Memo to File
STATISTICAL REVIEW AND EVALUATION

NDA #:	205-053 (dated January 25, 2013)
Sponsor:	Merck
Name of Drugs:	Noxafil (posaconazole) tablets
Indication:	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.
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) Tablets. Posaconazole is currently approved as an oral suspension for the indications 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. It 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, a posaconazole oral tablet was developed with a reduced food effect and similar exposures in the fed and fasting state.

The development program for posaconazole tablet for the prophylaxis indication was based on a PK bridging strategy to the posaconazole oral suspension. Five clinical studies in healthy volunteers and one pivotal uncontrolled clinical study in patients were conducted with posaconazole oral tablet. The pivotal clinical study conducted in patients was primarily designed to fully characterize the PK and assess safety of posaconazole

tablet in neutropenic subjects (AML and MDS) and subjects who had undergone a HSCT and were under treatment for GVHD. Efficacy was not a primary variable to be assessed in this study and was limited to a descriptive assessment. This study (P05615) was a two part study. In part 1, two sequential and escalating dosing cohorts (200 mg and 300 mg) were evaluated with serial PK sampling to characterize the PK profile. Only neutropenic subjects were enrolled in Part 1. In Part 2, all subjects received the 300 mg dose regimen and the population was expanded to also include subjects who had undergone a HSCT. Sparse PK sampling was performed on all subjects in Part 2. In Part 1, 20 patients received 200 mg and 34 patients received 300 mg. In Part 2, 176 patents received 300 mg. In the 200 mg cohort, 2 subjects were diagnosed with an invasive fungal infection (IFI). One was diagnosed with aspergillosis of the lung and blood and the other was diagnosed with fusarioisis of the lung, sinus, and blood. Both subjects died. In the 300 mg cohort, 1 subject was diagnosed with a fungal infection of the pleura (*Candida glabrata)*. An additional 9 subjects were diagnosed with a possible IFI although no mycological evidence of infection was identified for these subjects. Eighteen subjects treated with 300 mg died by 65 days.

Since there are no comparative efficacy studies, there is no formal statistical review for this NDA.

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/s/

CHERYL A DIXON
11/06/2013

KAREN M HIGGINS
11/09/2013