAAP)
Dominic Chiapperino (DAAAP)
Kim Updegraff (DPP)
Yun Xu (OCP)

Agenda

9:00	NDA	205053	Noxafil (posaconazole) Partial Waiver/Deferral/Plan/ Appropriately Labeled
9:20			(b) (4)
9:40			

Noxafil Partial Waiver/Deferral/Plan/Appropriately Labeled

- NDA 205053, Noxafil (posaconazole), tablet seeks marketing approval for the Prophylaxis of invasive Aspergillus and Candida infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy.
- The application was submitted on January 25, 2013, and has a PDUFA goal date of November 25, 2014.
- The application triggers PREA as a new dosage form.
- A waiver is being requested for pediatric patients aged birth to less than 2 years of age because studies are impossible or highly impractical.
- *Division justification for waiver*: It would be impractical to study posaconazole prophylaxis in this age group < 2 years old with hematologic malignancies. Antifungal prophylaxis for immunocompromised patients is rarely used in the age group < 2 years of age because the incidence of acute leukemia and lymphoma in pediatric patients, especially with AML and ALL, begins to increase after the age of 2 years, with peaks between 2 and 5 years of age. The applicant conducted a survey of investigator sites to confirm this point. The clinical reviewer conducted a literature review of hematological malignancies in children < 2 years old and agrees with the applicant's assessment. A waiver was granted for the age group < 2 years old for the same indication for the currently FDA-approved posaconazole oral suspension, NDA 22-003.
- The Division noted that at least 12-15 patients would be necessary for PK studies in those aged 1-2 years. The sponsor plans to also conduct an IV to suspension PK study in the youngest pediatric patients.
- A deferral is being requested for pediatric patients ages 2 years to less to less than 13 years because adult studies have been completed and the product is ready for approval.
- The posaconazole tablet was developed to overcome the exposure limitations of posaconazole oral suspension and the clinical program for the posaconazole tablet in adults is completed. The applicant's NDA contains five PK and tolerability studies of the tablet in healthy adult volunteers and one clinical study (n=230) in immunocompromised adult patients receiving posaconazole tablet as prophylaxis against invasive fungal infections.

- The Division will have to request the timeline of studies for this product.
- The PeRC agreed to the proposed timelines for the deferred studies.

PeRC Recommendations:

- The PeRC recommended to the Division to grant a partial waiver in pediatric patients aged birth to less than 1 year because studies are impossible or highly impractical. The PeRC noted that there would be a population of patients between 1 and 2 years of age that could be studied and that would likely use the product, if approved. Therefore the PeRC recommends that the Division decrease the age for the partial waiver to less than 1 year of age rather to less than 2 years of age.
- The PeRC recommended to the Division to grant a deferral for pediatric patients ages 1 year to less than 13 years because the product is ready for approval in adults. (see comments above)

Additional PeRC Recommendations:

- The first PREA PMR for deferred studies would include a PK, safety and tolerability study in this age group. The second PREA PMR study would be an efficacy study which could be released later if efficacy can be extrapolated.
- (b) (4)

(b) (4)

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GEORGE E GREELEY
11/06/2013

From: Grossman, Scott L.
To: Rodgers, Alison
Subject: RE: NDA 205053 Request for Information
Date: Tuesday, October 08, 2013 10:33:44 AM

Hi Alison –

I am confirming receipt of the email. I will forward this urgent request to the Team.

Scott

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Tuesday, October 08, 2013 10:31 AM
To: Grossman, Scott L.
Subject: NDA 205053 Request for Information
Importance: High

Hi Scott,

Please note the following request for information regarding Subject No. 4/000041 in STUDY P05615:

Please provide more information regarding Subject No. 4 /000041 who developed skin exfoliation on Day 12. Please provide more details regarding the skin exfoliation and the suspected etiology. It would be helpful if you could provide a case narrative.

Please provide this information by tomorrow if at all possible.

Please let me know if you have questions.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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/s/

ALISON K RODGERS
10/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205053 **INFORMATION REQUEST**

Merck Sharp & Dohme Corp.
Attention: Scott L. Grossman, Senior Liaison, Global Regulatory Affairs
351 North Sumneytown Pike, PO Box 1000
Mailstop UG2CD48
North Wales, PA 19454-2505

Dear Dr. Grossman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Noxafil ® (posaconazole) Tablet.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by September 27, 2013, in order to continue our evaluation of your NDA.

We have the following comments and requests for information.

1. In the FDA's information request (IR) dated August 28, 2013, we noted that the proposed acceptance criterion of Q = (b)(4)% at (b)(4) minutes for the buffer stage was not supported by the available dissolution data and we recommended the implementation of an acceptance criterion of Q = (b)(4)% at (b)(4)

   In the September 10, 2013 submission, you proposed an acceptance criterion of Q = (b)(4)% at (b)(4) minutes. To support your proposal you cited a limited number of clinical batches (2) and formal stability study batches (3), which were manufactured (b)(4)". Also, you mentioned that batches manufactured with parameters mimicking normal process variability would likely not meet the acceptance criterion of Q = (b)(4)% at (b)(4) minutes (b)(4)

   A buffer stage acceptance criterion of Q = (b)(4)

   Setting of dissolution acceptance criteria is typically based on the performance of the clinical trial batches. In the absence of pharmacokinetic data from batches that meet Q = (b)(4)% only after (b)(4) minutes or (b)(4) minutes, or of an in vitro in vivo correlation, neither time point is acceptable for control of product performance. Therefore, we continue to recommend an acceptance criterion of

Q = (b)(4)% at 135 minutes (5 minutes for pH change plus 10 minutes after pH change). Nevertheless, we are willing to accept a buffer stage acceptance criterion of Q= (b)(4)% at 145 minutes (5 minutes for pH change plus 20 minutes after pH change). If you agree with our recommendation, implement this dissolution criterion and provide the revised specifications table for your drug product with this update. Note that if additional dissolution data from other clinical/ pharmacokinetics batches become available, testing at a later time point could be reconsidered.

Additionally, we note that Stage 2 testing of (b) (4)% of batches is not inconsistent with regulatory expectations.

2. Protocol (b) (4) (eCTD Section 5.3.3.1 (b) (4)) describes a study to evaluate the effect of concomitant medications. The investigational drug product is identified as Batch No. W-H03945 / Lot No.: 06-56592-X-011 (formulation no. FM005241-5-1). Elsewhere in application the product is identified as Tablet D-green.

(b) (4)

We understood that the only difference between Tablet D-green and the commercial image, Tablet D-yellow, was the film coating color. However, the use of (b) (4) green tablets (Tablet D-green) and (b) (4) yellow tablets (Tablet D-yellow) does not appear to be described elsewhere in the application. The drug product manufacturing process development report (b) (4). Please explain the differences (e.g., manufacturing equipment and processes parameters, (b) (4) identify the product batches manufactured with each form, and discuss the potential impact on (b) (4) processing.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 - 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
09/20/2013

From: Rodgers, Alison
To: Grossman, Scott L. <scott_grossman2@merck.com> (scott_grossman2@merck.com)
Subject: Follow-Up
Date: Tuesday, September 10, 2013 9:44:00 AM

Hi Scott,

I am so sorry for the delay in getting back to you. I wanted to let you know that your proposals regarding submission of the PK data and the Clinical Study Report for the food effect study are acceptable. (b) (4)

Also, as per the Discipline Review Letter from Clinical Pharmacology (July 22, 2013), if the Noxafil Tablet NDA is approved, the labeling will be (b) (4) Noxafil Tablets are to be given with food.

I have not had a chance to look at NDAs 22003 and 22027. I will still get back to you regarding the preferred communication strategy.

Please let me know if you have any questions.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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/s/

ALISON K RODGERS
09/10/2013

From: Grossman, Scott L.
To: Rodgers, Alison
Subject: RE: NDA 205053 - Noxafil - Request for Clarification
Date: Wednesday, August 28, 2013 10:36:21 AM

Hi Alison,

I wanted to update you on the below. I am working on times for a meeting and I found 2 options that appear to work for the Merck Team:

- Tomorrow 1:00-2:00
- Friday 11:00-12:00

Will either of these work for you and Dr. (b) (4)?

In the meantime the CMC Team has provided me the following below written response to your question:

(b) (4)

Assuming you would still like to have a meeting please let me know if either of the above times would be acceptable.

Thanks,

Scott

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Tuesday, August 27, 2013 2:08 PM
To: Grossman, Scott L.
Subject: RE: NDA 205053 - Noxafil - Request for Clarification

Thanks, Scott.
No, it is just the question below.

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

From: Grossman, Scott L. [mailto:scott_grossman2@merck.com]
Sent: Tuesday, August 27, 2013 2:06 PM
To: Rodgers, Alison
Subject: RE: NDA 205053 - Noxafil - Request for Clarification

Hi Alison,

I will confirm the correct contact person, and availability this week. Are there issues beyond the question below? I just want to be sure to have the correct people as part of the discussion.

Scott

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Tuesday, August 27, 2013 2:04 PM
To: Grossman, Scott L.
Subject: RE: NDA 205053 - Noxafil - Request for Clarification
Importance: High

Hi Scott,

I wanted to find out with whom we could speak regarding the question I sent yesterday. The reviewer who needs the information, Dr. (b) (4), thinks that it might be easier and more efficient to talk by phone.

Please let me know at your earliest convenience.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

From: Grossman, Scott L. [mailto:scott_grossman2@merck.com]
Sent: Monday, August 26, 2013 12:18 PM
To: Rodgers, Alison
Subject: RE: NDA 205053 - Noxafil - Request for Clarification

Hi Alison,

I am just confirming receipt of the email. I will forward this to my CMC colleagues.

Scott

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Monday, August 26, 2013 11:04 AM
To: Grossman, Scott L.
Subject: NDA 205053 - Noxafil - Request for Clarification

Hi Scott,

Please see the following request for clarification:

(b) (4)

Please respond by August 30, 2013 if possible.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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ALISON K RODGERS
08/29/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20503 **INFORMATION REQUEST**

Merck Sharp & Dohme Corp.
Attention: Scott L. Grossman, Senior Liaison, Global Regulatory Affairs
251 North Sumneytown Pike, PO Box 1000
Mailstop UG2CD48
North Wales, PA 19454-2505

Dear Dr. Grossman:

Please refer to your New Drug Application (NDA) submitted January 25, 2013 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Noxafil ® (posaconazole) Tablet.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by September 9, 2013, in order to continue our evaluation of your NDA.

Your proposed acceptance criterion of Q = (b) (4)% at (b) (4) for the buffer stage is not supported by the provided dissolution data and is not acceptable. It is recommended that you implement an acceptance criterion of Q = (b) (4)% at 15 minutes after pH change (135 minutes of continuous testing) for the buffer stage. Provide the revised specification table for your drug product with the updated acceptance criteria for the dissolution test.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402-3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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RAPTI D MADURAWE
08/28/2013

From: Rodgers, Alison
To: "Grossman, Scott L."
Subject: RE: NDA 205053 - Noxafil - Request for Microbiology Information
Date: Thursday, August 08, 2013 10:30:00 AM

Hi Scott,

Thank you for your quick response. We apologize for any confusion. While the protocol under discussion does not explicitly state that microbiological procedures were performed on clinical specimens, it is apparent to the clinical microbiology reviewer (based on information provided elsewhere in the NDA submission) that the types of studies described in our Information Request (microscopy, fungal identification, serology, etc.) were performed during the course of Study P05615 (e.g. page 686 of Clinical Study Report synopsis: "Aspergillosis was diagnosed on Day (b) (6) in lung (radiographic evidence), blood (culture and serology) and catheter tip (culture)." Please provide the procedural details (as described in the IR) pertaining to these microbiological assays.

Please let me know if you have any questions.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

From: Grossman, Scott L. [mailto:scott_grossman2@merck.com]
Sent: Tuesday, August 06, 2013 7:16 PM
To: Rodgers, Alison
Subject: RE: NDA 205053 - Noxafil - Request for Microbiology Information

Hi Alison,

My apologies, but I am having difficulty finding where in P05615 we stated that "samples from some patient sites were collected for microbiological analysis (including microscopy, specimen culture, and serological testing)." Could you please identify exactly where in the NDA we made this statement?

Thank You,

Scott

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]

Sent: Tuesday, August 06, 2013 12:58 PM
To: Grossman, Scott L.
Subject: NDA 205053 - Noxafil - Request for Microbiology Information

Hi Scott,

Please see our request for microbiology information regarding NDA 205053 below. Please let me know when you plan to respond.

You state in the protocol for Study PO5615 that during treatment, samples from some patient sites were collected for microbiological analysis (including microscopy, specimen culture, and serological testing). Please submit the following information:

1. *The names and locations of the laboratories where the specimens or isolates were tested.*
2. *The storage conditions and transportation arrangements for specimens that were shipped from one laboratory or collection site to another site for preliminary or confirmatory testing.*
3. *Details of procedures for microbiologic tests (including specimen collection, microscopy, isolate identification, and fungal serology).*
4. *Quality control results for microbiologic tests, as appropriate (e.g. fungal serology).*

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research
Phone: 301-796-0797
Fax: 301-796-9882

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ALISON K RODGERS
08/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205053

DISCIPLINE REVIEW LETTER

Merck Sharp & Dohme Corp.
Attention: Scott L. Grossman, PhD
Liaison, Global Regulatory Affairs
351 North Sumneytown Pike
P.O. Box 1000, Mailstop UG2CD48
North Wales, PA 19454-2505

Dear Dr. Grossman:

Please refer to your January 25, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Noxafil (posaconazole) Tablets, 100 mg.

Based upon our current review of the study reports included in the NDA submission, and your March 5, 2013 response to our request for information regarding food intake during the conduct of Study P05615, we have concluded that you have not provided sufficient data to adequately support your proposed dosing and administration recommendation that Noxafil Tablets (b) (4) . In light of our conclusion, and if this NDA is approved, we will alter the proposed labeling to indicate that Noxafil Tablets be given with food because it is expected that food intake would increase the systemic bioavailability of posaconazole from the tablet formulation, as was observed with Noxafil Oral Suspension.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Philip Colangelo, PharmD, PhD
Clinical Pharmacology Team Leader
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

PHILIP M COLANGELO
07/22/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205053 **INFORMATION REQUEST**

Merck Sharp & Dohme Corp.
Attention: Scott L. Grossman, Ph.D.
Director, Worldwide Regulatory Affairs
351 North Sumneytown Pike
PO Box 1000
North Wales, PA 19454-2505

Dear Dr. Grossman:

Please refer to your New Drug Application (NDA) submitted January 25, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Posaconazole (Noxafil) Tablets.

We also refer to your May 8, 2013, submission, containing a response to our information request dated April 9, 2013.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by June 27, 2013 in order to continue our evaluation of your NDA.

1. We reiterate that the proposed regulatory dissolution test is not acceptable. Posaconazole delayed-release tablets should be tested in accordance with USP<711>, Dissolution, Delayed-Release Dosage Forms. The acid stage is 2 hours long and buffer should be added immediately after removal of the sample aliquots. You have not provided any scientific evidence that the dissolution test for posaconazole delayed-release tablets cannot be performed in accordance with USP<711>, Dissolution, Delayed-Release Dosage Forms. Please revise the dissolution test accordingly.

   Paddle speed (75 rpm (b) (4)) should be re-evaluated in the context of the revised dissolution procedure.

   Note that the USP recommended acid stage medium consists of 0.1 N HCl. Please provide your rationale for the use of 0.01 N HCl rather than 0.1 N HCl.

   In order to justify inclusion of the surfactant in the acid stage, please provide dissolution profiles and data obtained when the surfactant is not present in the acid stage but is introduced with the buffer. The use of the minimum amount of surfactant is recommended (see comment below).

2. [redacted]

As an alternative to calorimetric or spectroscopic analysis of solid state form, it may be feasible to use a suitably discriminating dissolution test to monitor the drug product for change in [redacted] form. We therefore recommend that you evaluate the ability of the proposed dissolution test method to [redacted] content. Note that inclusion of surfactant ([redacted]% polysorbate 80 is proposed) is expected to decrease the sensitivity of the dissolution test to crystalline content. It is therefore recommended that you evaluate dissolution media that do not contain surfactant.

3. Please include the test for moisture content to the drug product specification.

4. As presented, Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls is not sufficiently detailed. A complete description of the commercial scale drug substance and drug product manufacturing processes is required and should include all process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in section 3.2.P.3.3 of the application. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70. Please note that an unexecuted commercial master batch record is preferred to a comparably detailed process description.

5. Please indicate when the date of manufacture is set for drug product batches [redacted].

6. We understand that [redacted] was used during development to monitor [redacted] drug substance concentration. Indicate if any in-process controls [redacted] are present during routine commercial manufacturing to monitor active content of the [redacted] or provide justification for not including such in-process controls.

If you have any questions, call Navdeep Bhandari, Regulatory Project Manager, at (240) 402-3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWE
06/06/2013

From: Rodgers, Alison
To: "Gunther, Barbara"
Cc: Atzingen, Sonia
Subject: RE: POS Tablets - Day 74 Issues Letter - Response and Questions
Date: Tuesday, April 16, 2013 4:47:00 PM

Hi Barbara,

I will let you know if we have additional questions regarding the demographic datasets.

You may submit the revised USPI and PPI in word. We do not need them in SPL at this point. You do not need to resubmit artwork for the bottle and carton at this time.

The CMC questions should come through me for now. I will let you and Sonia know if that changes.

Please let me know if you have additional questions.

Thank you,

Alison

Alison K. Rodgers
Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

From: Gunther, Barbara [mailto:barbara.gunther@merck.com]
Sent: Friday, April 12, 2013 5:47 PM
To: Rodgers, Alison
Cc: Atzingen, Sonia
Subject: POS Tablets - Day 74 Issues Letter - Response and Questions

Hi Alison,

Please find following a response for Clinical Request 1 and questions for you based on the POS Tablets Day 74 Issues letter:

Clinical

1. Provide a demographic dataset for each of the five clinical pharmacology studies.

Response :The pooled demographic datasets DEM were submitted to FDA in M5,
Multiple dose study P05637 is under
M5\DATASETS\ISS\ISS12MD\ANALYSIS\LEGACY\DATASETS\DEM.XPT
And other 4 single dose studies are under
M5\DATASETS\ISS\ISS12SD\ANALYSIS\LEGACY\DATASETS\DEM.XPT

Question re Labeling Request: We request that you resubmit labeling that addresses this issue by April 30, 2013. The resubmitted labeling will be used for further labeling discussions.
We can submit the revised USPI (not in SPL format) and the PPI by April 30th. Is this acceptable?
If SPL format necessary, we will submit it as soon as it is available, but it will be after April 30th.
Is it necessary to resubmit the Artwork (bottle and carton) at this time? If so, we can submit the artwork when available, but it may be after April 30th.

Sonia is the CMC Liaison for POS Tablets, so I have copied her on this email. She would like to know if there is a CMC FDA Project Manager involved to handle CMC questions or will you be handling all aspects.

Thanks and BR,
Barbara

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/s/

ALISON K RODGERS
04/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205053

FILING COMMUNICATION

Merck Sharp & Dohme Corp.
Attention: Barbara Gunther, MA, MBA
Associate Director & Liaison
Global Regulatory Affairs
2015 Galloping Hill Road, MS 3175
Kenilworth, NJ 07033

Dear Ms. Gunther:

Please refer to your New Drug Application (NDA) dated January 25, 2013, received January 25, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Noxafil (posaconazole) Tablets, 100 mg.

We also refer to your amendments dated February 15, and March 5, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 25, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 30, 2013.

During our filing review of your application, we identified the following potential review issues:

Clinical Pharmacology

1. Based on our review of the study reports included in the NDA submission (b) (4)

Study P065615, [redacted] (b) (4)

The following reasons provide our rationale:

[redacted] (b) (4)

After we complete our review of all study reports submitted in this NDA, we will determine whether you have provided adequate information to support label statements that Noxafil Tablets [redacted] (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application 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 application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Clinical

1. Provide a demographic dataset for each of the five clinical pharmacology studies.

Chemistry, Manufacturing, and Controls

2. We acknowledge that you cross-reference NDA 22003 for the posaconazole drug substance information. However, to facilitate our review, please provide the following:
    a. A tabulation of the current drug substance specification,
    b. A summary of each change made to the manufacture of the posaconazole drug substance since the original approval of NDA 22003 (including a list of approved and pending supplements), and,
    c. Location (e.g., section number, page number, submission date, etc., as appropriate) of the change information as given above.

Biopharmaceutics

3. The proposed regulatory dissolution test is not acceptable. Posaconazole delayed-release tablets should be tested in accordance with USP<711>, Dissolution, Delayed-Release Dosage Forms. Please note that the acid stage is 2 hours long. Buffer should be added immediately after removal of the sample aliquots. In addition, inclusion of surfactant in the acid stage is not warranted and the (b) (4) paddle speed is not justified.

   Develop a discriminatory dissolution method in accordance with the USP dissolution monograph. Deviations from the USP method should be justified with supporting data. The dissolution report should include individual (n=12) and mean data, %RSD, and profiles.

4. As a delayed-release product, the potential impact of alcohol induced dose dumping should be evaluated. Please conduct an in vitro alcohol dose dumping study in 0.1 N HCl dissolution media containing 0%, 5%, 10%, 20% and 40% alcohol. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.

   The shape of the dissolution profiles should be compared to determine if the delayed release characteristics are maintained. The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference). The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments.

5. As a delayed-release product, the correct established name for the drug product is 'posaconazole delayed-release tablets'. This should be reflected in all product labeling.

6. Confirm that the dissolution data reported in P.2.3 Manufacturing Process Development were obtained using the originally proposed regulatory method. If not, the specific methods should be indicated. Where only mean values (or plots of mean values) are reported, please provide individual values and %RSD along with the mean results.

During our preliminary review of your submitted labeling, we have identified the following labeling format issue in the Highlights section:

1. Dosage Forms and Strengths - For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

We request that you resubmit labeling that addresses this issue by April 30, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for 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.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

Additionally, we acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

John J. Farley, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JOHN J FARLEY
04/09/2013

From: Rodgers, Alison
To: "Gunther, Barbara"
Subject: RE: POS Follow-up questions
Date: Tuesday, March 19, 2013 10:36:00 AM

Hi Barbara,

I am sorry for the delay in getting back to you. You should receive a letter soon regarding the deferral request for NDA 22003.

We do not have additional questions regarding the food intake data for study 05615 at this time.

We will issue a letter by day 74 which will list the timelines for the review.

I hope this is at least somewhat helpful.

Take care,

Alison

Alison K. Rodgers
Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

From: Gunther, Barbara [mailto:barbara.gunther@merck.com]
Sent: Sunday, March 17, 2013 10:05 PM
To: Rodgers, Alison
Subject: POS Follow-up questions

Hi Alison,

Hope all is well. I just wanted to see if you had any questions or any further information for me.

POS Oral Suspension NDA 22-003: Any word on the (b) (4) ?

POS Tablet NDA 205053: I know it is early to ask, but can you give any idea on whether or not Priority Review will be granted? If you can't tell me now, will we know by March 26th?

POS Tablet NDA 205053: I previously responded to your query regarding food intake re P05615. Do you have any further queries?

Best regards,
Barbara

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ALISON K RODGERS
03/27/2013

From: Gunther, Barbara
To: Rodgers, Alison
Subject: RE: NDA 205053 - Request for Information
Date: Sunday, March 03, 2013 3:14:58 PM

Hi Alison,

I confirm receipt of your email and will respond as soon as possible.

Best regards,
Barbara

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Friday, March 01, 2013 4:33 PM
To: Gunther, Barbara
Subject: NDA 205053 - Request for Information
Importance: High

Hi Barbara,

Please note the following request for information:

Please provide the food intake data in individual patients in Study P05615. If you already submitted the data, please inform us of the location of the data. These data are important to determine the dosing recommendation of posaconazole tablets in terms of food intake.

Please provide the information as soon as possible.

Please let me know if you have questions.

Please confirm receipt of this email.

Thank you,

Alison

Alison K. Rodgers
Regulatory Health Project Manager
FDA/CDER
Division of Anti-Infective Products
Phone: 301-796-0797
Fax: 301-796-9882
Email: alison.rodgers@fda.hhs.gov

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ALISON K RODGERS
03/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205053

NDA ACKNOWLEDGMENT

Merck Sharp & Dohme Corp.
Attention: Barbara Gunther, MA, MBA
Associate Director & Liaison
Global Regulatory Affairs
2015 Galloping Hill Road, MS 3175
Kenilworth, NJ 07033

Dear Ms. Gunther:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Noxafil (Posaconazole) Tablets, 100 mg

Date of Application: January 25, 2013

Date of Receipt: January 25, 2013

Our Reference Number: NDA 205053

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 26, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. 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 Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
02/15/2013