CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205596Orig1s000

STATISTICAL REVIEW(S)

Memo to File
STATISTICAL REVIEW AND EVALUATION

NDA #:	205-596 (dated September 13, 2013)
Sponsor:	Merck
Name of Drugs:	Noxafil (posaconazole) intravenous solution
Indication:	Prophylaxis of 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) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Cheryl Dixon, Ph.D.
Concurring Reviewer:	Karen Higgins, Sc.D.
Medical Division:	Division of Anti-Infective Products
Medical Reviewer:	Elizabeth O'Shaughnessy, M.D.
Project Manager:	Alison Rodgers

Summary:
This NDA is for Noxafil (posaconazole) intravenous solution. Posaconazole is currently approved as an oral suspension and oral tablet for the indication of prophylaxis of invasive *Aspergillus* and *Candida* infections in patients, 13 years of age and older, who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy. The oral suspension is also approved for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole. In order to increase the absorption of posaconazole oral suspension, it is necessary to take posaconazole oral suspension multiple times per day with a full meal. Therefore, the posaconazole oral tablet was developed with a reduced food effect and similar exposures in the fed and fasting state. The intravenous solution was developed as an alternate to these oral formulations when a patient is unable to take and/or absorb an oral formulation.

The development program for posaconazole intravenous solution for the prophylaxis indication was based on a pharmacokinetic (PK) bridging strategy to the posaconazole oral suspension. Three clinical studies in healthy volunteers and one pivotal uncontrolled

clinical study (P05520)in patients were conducted with posaconazole intravenous solution. The pivotal clinical study conducted in patients was primarily designed to fully characterize the PK and assess safety of posaconazole intravenous solution in neutropenic subjects (acute myelogenous leukemia, AML and myelodysplastic syndrome, MDS) and subjects who had undergone a HSCT and were under treatment for GVHD considered to be at high risk for developing invasive fungal infections. Efficacy was not a primary variable to be assessed in this study and was limited to a descriptive assessment.

P05520 was a Phase 1b/3 study. The study consisted of a single dose part (Cohort 0), a Phase 1b dose-ranging portion (Cohorts 1 and 2), and a Phase 3 portion to provide additional safety and PK data at the final dose chosen (Cohort 3). In the Phase 1b portion, two sequential and escalating dosing cohorts (posaconazole intravenous solution at 200 mg in Cohort 1 and 300 mg in Cohort 2 for 14 days, followed by posaconazole oral suspension at 400 mg BID for a total treatment duration of up to 28 days) were evaluated with serial PK sampling to characterize the PK profile of posaconazole intravenous solution. The subject population for the Phase 1b portion included subjects with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia. In the Phase 3 portion, all subjects received the 300 mg dose regimen and the population was expanded to also include additional subjects at risk of a fungal infection, subjects who had undergone an HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. Ten subjects received a single 200 mg dose of posaconazole intravenous solution, 21 subjects received multiple dosing of 200 mg posaconazole intravenous solution (following 200 mg BID on Day 1), and 237 subjects received multiple dosing of 300 mg daily (following 300 mg BID on Day 1).

The evaluation of efficacy in the study was descriptive in nature based upon the investigator's assessment of clinical response. A subject was counted as a clinical failure if one or more of the following criteria were met:

1. The subject was diagnosed by the investigator with a probable or proven invasive fungal infection (IFI),
2. The subject was confirmed to have died during the study (up to and including Day 70),
3. The subject discontinued study therapy for any reason,
4. The subject received systemic antifungals for empiric treatment of fungal infections for more than 4 days while the subject was receiving study treatment.

A Day 65 survival assessment was also performed, which included death at any time through Day 65 + 5 days. The protocol specified that these endpoints were to be assessed only in Cohort 3 but for completeness the results are presented for all subjects who received multiple dosing of 300 mg in both Cohorts 2 and 3 combined and those who received multiple dosing of 200 mg in Cohort 1.

Overall, 75 of the 237 (32%) subjects who received multiple dosing of 300 mg were clinical failures. There were 3 subjects with a proven or probable invasive fungal infection (1 in Cohort 2 and 2 in Cohort 3). Two were diagnosed with a pulmonary

mycosis and one was diagnosed with probable aspergillosis. Six subjects received systemic antifungals for empiric treatment of fungal infections for more than 4 days while on study drug. For those who received multiple dosing of 300 mg, 210 (89%) were confirmed to be alive through Day 65. There were 16 confirmed deaths and 11 subjects were missing the Day 65 survival assessment. Three additional deaths were reported during the follow-up period (after Day 70).

Of the 21 subjects who received multiple dosing of 200 mg, 7 (33%) were clinical failures. One subject was diagnosed with candidemia and upon autopsy disseminated aspergillosis was found. No subject received systemic antifungals for empiric treatment of fungal infections while on study drug. Twenty of the 21 subjects (95%) who were treated with multiple doses of 200 mg survived through Day 65.

Since there are no comparative efficacy studies, there is no formal statistical review for this NDA. For further details on P05520, refer to the Clinical and Clinical Pharmacology reviews.

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

/s/

CHERYL A DIXON
02/05/2014

KAREN M HIGGINS
02/05/2014