CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205053Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

Division of Anti-Infective Products
Clinical Microbiology Review
New Drug Application

Date Company Submitted:02/15/2013
Date Received by CDER: 02/15/2013
Date Assigned: 02/17/2013
Reviewer: Lynette Y. Berkeley

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DRUG CATEGORY:
Antifungal

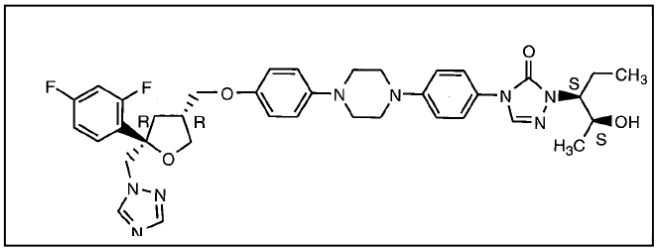
INDICATION:
Prophylaxis of Invasive Fungal Infections

PRODUCT NAMES:
a. PROPRIETARY: NOXAFIL®

b. Established Name: Posaconazole MK-5592/ SCH-56592

CHEMICAL:
4-[4-[4-[[(3*R*,5*R*)-5-(2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one.

STRUCTURAL FORMULA:



Molecular Weight: 700.8 Da.
Molecular Formula: $C_{37}H_{42}F_2N_8O_4$

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

Dosage form: Tablets
Route of Administration: Oral
Dosage: 300 mg (Three 100 mg tablets) Twice a day for the first day, then 300 mg(three 100mg tablets) once /day thereafter
Strength: 100 mg
Duration of treatment: Based on recovery from neutropenia or immunosuppression

DISPENSED

Rx.

RELATED DOCUMENTS

IND (b) (4)
IND 51,662 – Posaconazole Oral Suspension
IND (b) (4)
NDA 22-003 – Noxafil, Prophylaxis of invasive *Aspergillus* and *Candida* infections
NDA 22-027 – Noxafil, Prophylaxis of Invasive *Aspergillus* and *Candida* Infections.

REMARKS

This NDA concerns a Posaconazole oral tablet. Microbiological information for the efficacy of prophylaxis with Posaconazole tablets is derived from data submitted in the oral suspension and IND (b) (4)

SUMMARY

Posaconazole tablet is being submitted for approval of a new solid oral tablet formulation
The tablet has been designed to release posaconazole in the small intestine, thus maximizing systemic absorption. The indications sought for the posaconazole tablet are the same as those currently approved for the oral suspension with the exception of oropharyngeal candidiasis.
Data in the study are based on historical experience working with the active ingredient in the oral suspension.
The tablet has been found to be effective in the treatment of *Aspergillus spp.* and *Candida* infections.

1. INTRODUCTION

The subject of this NDA is Noxafil tablet, the active ingredient of which is posaconazole, a triazole antifungal drug. It acts against susceptible fungi by inhibiting the synthesis of ergosterol a major component of the cell membrane of fungi.
Posaconazole (POS) oral suspension was initially approved in 2005 in Europe for the treatment of a number of fungal infections including invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;

1) fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
2) chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole; and
3) coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

Additional infections with fungal origins were added in 2006. These included treatment of patients

- who were receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
- hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease (GVHD) and who are at high

risk of developing invasive fungal infections.

- the treatment of oropharyngeal candidiasis as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor.

Posaconazole oral suspension was approved in 2006 in the US for the prophylaxis of invasive A*spergillus* and *Candida* infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy. Posaconazole oral suspension is also approved in the US for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.
Posaconazole oral suspension is currently approved in more than 80 countries. The exact indications differ across the various countries where POS is approved

This application is being submitted for approval of a new solid oral tablet formulation of Posaconazole. The tablet has been designed to release posaconazole in the small intestine, thus maximizing systemic absorption. The tablet has been shown to be safe and well tolerated, to provide optimal pharmacokinetic exposures. It can be administered once daily after twice daily dosing on the 1st day (b) (4). The indications sought for the posaconazole tablet are the same as those currently approved for the oral suspension in each country, respectively, with the exception of oropharyngeal candidiasis. Data in the study are based on historical experience working with the active ingredient in the oral suspension.

2. BACKGROUND

ANTIMICROBIAL SPECTRUM OF ACTIVITY
Posaconazole is active against *Candida spp*. except *Candida krusei*, *Cryptococcus neoformans, Trichosporon spp., Aspergillus spp. and* Zygomycetes*,* dimorphic fungi *Blastomyces dermatiditis, Coccidiodes spp.* and *Histoplasma capsulatum*, *Penicillium Marneffei and P.boydii.* Additionally, posaconazole has shown activity against isolates of *Candida spp.*, and *Aspergillus spp.* that have shown resistance to fluconazole, voriconazole and itraconazole.

MECHANISM(S) OF ACTION
Posaconazole is a triazole antifungal agent that blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-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

Clinical Microbiology

Efficacy Results from Protocol 05615

P05615 was a single pivitol study conducted in the target patient population of severely immunocompromised patients treated with the POS tablet. The trial design utilized for P05615 was a single-arm, open-label, uncontrolled, multicenter study. The main objective of the study was to evaluate the PK, safety, and tolerability of a new oral formulation (POS tablet) of POS in subjects at risk for an invasive fungal infection. The efficacy of oral POS suspension had been well established in Jang et al (2010) . Hence, the pivotal study with the POS tablet (P05615) was not predominantly designed as an efficacy study. Instead, in the setting of known exposure/response relationships for POS, the available PK and safety data from P05615 would bridge to the existing data (including efficacy data) with the oral suspension. In order to conduct the initial evaluation of POS tablet in patients, the first part of P05615 (Part 1 or Phase 1B) was designed to evaluate dosing of POS tablet in small cohorts of patients at risk for an Invasive Fungal Infection (IFI). The subject population selected for Part 1 of the study was the patient population at greatest risk of an IFI and for whom taking POS oral suspension with a high fat meal may have been difficult due to nausea and vomiting following chemotherapy. P05615 enrolled patients at risk for GVHD in addition to patients under treatment for GVHD.

Efficacy Conclusions from P05615

As efficacy was not a primary variable to be assessed in the POS tablet study (P05615), and as efficacy was limited to a descriptive assessment in P05615, a detailed comparison of the POS tablet findings to the prior POS oral suspension findings is limited. Nonetheless, the reported efficacy findings for POS tablet are generally consistent with the efficacy findings previously reported for POS oral suspension in similar patient populations receiving prophylaxis. The IFI and survival data for POS tablet compare favorably with the corresponding data previously reported for POS oral suspension clinical trials when POS oral suspension was used as antifungal prophylaxis (P01899 and C/I98/316).

These data support the use of the POS tablet as prophylaxis for patients who may benefit from this formulation. Furthermore, these data support the use of POS tablet in the treatment of IFIs, as exposures with the POS tablet were achieved at or above those previously shown to be effective in the treatment of IFIs with the POS oral suspension.

The bridging Phase 1b/3 clinical study (P05615) of POS tablet in patients demonstrated that POS tablet 300 mg daily (following 300 mg BID on Day 1) was safe and achieved an exposure profile that has been shown to be effective in both the prophylaxis as well as the treatment of IFIs. Although limited, the descriptive efficacy data with the POS tablet in the prophylaxis setting are generally consistent

with those seen with POS oral suspension in prior pivotal studies. These data support the use of the POS tablet as prophylaxis or as salvage treatment of IFIs in the patients populations that may benefit from this formulation.

- Overall, the incidence of IFI in this study was relatively low and similar to that previously reported for POS oral suspension. In this study, there was no adjudication or review of IFI diagnosis. The reported IFI diagnosis was based upon investigator judgment.
- In this study, survival assessment at Day 65 was high. The survival assessment indicated that 90% and 91% of subjects in the 200 mg dosing cohort and the 300 mg dosing cohort, respectively, were alive at Day 65.

REFERENCES

Jang1, S., P. Colangelo and J. Gobburu. Exposure–Response of Posaconazole Used for Prophylaxis Against Invasive Fungal Infections: Evaluating the Need to Adjust Doses Based on Drug Concentrations in Plasma Clinical pharmacology & Therapeutics. Vol. 88:1. 2010

Lynette Y. Berkeley, Ph.D., M.T. (ASCP),
Microbiologist,
October, 29, 2013

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

/s/

LYNETTE Y BERKELEY
10/29/2013

KERRY SNOW
10/29/2013

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 205053 **Applicant: Merck** **Stamp Date: 01/25/2013**

Drug Name: Noxafil (Posaconazole tablet) **NDA Type: Standard**

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

	Content Parameter	Yes	No	Comments
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?	X		
2	Is the microbiology information (preclinical/nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		There are minimal microbiology data. Which is presented in a format that can allow the review to begin.
3	Is the microbiology information (preclinical/nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant submitted *in vitro* 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?	X		The label will be based on data submitted in a previous Noxafil submission
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			NA
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?			NA
7	Has the applicant submitted the clinical microbiology datasets in a format which intents to correlate baseline pathogen with clinical and microbiologic outcome?	X		
8	Has the applicant submitted 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?			NA
9	Has the applicant submitted a clinical microbiology dataset in an appropriate/standardized format which intents to determine resistance development by correlating changes in the phenotype (such as *in vitro* susceptibility) and/or genotype (such as mutations) of the baseline pathogen with clinical and microbiologic outcome?			NA

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

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
10	Has the applicant used standardized or nonstandardized 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?	X		
11	Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		The applicant has submitted draft labeling but there are some additions to be made.
12	Has the applicant submitted annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?			Please see #11
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?	X		
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?		X	

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes

This submission is linked to the oral suspension of Noxafil (posaconazole) which is approved by the Agency for the treatment of invasive Aspergillosis and *Candida* infections. One limitation of the oral suspension is the need to take it multiple times a day and to take it with food. On the other hand, the tablet can be taken once daily (b) (4) (b) (4). The data for the tablet formation will be taken from that supplied for the suspension.

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.

There are no review issues

Lynette Y. Berkeley, PhD, M.T (ASCP) March 01, 2013

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

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

Reviewing Microbiologist	Date
Kerry Snow, MS, MT(ASCP)	12 March 2013
Microbiology Team Leader	Date

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

/s/

LYNETTE Y BERKELEY
03/12/2013