

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205596Orig1s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**

# Product Quality Microbiology Review

February 12, 2014

**NDA:** 205596

**Drug Product Name**

**Proprietary:** POS IV solution

**Non-proprietary:** posaconazole for injection, 18 mg/mL

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
September 12, 2013	September 13, 2013	September 23, 2013	September 23, 2013

**Submission History (for 2<sup>nd</sup> Reviews or higher) – N/A**

**Applicant/Sponsor**

**Name:** Merck Sharp & Dohme Corp

**Address:** 351 North Sumneytown Pike, North Wales, Pa  
19454

**Representative:** Scott L. Grossman, Ph.D., Director, Global R. A.

**Telephone:**

**Name of Reviewer:** Vinayak B. Pawar, Ph.D.

**Conclusion:** Recommend Approval

## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA
  2. **SUBMISSION PROVIDES FOR:** Intravenous formulation for posaconazole (POS IV) solution.
  3. **MANUFACTURING SITE:** Schering-Plough (Brinny) Co., Brinny, Innishannon, County Cork, Ireland.
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 18 mg/mL in a 20 mL vial for intravenous injection.
  5. **METHOD(S) OF STERILIZATION:** (b) (4)
  6. **PHARMACOLOGICAL CATEGORY:** A broad-spectrum triazole antifungal agent.
- B. **SUPPORTING/RELATED DOCUMENTS:** None
- C. **REMARKS:** The subject original NDA provides for an intravenous formulation for POS IV solution. This is an electronic submission assigned for a priority review status.

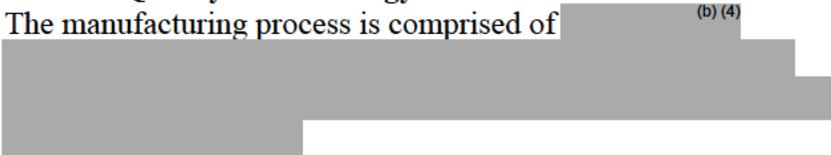
**filename:** N205596R1

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**Executive Summary****I. Recommendations**

- A. **Recommendation on Approvability** - Recommend Approval.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

**II. Summary of Microbiology Assessments**

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** -  
The manufacturing process is comprised of (b) (4)  

- B. **Brief Description of Microbiology Deficiencies** – None.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – None
- D. **Contains Potential Precedent Decision(s)** -  Yes  No

**Administrative**

- A. **Reviewer's Signature** \_\_\_\_\_  
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, OPS/CDER
- B. **Endorsement Block** \_\_\_\_\_  
John W. Metcalfe, Ph.D., Sr. Review Microbiologist, OPS/CDER
- C. **CC Block**  
N/A

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/s/  
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VINAYAK B PAWAR  
02/14/2014

JOHN W METCALFE  
02/14/2014  
I concur.

## MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

**NDA Number: 205,596**

**Applicant: Merck Sharp & Dohme Corp.**

**Stamp Date: 09/13/2013**

**Drug Name:  
POSACONAZOLE IV**

**NDA Type: 505 (b)(1)**

On **initial** overview of the NDA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
1	Is the microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	<b>X</b>		
2	Is the microbiology information (preclinical/nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	<b>X</b>		
3	Is the microbiology information (preclinical/nonclinical and clinical) legible so that substantive review can begin?	<b>X</b>		
4	On its face, has the applicant <u>submitted</u> <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	<b>X</b>		Data submitted in Posaconazole Oral suspension - Noxafil (NDA 022,003) already approved.
5	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	<b>X</b>		
6	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	<b>X</b>		
7	Has the applicant <u>submitted</u> the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcome?	<b>X</b>		Data submitted in Approved Oral suspension
8	Has the applicant <u>submitted</u> draft/proposed interpretive criteria/breakpoint along with quality control (QC) parameters and interpretive criteria, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA/BLA studies, and in a manner to allow substantive review to begin?	<b>X</b>		
9	Has the applicant <u>submitted</u> a clinical microbiology dataset in an appropriate/standardized format which intends to determine resistance development by correlating changes in the phenotype (such as <i>in vitro</i> susceptibility) and/or genotype (such as mutations) of the baseline pathogen with clinical and microbiologic outcome?			N/A
10	Has the applicant used standardized or nonstandardized			Much of the data

File name: 5\_Microbiology Filing Checklist for a NDA or Supplement 010908

## MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
	methods for measuring microbiologic outcome? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	<b>X</b>		hhave been presented in the Approved applications for Posaconazole Oral suspension
11	Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	<b>X</b>		
12	Has the applicant <u>submitted</u> annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	<b>X</b>		
13	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	<b>X</b>		
14	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		<b>X</b>	

**IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? YES**

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Lynette Y. Berkeley	10/24/2013
Reviewing Microbiologist	Date
Kerry Snow	10/24/2013
Microbiology Acting Team Leader	Date

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/s/  
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LYNETTE Y BERKELEY  
10/24/2013

KERRY SNOW  
10/25/2013

## PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 205596

**Applicant:** Merck Sharp & Dohme Corporation

**Letter Date:** September 12, 2013

**Drug Name:** Posaconazole IV, 18 mg/mL  
**NDA Type:** Original NDA

**Stamp Date:** September 13, 2013

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Section 3.2.P.3.3
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Section 3.2.P.3.5
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		No preservative added. CCI - Section 3.2.P.2.5.7
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Section 3.2.P.5.1 7 Methods Validation pkg. Section 3.2.R.3.P.
7	Has the applicant submitted the results of analytical method verification studies?	X		Bacterial Endotoxins Gel-Clot limit test per USP <85> or Ph. Eur 2.9.17 with drug product specifications at NMT (b) (4). Sterility Test per USP <71>.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?			N/A
10	Is this NDA fileable? If not, then describe why.	X		

**Additional Comments:** This NDA application is for an intravenous presentation of Posaconazole (Posaconazole IV solution). Posaconazole has been approved for US market as Noxafil® (Posaconazole oral suspensions under NDA 22-003 & NDA 22-027).

\_\_\_\_\_  
**Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, Primary Reviewer**

\_\_\_\_\_  
**Date**

\_\_\_\_\_  
**Stephen Langille, Ph.D., Sr. Review Microbiologist, Secondary reviewer**

\_\_\_\_\_  
**Date**

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/s/  
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VINAYAK B PAWAR  
10/23/2013

STEPHEN E LANGILLE  
10/23/2013

Division of Anti-Infective Products  
Clinical Microbiology Review

NDA 205596  
Date Review Completed: 12/15/2013

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Date Company Submitted: 09/13/2013  
Date Received by CDER: 09/13/2013  
Date Assigned: 09/14/2013  
Reviewer: Lynette Y. Berkeley

**SPONSOR**

Merck Sharp & Dohme Corp.  
351 North Sumneytown Pike,  
PO Box 1000  
MAILSTOP UG2CD48  
North Wales, PA 19454-2505

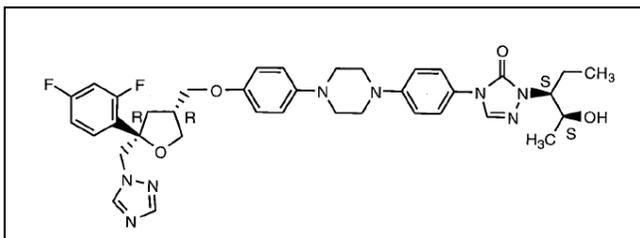
**CONTACT PERSON**

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

**DRUG PRODUCT NAME**

Proprietary: Noxafil  
Established: Posaconazole MK-5592/ SCH-56592  
Chemical name: 4-(4-(4-(4-(((3r,5r)-5-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)oxolan-3-yl)methoxy)phenyl)piperazin-1-yl)phenyl)-2-((2s,3s)-2-hydroxypentan-3-yl)-1,2,4-triazol-3-one-

**Chemical Structure**



Molecular formula: C<sub>37</sub>H<sub>42</sub>F<sub>2</sub>N<sub>8</sub>O<sub>4</sub>  
Molecular weight : 700.8 Da

**PROPOSED INDICATION**

Prophylaxis of invasive *Aspergillus* or *Candida* infections in patients, (b) (4) years of age and older, who are at high risk of developing these infections because they are severely immunocompromised.

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**PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION  
AND DURATION OF TREATMENT**

Dosage form: IV solution

Route of Administration: IV

Dosage: 300 mg BID (600 mg) on Day 1 and 300 mg QD after Day 1

Strength: 18 mg/mL

Duration of treatment: Varied

**DISPENSED**

Rx.

**RELATED DOCUMENTS**

Reference is made to the following active INDs held by the applicant:

- IND 51,316 – Posaconazole Capsules/Tablets
- IND 51,662 – Posaconazole Oral Suspension
- IND 75, 061 – Posaconazole IV solution

Reference is also made to the following NDAs held by the applicant:

- NDA 22,003 – Noxafil®, Oral Suspension, Prophylaxis of Invasive *Aspergillus* and *Candida* Infections
- NDA 22,027 – Noxafil®, Oral Suspension, Treatment of Oropharyngeal Candidiasis Including Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole
- NDA 205,053 (under review) – Noxafil® Tablet, Prophylaxis of Invasive *Aspergillus* and *Candida* infections

**REMARKS**

The sponsor has provided a background of summaries of pharmacokinetic studies related to various doses of posaconazole in healthy adults.

This application presents PK, safety and tolerability activity for support of the registration of the POS IV solution for treatment of infections caused by *Aspergillus spp.* and *Candida spp.*

**INTRODUCTION**

Posaconazole is a second-generation triazole antifungal agent with a broad spectrum of activity. Posaconazole (Noxafil) has been approved by FDA for the treatment of oropharyngeal candidiasis and invasive aspergillosis and oropharyngeal candidiasis refractory to itraconazole and fluconazole. The preparation used for the treatment of these indications was an oral suspension. Noxafil is administered as a suspension of 2.5 mL or 10 mL b.i.d or 5.0 mL t.i.d.

POS oral suspension was approved in 2006 in the US for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, who are at high

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risk of developing these infections because of being severely immunocompromised, such as being hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or having hematologic malignancies with prolonged neutropenia from chemotherapy. POS oral suspension is also approved in the US for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.

The major limitations of posaconazole oral suspension are (1) the need to administer this formulation multiple times in a day and (2) the need to take the drug with food (high fat food preferred) to enhance exposures. In spite of administration in multiple doses with food, posaconazole suspension is unable to achieve sufficient target exposures in many subjects. Patients with 25% of neutropenia achieve an average exposure ( $C_{avg}$  at steady state) of 322 ng/mL when taking POS oral suspension 200 mg t.i.d with food.

This application is being submitted for approval of a new IV formulation of POS (concentrate for solution for infusion, hereafter referred to as POS IV solution). The indications sought for POS IV solution are the same as those currently approved for POS oral suspension in each country, respectively, with the exception of oropharyngeal candidiasis.

The IV formulation of POS has been developed to allow for administration of POS to patients unable to take an oral medication or for whom absorption is a concern. This application demonstrates favorable PK, safety and tolerability and supports the registration of the POS IV solution.

### BACKGROUND

This is a 505 (b)(1) submission. The indication is prophylaxis for invasive *Aspergillus* and *Candida* infections in patients, (b) (4) years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT), graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy. All of the microbiology information except for one study that evaluated the efficacy of an intravenous formulation of posaconazole in the prophylactic treatment of *Aspergillus fumigatus* pulmonary infections in immunocompromised mice was based on the following studies

- IND 51,316 – Posaconazole Capsules/Tablets
- IND 51,662 – Posaconazole Oral Suspension
- IND 75, 061 – Posaconazole IV solution

Reference is also made to the following NDAs held by the applicant:

- NDA 22,003 – Noxafil®, Oral Suspension, Prophylaxis of Invasive *Aspergillus* and *Candida* Infections
- NDA 22,027 – Noxafil®, Oral Suspension, Treatment of Oropharyngeal Candidiasis Including Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole

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- NDA 205,053 (under review) – Noxafil® Tablet, Prophylaxis of Invasive *Aspergillus* and *Candida* infections.

### NON-CLINICAL INFORMATION

#### ANTIMICROBIAL SPECTRUM OF ACTIVITY

Posaconazole is active against *Candida spp.* except *Candida krusei*, *Cryptococcus neoformans*, *Trichosporon spp.*, *Aspergillus spp.* and Zygomycetes. Dimorphic fungi *Blastomyces dermatitis*, *Coccidioides spp.* and *Histoplasma capsulatum*, *Penicillium marneffeii*, *P.boydii* and *Mucor spp.* Additionally, posaconazole has shown activity against strains of *Candida spp.*, and *Aspergillus spp.* that have shown resistance to fluconazole, voriconazole and itraconazole.

#### MECHANISM(S) OF ACTION

Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14 $\alpha$ -demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane. The action is fungistatic.

#### MECHANISM(S) OF RESISTANCE

Resistance to posaconazole has not been reported. However, clinical isolates of *Candida albicans* and *Candida glabrata* with decreased susceptibility to posaconazole were observed in oral swish samples taken during prophylaxis with posaconazole and fluconazole, suggesting a potential for development of resistance. These isolates also showed reduced susceptibility to other azoles, suggesting cross-resistance between azoles. The clinical significance of these findings is not known.

#### ANIMAL STUDIES

Efficacy of an intravenous formulation of posaconazole in the prophylactic treatment of *Aspergillus fumigatus* pulmonary infections in immunocompromised mice is outlined below.

In this study, the POS IV formulation was evaluated for efficacy against *A. fumigatus* ND158. The MIC for POS against *A. fumigatus* ND158 was 0.125  $\mu$ g/mL in two immunocompromised mouse models of pulmonary infection. The intranasal infection model used a liquid conidial suspension, while the inhalation flask model used a dry conidial cloud for inoculation of the mice. The inhalation flask model was used extensively in the early efficacy evaluations of oral POS against various *Aspergillus* strains. For *A. fumigatus* strain ND158, the doses that resulted in 50% survival were 29.9 and 2.6 mg/kg when the drug was administered therapeutically and prophylactically, respectively. The results of the studies with the POS IV formulation are shown in Fig. 1. The inocula in the two models were similar,  $7.9 \times 10^6$  CFU/mouse for the intranasal and  $7.2 \times 10^6$  CFU/mouse for the

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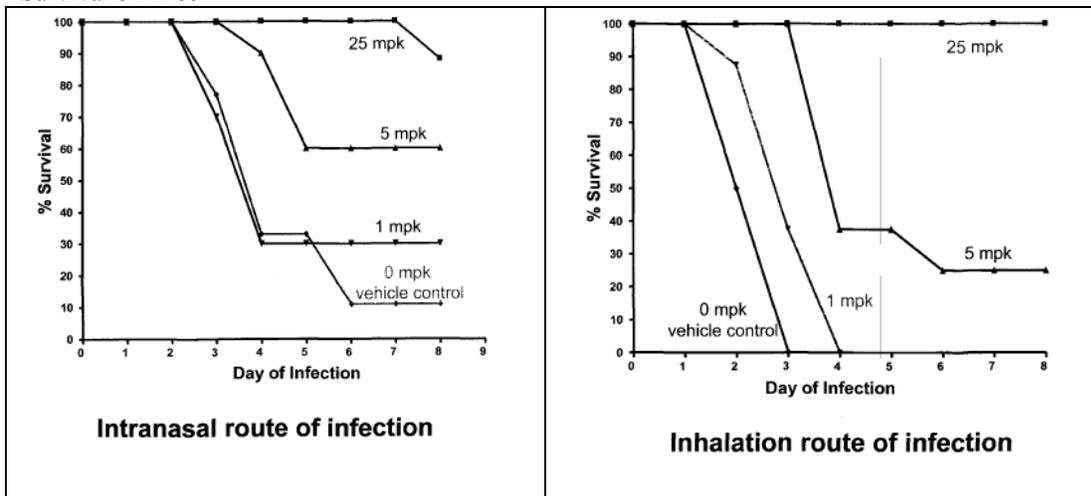
## Clinical Microbiology Review

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inhalation flask model, as determined from lung burdens of model and untreated mice 1 hr postinfection. However, the inhalation flask model was more lethal (3 to 5 days for 100% lethality) than the intranasal model - 7 days for 100% lethality. The POS IV formulation was similarly protective against lethality in both models (Fig. 1). The highest dose tested, 25 mg/kg, provided 88 to 100% survival through 8 days postinfection in both models. The middle dose, 5 mg/kg, resulted in intermediate survival, 60 to 75% in the intranasal model and 25 to 38% in the inhalation flask model. The low dose, 1 mg/kg, provided 30 to 50% survival in the intranasal model, and was completely ineffective (0% survival at day 4) in the inhalation flask model. The survival results were reflected in the lung burdens of the surviving mice.

Figure 1: Intranasal and Inhalation Models, *A.fumigatus* ND158: Effect of POS IV Formulation on Survival of Mice



**LABEL**  
MICROBIOLOGY SECTION

### Sponsor's version 12.4 Microbiology

#### ***Mechanism of Action:***

Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14 $\alpha$ -demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane. This may be responsible for the antifungal activity of posaconazole.

#### ***Activity in vitro:***

Posaconazole has *in vitro* activity against *Aspergillus fumigatus* and *Candida albicans*, including *Candida albicans* isolates from patients refractory to itraconazole or fluconazole or both drugs [see *Clinical Studies (14)*, *Indications and Usage (1)* and *Dosage and Administration (2)*].

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NDA 205596  
Date Review Completed: 12/15/2013

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**Microbiology Version**

**12.4 Microbiology**

***Mechanism of Action:***

*Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14 $\alpha$ -demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane. This may be responsible for the antifungal activity of posaconazole.*

***Activity in vitro:***

*Posaconazole has in vitro activity against Aspergillus fumigatus and Candida albicans, including Candida albicans isolates from patients refractory to itraconazole or fluconazole or both drugs [see Clinical Studies (14), Indications and Usage (1) and Dosage and Administration (2)].*

Concurrence:  
Kerry Snow, MS  
Clinical Microbiology Team Leader  
17 December 2013

Lynette Y. Berkeley , PhD, MT (ASCP)  
Microbiologist, DAIP  
December 18, 2013

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/s/  
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LYNETTE Y BERKELEY  
12/18/2013

KERRY SNOW  
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