

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205596Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205596

SUPPL #

HFD #

Trade Name Noxafil Injection, 18 mg/mL

Generic Name Posaconazole

Applicant Name Merck Sharp & Dohme Corp.

Approval Date, If Known

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 (See Note)

NOTE: The pivotal study (P05520) for this NDA was a PK and safety study with some efficacy data (secondary endpoint) which will not be used to support efficacy in labeling. P05520 was not designed as an efficacy study. The available PK and safety data from P05520 bridges to the existing data (including efficacy data) with the oral suspension. The clinical safety information in Study P05520 provided the support for the safety of posaconazole IV in neutropenic subjects undergoing chemotherapy for leukemia and recipients of allogeneic hematopoietic stem cell transplant (HSCT) and patients with GVHD.

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?

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).

NDA# 22003 Noxafil Oral Suspension, 40 mg/ml

NDA# 205053 Noxafil Delayed-Release Tablets, 100 mg

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 X (See Note)

NOTE: The pivotal study (P05520) for this NDA was a PK and safety study with some efficacy data (secondary endpoint) which will not be used to support efficacy in labeling. P05520 was not designed as an efficacy study. The available PK and safety data from P05520 bridges to the existing data (including efficacy data) with the oral suspension. The clinical safety information in Study P05520 provided the support for the safety of posaconazole IV in neutropenic subjects undergoing chemotherapy for leukemia and recipients of allogeneic hematopoietic stem cell transplant (HSCT) and patients with GVHD.

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: Alison Rodgers
Title: Regulatory Project Manager
Date: February 25, 2014

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

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
03/18/2014

KATHERINE A LAESSIG
03/18/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 205596 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Noxafil injection, 18 mg/mL Established/Proper Name: Posaconazole Dosage Form: Injection		Applicant: Merck Sharp & Dohme, Corp. Agent for Applicant (if applicable):
RPM: Alison Rodgers		Division: Anti-Infective Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>Note: 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.</i></p>

❖ Actions <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is 3-13-14 • Previous actions <i>(specify type and date for each action taken)</i> 	X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
❖ 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 _____	<input type="checkbox"/> Received
❖ Application Characteristics ³	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) 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., new listed drug, patent certification revised).

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.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 3
 (confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- 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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	X No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

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 <i>(including approval letter with final labeling)</i>	Action(s) and date(s) 3-13-14
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	X Included
• Original applicant-proposed labeling	X Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	X Included
• Original applicant-proposed labeling	X Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	X Included
❖ Proprietary Name	N/A Product name previously approved.
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	
• Review(s) <i>(indicate date(s))</i>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 10/11/13 DMEPA: 2/10/14 DMPP/PLT (DRISK): 2/6/14 OPDP: 2/14/14 SEALD: None – See email dated 3-12-14 CSS: None Other: None
Administrative / Regulatory Documents	
❖ Administrative Reviews <i>(e.g., RPM Filing Review⁴/Memo of Filing Meeting)</i> <i>(indicate date of each review)</i>	2-24-14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	X Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>1/29/14</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	3/14/14; 3/14/14; 3/14/14; 2/25/14; 2/25/14; 2/24/14; 2/21/14; 2/20/14; 2/14/14; 2/10/14; 11/26/13; 11/8/13; 10/15/13; 10/7/13
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	11/25/13
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	X N/A X No mtg X No mtg X N/A X N/A N/A
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	X No AC meeting N/A
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	X None
Division Director Summary Review (<i>indicate date for each review</i>)	3-13-14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	2-27-14
PMR/PMC Development Templates (<i>indicate total number</i>)	3-13-14
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	X No separate review 3/13/14; 2/27/14; 12/5/13 X None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	See section 9.5, page 58, of clinical review dated 2/27/14
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	X None

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A X None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	X None requested
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	12/18/14; 10/25/13
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	X No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	2/5/14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	X No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	See Cross-Discipline Team Leader review dated 2-27-14
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	2/19/14; 11/4/13
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	Inspections Waived 11/25/13
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	X No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	X No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	2-27-14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	X None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	X None requested

Product Quality	<input type="checkbox"/> None
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	X No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	X No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	3/13/14; 2/20/14; 11/13/13
❖ Microbiology Reviews X NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	2/14/14; 10/23/13
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	2/20/14
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> 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) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 2-27-14 X Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	X Completed

⁵ 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.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	X Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	X Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	X Done
❖ Ensure Pediatric Record is accurate	X Done
❖ Send approval email within one business day to CDER-APPROVALS	X Done

From: [MacDonald, Laurie](#)
To: [Rodgers, Alison](#)
Subject: RE: Proposed PI for Noxafil IV
Date: Friday, March 14, 2014 11:16:07 AM

Hi Alison,

I am confirming that Merck accepts the proposed revisions to the PI for Noxafil IV.

Best regards,
Laurie

Laurie J. MacDonald, MD
Executive Director, Global Regulatory Affairs
Therapeutic Area Lead - Infectious Diseases
Merck & Co., Inc.
Phone: 267-305-5540

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Friday, March 14, 2014 10:29 AM
To: MacDonald, Laurie
Subject: FW: Proposed PI for Noxafil IV
Importance: High

Hi Laurie,
I know you called, but I don't think I received written confirmation of your acceptance of our revised label. Could you please send me a note for our files.
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: Rodgers, Alison
Sent: Thursday, March 13, 2014 3:10 PM
To: MacDonald, Laurie (laurie_macdonald@merck.com)
Subject: Proposed PI for Noxafil IV
Importance: High

Hi Laurie,

Please find attached our proposed revisions to the PI for Noxafil IV. Please see track changes in highlights, and sections 2 and 11. Please respond by 4:00 PM 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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/s/

ALISON K RODGERS
03/14/2014

Rodgers, Alison

From: MacDonald, Laurie <laurie_macdonald@merck.com>
Sent: Thursday, March 13, 2014 2:33 PM
To: Rodgers, Alison
Subject: RE: Noxafil IV Draft CMC PMCs

Hi Alison,

I would ask that you please confirm receipt. Please let me know if you have any questions about the proposed timelines.

Best regards,
Laurie

Laurie J. MacDonald, MD
Executive Director, Global Regulatory Affairs
Therapeutic Area Lead - Infectious Diseases
Merck & Co., Inc.
Phone: 267-305-5540

From: MacDonald, Laurie
Sent: Thursday, March 13, 2014 2:27 PM
To: Rodgers, Alison
Subject: RE: Noxafil IV Draft CMC PMCs

Hi Alison,

Merck agrees with the draft CMC PMCs for Noxafil IV. Please find the proposed timelines in the attached document.

Best regards,
Laurie

Laurie J. MacDonald, MD
Executive Director, Global Regulatory Affairs
Therapeutic Area Lead - Infectious Diseases
Merck & Co., Inc.
Phone: 267-305-5540

From: Rodgers, Alison [<mailto:Alison.Rodgers@fda.hhs.gov>]
Sent: Thursday, March 13, 2014 1:06 PM
To: MacDonald, Laurie
Subject: Noxafil IV Draft CMC PMCs
Importance: High

Hi, Laurie,

Please review the attached draft CMC PMCs for Noxafil IV. Please let me know if you agree and provide timelines by 3:00 PM if possible. Please let me know if you have questions.

Once we have reached agreement on the document, you can then submit a formal document to me via email and I will take it to the document room for entry into our system today.

Please confirm receipt of this email.

Thank you,

Alison

Allison 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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PMC 1:

Provide USP <788> test results using both Method 1 and Method 2 for the diluted infusion solutions of posaconazole injection in D5W and Normal Saline at drug product release and at annual stability test time points for 10 commercial batches of the drug product, Noxafil Injection, 300 mg.

Final Protocol Submission: 6/30/14
Trial Completion: 6/30/18
Final Report Submission: 9/30/18*

*Final report will include 3 year stability test time-point for 10 batches

PMC 2:

Conduct and provide the results of a detailed root-cause analysis of the particulate formation reported in Section 3.2.P.2.6 of the NDA for infusion solutions of posoconazole in 5% Dextrose and Normal Saline. This analysis should include evaluation of conditions under which particulates can be formed, the potential causes for the observed precipitation, an evaluation of whether particulate matter is more likely to appear in infusions solutions of newly manufactured batches of posaconazole injection, and if "batch aging" is likely to reduce particulates. Use both USP<788> Method 1 and Method 2 in your analysis. For particulates observed, identify the particulate matter.

Final Protocol Submission: 6/30/14
Trial Completion: 12/31/14
Final Report Submission: 3/31/15

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ALISON K RODGERS
03/14/2014

From: Rodgers, Alison
To: "[MacDonald, Laurie](#)"
Subject: RE: Noxafil PI Labeling - One additional revision
Date: Thursday, March 13, 2014 4:26:00 PM

Thanks, Laurie!

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: MacDonald, Laurie [mailto:laurie_macdonald@merck.com]
Sent: Thursday, March 13, 2014 4:26 PM
To: Rodgers, Alison
Subject: RE: Noxafil PI Labeling - One additional revision

Hi Alison,

I am confirming that Merck accepts the proposed revision.

Best regards,
Laurie

Laurie J. MacDonald, MD
Executive Director, Global Regulatory Affairs
Therapeutic Area Lead - Infectious Diseases
Merck & Co., Inc.
Phone: 267-305-5540

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Thursday, March 13, 2014 4:07 PM
To: MacDonald, Laurie
Subject: Noxafil PI Labeling - One additional revision

Hi Laurie,

As promised, please see one additional revision (sentence added) to the co-administration instructions. Please confirm if you accept the revision.

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
03/14/2014

Rodgers, Alison

m: Adebowale, Abimbola O
t: Wednesday, March 12, 2014 5:14 PM
To: Rodgers, Alison
Cc: Adebowale, Abimbola O
Subject: RE: NDA 205596 (NOXAFIL Injection): revised draft PI and PPI

Hi Alison,

Thank you for the e-mail and confirming that NDA 205596 will be approved tomorrow. I discussed this with my TL and it was decided that if we provide a SRPI review within the next 24 hours, the division will not have enough time to correct the format SRPI deficiency items prior to approval action tomorrow. Therefore, SEALD will not be completing an end-of-cycle SRPI review for this application.

Thank you,
Abi

From: Rodgers, Alison
Sent: Wednesday, March 12, 2014 4:38 PM
To: Adebowale, Abimbola O
Subject: RE: NDA 205596 (NOXAFIL Injection): revised draft PI and PPI

Hi Abi,
We do plan to approve 205596 tomorrow.
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: Adebowale, Abimbola O
Sent: Wednesday, March 12, 2014 3:10 PM
To: Rodgers, Alison
Subject: RE: NDA 205596 (NOXAFIL Injection): revised draft PI and PPI

Ok-Alison, thank you for the update. I will wait to hear from you after 3 PM.
Abi

From: Rodgers, Alison
Sent: Wednesday, March 12, 2014 2:34 PM
To: Adebowale, Abimbola O
Subject: FW: NDA 205596 (NOXAFIL Injection): revised draft PI and PPI
Importance: High

Hi Abi,

I left you a voice message, but wanted to send an email as well. I will know later this afternoon for sure, but it seems it's possible this NDA could be approved tomorrow. There would be language added to the label regarding use of an in-line filter. I will get back to you after our 3:00 meeting.

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: Rodgers, Alison
Sent: Monday, March 10, 2014 12:28 PM
To: Adebowale, Abimbola O
Subject: FW: NDA 205596 (NOXAFIL Injection): revised draft PI and PPI
Importance: High

Hi Abi,
Please see below.
Thanks,
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: Rodgers, Alison
Sent: Monday, March 10, 2014 12:19 PM
To: Eshete, Abel
Subject: FW: NDA 205596 (NOXAFIL Injection): revised draft PI and PPI
Importance: High

Hi Abi,

Attached is the PI (track changes and clean versions) for NDA 205596. The PDUFA date is this Thursday, 3/13. However, it is likely that we are going to extend the clock or issue a CR. We have a telecon with Merck at 4:00 this afternoon, and should know after that what the action will be.

The PPI is also attached, but I don't believe you review that.

Please let me know if you have questions.

Thank you,

Alison

Alison K. Rodgers
Senior Regulatory Health Project Manager
Division of Anti-Infective Products
Center for Drug Evaluation and Research

Rodgers, Alison

m: ees_admin@fda.gov
t: Thursday, February 27, 2014 1:11 PM
To: Rodgers, Alison; Godwin, Francis; Salganik, Maria*; Spain, Nancy *; Bhandari, Navdeep; Li, Xuhong; Kyada, Yogesh*
Subject: Overall OC Recommendation NDA 205596/000 Decision: ACCEPTABLE, Decision Date: 02/27/2014, Re-evaluation Date: 05/31/2015

This is a system generated email message to notify you that the Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send an email to EESQUESTIONS (EESQUESTIONS@cderr.fda.gov).

To contact the EES technical staff, send an email to CDER EES Help (EESHHELP@fda.hhs.gov). Thank you.

From: Bhandari, Navdeep
To: ["laurie_macdonald@merck.com"](mailto:laurie_macdonald@merck.com)
Subject: NDA 205596 - IR
Date: Tuesday, February 25, 2014 8:21:00 AM

Hello Laurie,

My team has asked that I convey the following comments to you. **Please provide a response by March 3, 2014.**

Reference is made to the Agency communication dated February 21, 2014 regarding the in-line filter. We request the following additional information regarding the compatibility of posaconazole IV with diluents. Please provide a response by March 3, 2014.

- 1. Section 3.2.P.2.6 of the NDA shows that the admixtures with the proposed diluents, 5% dextrose (D5W) and 0.9% sodium chloride (NS), frequently exceeded USP<788> recommended particulate matter limits for large volume injections. What is the nature of the particulate matters formed in the admixture solutions and the probable cause(s) for particulate formation, if known?*
- 2. We note that no particulate matter failures were observed in the compatibility study of an aged drug product (30-month old). Also, it appears the particulate matter levels were much higher at the 3-month time point versus later time points (including a 24-month time point) for several primary stability batches of the drug product. Is there any explanation for these observations?*
- 3. In addition to D5W and NS, were other diluents evaluated in the compatibility studies? Also, were different brands of D5W and NS evaluated in the compatibility studies? Please submit the data, if available.*
- 4. Did you evaluate the admixture compatibility with other types of in-line filters (i.e., other than the PES filter reported)? Please submit the data, if available.*

Thank you,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/CDER/FDA
240-402-3815

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/s/

NAVDEEP BHANDARI
02/25/2014

Rodgers, Alison

From: Rodgers, Alison
Sent: Tuesday, February 25, 2014 8:26 AM
To: MacDonald, Laurie (laurie_macdonald@merck.com)
Subject: NDA 205596 Draft Postmarketing Requirements
Attachments: PMR.doc

Hi Laurie,

Please find attached our draft PMRs for NDA 205596. Please confirm your agreement by Friday, February 28, 2014.

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*

2132-1: Conduct a trial in patients, ages 2 to < 18 years, to evaluate the pharmacokinetic (PK), safety, and tolerability of two new formulations of posaconazole (IV solution and/or new age-appropriate oral formulation) in immunocompromised pediatric patients with known or expected neutropenia.

Final Protocol Submission: 09/30/14

Trial Completion: 06/30/17

Final Report Submission: 09/30/17

If the trial for PMR 2132-1 fails to find a pediatric dosing regimen that provides pediatric patients with exposures similar to those in adult patients, then the following efficacy trial (PMR 2132-2) will be required, provided a safe and tolerable dosage regimen can still be identified. If the trial for PMR 2132-1 is successful in determining a pediatric dosing regimen, you may request release from PMR 2132-2.

2132-2: Conduct a comparative, double-blind, randomized, multi-center trial, in patients ages 2 to < 18 years, to evaluate the safety, efficacy, and tolerability of posaconazole for the prophylaxis of invasive fungal infections (IFI) in pediatric patients with known or expected neutropenia.

Final Protocol Submission: 09/30/17

Trial Completion: 11/30/20

Final Report Submission: 03/31/21

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ALISON K RODGERS
02/25/2014

From: Rodgers, Alison
To: [MacDonald, Laurie \(laurie_macdonald@merck.com\)](mailto:Laurie_macdonald@merck.com)
Subject: FW: Noxafil IV Labeling
Date: Friday, February 21, 2014 11:48:00 AM
Attachments: [Noxafil OPDP Labeling Review \(3\).doc](#)
[205596 DMPP PPI Jan-2014 marked.docx](#)
Importance: High

Hi Laurie,

With regard to the draft label for Noxafil IV sent yesterday, please address our question regarding the in-line filter as soon as possible before February 27, 2014.

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

From: Rodgers, Alison
Sent: Thursday, February 20, 2014 4:04 PM
To: MacDonald, Laurie (laurie_macdonald@merck.com)
Subject: Noxafil IV Labeling
Importance: High

Hi Laurie,

Please find attached draft labeling for the Package Insert and Patient Package Insert for Noxafil IV. Please respond by February 27, 2014. Please note that I have scheduled time on February 28, at 11:00 AM – 12:00 PM, for labeling negotiations if needed. Please let me know if your team is available at that time.

Please confirm receipt of this email.

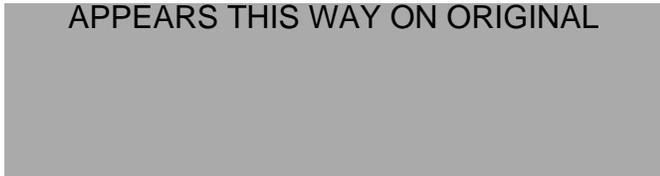
Thank you,

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*

APPEARS THIS WAY ON ORIGINAL



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ALISON K RODGERS
02/24/2014

From: Rodgers, Alison
To: [MacDonald, Laurie \(laurie_macdonald@merck.com\)](mailto:Laurie_macdonald@merck.com)
Subject: Noxafil IV Labeling
Date: Thursday, February 20, 2014 4:04:00 PM
Attachments: [Noxafil OPDP Labeling Review \(3\).doc](#)
[205596 DMPP PPI Jan-2014 marked.docx](#)
Importance: High

Hi Laurie,

Please find attached draft labeling for the Package Insert and Patient Package Insert for Noxafil IV. Please respond by February 27, 2014. Please note that I have scheduled time on February 28, at 11:00 AM – 12:00 PM, for labeling negotiations if needed. Please let me know if your team is available at that time.

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
02/24/2014

From: Rodgers, Alison
To: ["MacDonald, Laurie"](#)
Subject: RE: Noxafil IV - Carton and Container Labeling
Date: Monday, February 24, 2014 12:55:00 PM

Hi Laurie,

Please change the statement, "Each vial contains: 300 mg posaconazole" to "Each vial contains: 300 mg posaconazole / 16.7 mL" on the container label.

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: MacDonald, Laurie [mailto:laurie_macdonald@merck.com]
Sent: Friday, February 21, 2014 4:30 PM
To: Rodgers, Alison
Subject: RE: Noxafil IV - Carton and Container Labeling

Hi Alison,

The Agency has requested that Merck remove the statement "Each vial contains: 300 mg of posaconazole" from the carton labeling for Noxafil IV. This statement also appears on the originally proposed container label (please see attached, statement is circled in red). The Agency's comments on the container labeling do not include a request for this statement to be removed. Could you please confirm that it is acceptable to keep the statement "Each vial contains: 300 mg of posaconazole" on the container labeling? Thanks!

Best regards,
Laurie

Laurie J. MacDonald, MD
Executive Director, Global Regulatory Affairs
Therapeutic Area Lead - Infectious Diseases
Merck & Co., Inc.
Phone: 267-305-5540

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Friday, February 14, 2014 11:26 AM
To: MacDonald, Laurie
Subject: Noxafil IV - Carton and Container Labeling

Hi Laurie,

Please find attached our comments regarding carton and container labeling for Noxafil IV. If you

agree, please resubmit carton and container labeling by February 28, 2014.

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
02/24/2014

NDA 205596

Noxafil IV

Carton and Container Labeling Comments:

A. Container Label

- i. Replace the statement 'Intravenous Solution' with 'Injection'. According to USP General Chapter <1121> Nomenclature, the dosage form of this product is an injection.
- ii. Replace the strength statement '300 mg per vial' with '300 mg/16.7 mL (18 mg/mL)'. According to USP General Chapter <1> Injections, the strength per total volume should be the primary and prominent expression on the principal display panel, followed by the strength per milliliter in parenthesis. For example,

300 mg/16.7 mL

(18 mg/mL)

B. Carton Labeling

- i. See both A.i and A.ii and revise carton labeling accordingly.
- ii. Remove the statement 'Each vial contains: 300 mg of posaconazole' from the principal display panel as the net quantity is revised.
- iii. Relocate the statement 'Each mL contains: 18 mg posaconazole' from the principal display panel to the side panel.
- iv. Per CFR 201.100 (b) (5) (iii), please include the quantity or proportion of all inactive ingredients on the carton label.

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/s/

ALISON K RODGERS
02/14/2014

From: [MacDonald, Laurie](#)
To: [Rodgers, Alison](#)
Subject: RE: NDA 205596 - Request for Information
Date: Monday, February 10, 2014 4:16:18 PM

Hi Alison,

I am confirming receipt.

Best regards,
Laurie

Laurie J. MacDonald, MD
Executive Director, Global Regulatory Affairs
Therapeutic Area Lead - Infectious Diseases
Merck & Co., Inc.
Phone: 267-305-5540

From: Rodgers, Alison [mailto:Alison.Rodgers@fda.hhs.gov]
Sent: Monday, February 10, 2014 3:41 PM
To: MacDonald, Laurie
Subject: NDA 205596 - Request for Information

Hi Laurie,

Regarding NDA 205596, you refer to results for alkaline phosphatase in the study report for Study 05520. We were unable to locate a dataset with the results for alkaline phosphatase.

Please direct us to the results in the datasets or add the results for alkaline phosphatase to the following datasets: Lab Results, Lab Sample Comments, and Lab units.

Please respond by Friday, February 14, 2014, if at all possible.

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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not the intended recipient, and have received this message in error, please notify us immediately by reply e-mail and then delete it from your system.

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/s/

ALISON K RODGERS
02/10/2014



NDA 205596

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Merck Sharp & Dohme Corp.
Attention: Scott L. Grossman, PhD
Director, 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 New Drug Application (NDA) dated September 12, 2013, received September 13, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Noxafil (posaconazole) IV Solution, 18 mg/mL.

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

Chemistry, Manufacturing, and Controls

1. We acknowledge that you cross-reference NDA 22003 for posaconazole drug substance information. However, to facilitate our review please provide a summary of changes made to the manufacture of the posaconazole drug substance since the original approval of NDA 22003 by including a list of approved and pending supplements (e.g., submission date, section number, page number, etc., as appropriate).
2. Provide a justification for the proposed (b) (4) (b) (4) level in the solution. Propose acceptance criteria for the (b) (4) or provide a justification for not including them.
3. In Section P.5.5. you reported that "Four potential degradation products were observed and characterized in Posaconazole Injection (b) (4) (b) (4) Please clarify what analytical method was used in these studies to detect the potential degradants in the Posaconazole Injection formulation and provide the detection limit for the method utilized.

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.

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. 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), and patient PI, and you believe the labeling is close to the final version.

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.

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}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE A LAESSIG
11/26/2013

MEMORANDUM

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

DATE: November 25, 2013

TO: John Farley, M.D., M.P.H.
Director
Division of Anti-Infective Products (DAIP)
Office of Antimicrobial Products (OAP)
Office of New Drugs

FROM: Sripal R. Mada, Ph.D.
GLP Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Charles Bonapace, Pharm.D.
Chief (Acting) - GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Recommendation to accept data from NDA 205-596,
Noxafil IV Solution from Merck Research Laboratories,
USA, without onsite inspections

The Division of Anti-Infective Products requested inspections of the analytical sites on November 13, 2013. The Division of Bioequivalence and GLP Compliance discussed with the Office of Clinical Pharmacology (OCP) the cancellation of inspections for the following study:

P05520: "Pharmacokinetics, Safety, and Tolerability of POS IV Solution Followed by POS Oral Suspension in Subjects at High Risk for Invasive Fungal Infections"

This memo clarifies the reasons for cancellation of the requested analytical inspections at the following two sites:

 (b) (4)

Merck Research Laboratories (f.k.a Schering-Plough Research Institute), 556 Morris Avenue, Summit, NJ 07901

On November 19, 2013, DBGLPC recommended to OCP the cancellation of the inspection request, for the following reasons:

- Study P05615 for NDA 205-053 was conducted at approximately the same time as study P05520 for NDA 205-596. Additionally, a cross-validation of assay methodology was conducted to link the concentrations obtained from Merck Research Laboratories with the concentrations obtained from (b) (4). Study P05615 was inspected at (b) (4) and at Merck Research Laboratories (f.k.a Schering-Plough Research Institute), Summit, NJ, from June 10-13, 2013 with no objectionable conditions identified.
- The same assay and method validations that were conducted for study P05615 were used for study P05520.
- OSI has inspected (b) (4) several times over the past few years, with no significant observations noted.
- Limited OSI resources require us to consider a risk-based approach to inspections when appropriate. This will optimize our resources and better serve the needs of the review divisions.

Conclusion:

We recommend that the analytical data from study P05520 be (b) (4) review without onsite inspections of (b) (4) and Merck Research Laboratories (f.k.a Schering-Plough Research Institute), Summit, NJ.

Sripal R. Mada, Ph.D.
GLP Branch, DBGLPC, OSI

cc:

CDER OSI PM TRACK

OSI/Moreno

OSI/DBGLPC/Taylor/Dejernett

OSI/DBGC/GLPB/Mada/Bonapace

OSI/DBGC/BB/Haidar

OMPT/CDER/OND/OAIP/Farley/Rodgers

OMPT/CDER/OTS/OCP/Lazor/Colangelo/Jang

Draft: SRM 11/18/2013

Edit: WHT 11/18/2013; SHH 11/21/2013; CB 11/22/2013

Page 3 - NDA 205-596, Noxafil IV Solution from Merck Research Laboratories, USA

File: BE6597; O:\BE\EIRCOVER\205596.mer.nox.doc

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/ Inspections/BE

Program/Analytical Sites/Schering-Plough, Summit, NJ

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compl

Program/Analytical Sites/ (b) (4)

FACTS: not generated

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/s/

SRIPAL R MADA
11/25/2013

CHARLES R BONAPACE
11/25/2013
Signing for William Taylor



NDA 205596

PRIORITY REVIEW DESIGNATION

Merck Sharp & Dohme Corp.
Attention: Scott L. Grossman, PhD
Director, 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 New Drug Application (NDA) dated September 13, 2013, received September 13, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Noxafil (posaconazole) IV Solution, 18 mg/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is March 13, 2014.

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 requirement/commitment requests by February 21, 2014.

While conducting our filing review we identified potential review issues and will communicate them to you on or before November 26, 2013.

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

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SUMATHI NAMBIAR
11/08/2013

From: Bhandari, Navdeep
To: ["scott_grossman2@merck.com"](mailto:scott_grossman2@merck.com)
Subject: NDA 205596
Date: Friday, October 04, 2013 12:15:00 PM
Importance: High

Hello Dr. Grossman,

Could you please provide me with the FEI number, contact name, contact fax number and contact phone number for the facility listed in the Section 3.2.P.3.1 in your recent submission for Schering-Plough Labo NV?

This facility is listed as a packaging facility for the drug product.

Thank you,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/CDER/FDA
240-402-3815

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/s/

NAVDEEP BHANDARI
10/15/2013



NDA 205596

NDA ACKNOWLEDGMENT

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

Dear Dr. Grossman:

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) IV Solution, 18 mg/mL

Date of Application: September 13, 2013

Date of Receipt: September 13, 2013

Our Reference Number: NDA 205596

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 November 12, 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
10/07/2013