CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-754

MICROBIOLOGY REVIEW

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

DATE: February 5, 2005

TO: NDA #: 21-754 and 21-506

FROM: Shukal Bala, Ph.D.
Microbiology Team Leader
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

SUBJECT: Micafungin

Introduction and Background:
The subject of this NDA is micafungin (FK463) an echinocandin with activity against 1,3-β-D-glucan synthase derived from *Candida albicans* and *A. fumigatus* but not mammalian cells. The preclinical studies supporting the activity of micafungin were reviewed earlier (for details see microbiology review dated 1-21-03, ———— . The clinical microbiologic evaluation of studies for the treatment of aspergillosis (FG 463-21-01 and 98-0-046) and candidiasis (FG 463-21-02, 98-0-47 and 97-7-003) was also included in the same microbiology review. In this submission the sponsor has included 2 clinical studies (FG 463-21-09 and 03-7-005) to support the efficacy of micafungin in patients with esophageal candidiasis. The primary microbiology review of this submission was assigned to Ms. Lynn Steele Moore. However, due to ———— , Ms. Moore was unable to complete the review. This microbiology team leader review discusses essential microbiologic findings abstracted from Ms. Moore's draft review of the study FG 463-21-09 and presents review of study 03-7-005 (not reviewed by Ms. Moore).

Clinical Microbiology:

Study FG 463-21-09 (information abstracted from Ms Moore's draft review):
This was a phase 2 dose ranging study of micafungin (50, 100, or 150 mg per day) in HIV patients with confirmed EC. Fluconazole (200 mg/day) was used as a comparator. A majority of the patients in the clinical trial were infected with *C. albicans*. Only 10 patients (4.6%) had *C. glabrata*, 4 (1.8%) had *C. tropicalis*, and 1 (0.5%) had *C. krusei*. Fifteen patients (6.9%) in this group were infected with more than one *Candida* species. There was no correlation of *in vitro* susceptibility of the baseline pathogen with clinical or microbiologic response.

The per protocol analysis of patients showed that both 100 mg and 150 mg doses appear to be better than 50 mg although mycological eradication was better in the 100 mg dose.

Study 03-7-005:
This was a phase III, randomized, double-blind, active control, multicenter study in patients with esophageal candidiasis from South Africa, Brazil, and Peru. Esophageal candidiasis was documented by clinical symptoms and confirmed by endoscopy. A majority of patients enrolled in the study had no prior history of esophageal candidiasis, had HIV, but did not receive antiretroviral therapy. CD4 cell count was <100 cells/ml in about 50% of the patients. In addition, tuberculosis was a frequent baseline condition. Micafungin (150 mg) or fluconazole (200 mg) were administered intravenously once daily for 14 days or for 7 days after resolution of clinical symptoms. Patients requiring treatment with another systemic or topical antifungal agent or those nonresponsive to prior systemic therapy were not eligible to participate in the study. The maximum duration of treatment was 42 days. Patients were evaluated at baseline, weekly, end of treatment (EOT; on day of last dose) and followed at 2 and 4 weeks after the last dose for clinical outcome which includes signs and symptoms for oropharyngeal candidiasis, laboratory parameters, and/or microbiologic response. Endoscopy was performed at EOT and follow up visits if clinically indicated. During endoscopy, mucosal lesions were biopsied and reviewed histologically. Esophageal brushings were obtained for cytological examination for fungal elements suggestive of yeast and cultured for identification of a fungal organism. Antifungal susceptibility testing was performed at centralized laboratory , according to the NCCLS M27A2 method using antibiotic medium 3 and RPMI 1640 and minimum inhibitory concentrations (MICs) determined at 24 and 48 hours.

Per protocol population was defined as all patients who received at least 10 doses of study drug and who did not have major protocol deviation(s). A majority of the subjects in the micafungin (n=189) and flucanozole (n=192) treated groups were infected with *Candida albicans*. *Candida* species was not identified in 6 and 8 subjects in the micafungin and fluconazole treated groups, respectively. Infections with more than one *Candida* species were identified in 7 patients in the micafungin arm and 8 patients in the fluconazole arm. The results in Tables 1 and 2 show micafungin to be as effective as fluconazole in the treatment of patients with infections due to *C. albicans*. However, the number of patients with infections due to *Candida* species other than *C. albicans* was too small to conclude activity against these species. The activity of micafungin is sustained until week 4 after the last dose. At week 2 and 4 after the last dose, relapse was observed in 5% and 8% of the patients, respectively treated with micafungin; in patients treated with fluconazole relapse was observed in 4% and 6% of the patients at week 2 and 4, respectively. The fungal species at the time of relapse were not identified. Also, there was no correlation of *in vitro* susceptibility of the pathogen at baseline with clinical or microbiologic response.

Table 1: Clinical and mycological response by pathogen from patients with esophageal candidiasis to micafungin and fluconazole

Treatment Group	EOT **			Week 2**		Week 4**		Relapse*/**	
	Clinical Success	Eradication	Overall Response	Clinical Success	Mycological Success	Clinical Success	Mycological Success	Week 2	Week 4
Micafungin									
Candida sp.	6/6	5/6	5/6	6/6	0/0	5/5	0/0	ND	ND
C. albicans	173/175 (98.9%)	133/175 (76%)	131/175 (74.9%)	145/151 (96%)	2/12 (16.7 %)	137/144 (95%)	1/5	9/175 (5.1%)	14/175 (8.0%)
C. tropicalis	1/1	1/1	1/1	1/1	0/0	1/1	0/0	ND	ND
C. albicans + C. glabrata	4/4	0/4	0/4	4/4	0/4	3/3	0/0	ND	ND
C. albicans + C. tropicalis	1/1	1/1	1/1	1/1	0/0	1/1	0/0	ND	ND
C. albicans + C. glabrata + C. krusei	1/1	0/1	0/1	1/1	0/0	0/0	0/1	ND	1/1
C. albicans + C. inconspicua	1/1	1/1	1/1	1/1	0/0	1/1	0/0	ND	ND
Total	187/189 (98.9%)	141/189 (74.6%)	139/189 (73.5%)	159/165 (96.4%)	2/16 (12.5%)	148/155 (95.5%)	1/6 (16.7%)	9/151 (6%)	15/152 (9.9%)
Fluconazole									
Candida sp.	8/8	5/8	5/8	6/7	0/0	6/7	0/0	1/8	
C. albicans	173/175 (98.9%)	139/175 (79.4%)	139/175 (79.4%)	153/157 (97.4 %)	5/12 (41.7 %)	142/146 (97.3 %)	0/5	7/175 (4%)	11/175 (6.3%)
C. krusei	1/1	0/1	0/1	1/1	0/0	1/1	0/0	ND	ND
C. albicans + C. glabrata	3/3	1/3	1/3	3/3	0/0	3/3	0/0	ND	ND
C. albicans + C. krusei	2/2	2/2	2/2	2/2	0/0	1/1	0/0	ND	1/2
C. albicans + C. glabrata + C. krusei	1/1	0/1	0/1	1/1	0/0	1/1	0/0	ND	ND
C. albicans + C. glabrata + Candida sp.	0/1	0/1	0/1	1/1	0/0	1/1	0/0	ND	ND
C. albicans + C. tropicalis	1/1	0/1	0/1	1/1	0/0	1/1	0/0	ND	ND
Total	189/192 (98.4%)	147/192 (76.6%)	147/192 (76.6%)	168/173 (97.1%)	5/12 (41.7%)	156/161 (96.9%)	0/5	8/183 (4.4%)	12/177 (6.8%)

*Clinical relapse ** n/N (%) ND=Not Done

Table 2: Clinical and mycological response by pathogen in patients with esophageal candidiasis treated with micafungin or fluconazole

Species	Micafungin*		Fluconazole*	
	Clinical Success n/N (%)	**Mycological Eradication n/N (%)**	**Clinical Success n/N (%)**	**Mycological Eradication n/N (%)**
C. albicans	180/182 (98.9%)	135/182 (74.2%)	180/183 (98.4%)	142/183 (77.6%)
C. glabrata	5/5	0/5	4/5	1/5
C. krusei	1/1	0/1	3/3	2/3
C. tropicalis	1/1	1/1	1/1	0/1
C. inconspicua	1/1	1/1	ND	ND

*includes patients with mixed infections

Conclusions:

Overall, the results from studies FG 463-21-02, 98-0-47, 97-7-003, and 03-7-005 show micafungin to be active against *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. parapsilosis* (Table 3).

Table 3: Clinical and mycological response by pathogen from patients treated with micafungin.

Species	Clinical Success n/N (%)	Mycological Eradication n/N (%)
C. albicans	287/307	211/297
C. glabrata	26/29	12/23
C. krusei	8/11	6/8
C. tropicalis	9/10	3/8
C. parapsilosis	7/10	7/8
C. rugosa	1/1	1/1
C. pelliculosa	1/1	1/1
C. guilliermondii	0/1	ND
C. kefyr	0/1	ND
C. inconspicua	1/1	1/1

From Ms. Moore's draft review of Study FG 463-21-09, the number of patients for which efficacy of micafungin was observed are unclear. Nevertheless, as described on page 2 the number of patients in study FG 463-21-09 with *Candida* species other than *C. albicans* is too small. Also, this does not alter the interpretation of activity of micafungin against *Candida* species other than *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. parapsilosis*.

4 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

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

/s/

Shukal Bala
2/18/05 10:50:13 AM
MICROBIOLOGIST