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RESEARCH**

APPLICATION NUMBER:
21-754

MEDICAL REVIEW

Deputy Office Director Review Memo

Applicant: Fujisawa Healthcare, Inc.
NDA #s: NDA 21-506 & NDA 21-754
Drug: Micafungin sodium for injection
Trade Name: Mycamine™
Indications: (1) Treatment of patients with esophageal candidiasis
(2) Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation

NDA 21-506

Date of submission: April 29, 2002
Date of resubmission: August 24, 2004

NDA 21-754

Date of submission: April 23, 2004
Date of Major Amendment: January 31, 2005
PDUFA goal date: May 24, 2005

RECOMMENDATIONS:

Approval for NDA 21-754 and NDA 21-506 for the following indications:

- Treatment of patients with esophageal candidiasis (NDA 21-754)
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (NDA 21-506)

Background

Fujisawa Healthcare, Inc. originally submitted an NDA (NDA 21-506) for Mycamine (micafungin sodium) for injection on April 29, 2002. The actions on this original submission were as follows: Approvable for the indication of prophylaxis in patients undergoing hematopoietic stem cell transplant.

Following the issuance of an Approvable letter for the indication prophylaxis in patients undergoing hematopoietic stem cell transplant, there were discussions with the company about approaches to satisfy the clinical deficiencies in the Approvable letter. NDA 21-754, Mycamine for the treatment of esophageal candidiasis, was submitted on April 23, 2004. NDA 21-506 was re-submitted on August 24, 2004 seeking the modified indication of prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

Other agents approved for the indications being sought in these NDAs include the following:

- Treatment of patients with esophageal candidiasis
 - Cancidas® (caspofungin acetate) (IV)
 - Diflucan® (fluconazole) (oral and IV)
 - Sporanox® (itraconazole) (oral solution)
 - Vfend® (voriconazole) (oral and IV)
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation
 - Diflucan® (fluconazole) (oral and IV)

NDA 21-506 and NDA 21-754

The Chemistry for Mycamine™ is discussed in Dr. Seggel's review and he has recommended approval for NDAs 21-506 and 21-754 with regards to Chemistry. Mycamine (micafungin sodium) for injection is a sterile lyophilized powder for reconstitution and intravenous infusion. Micafungin sodium is light sensitive and therefore the drug product vials are wrapped in a UV protective material and the diluted infusion solution should also be protected from light, as stated in the Mycamine product label. Dr. Riley's Product Quality Microbiology Review also recommends approval for NDAs 21-506 and 21-754.

The Pharmacology/Toxicology studies for Mycamine are summarized in Dr. McMaster's review. His review notes that in animal studies the target organs are primarily the liver and testes. The Animal Toxicology section of the label describes the liver changes noted in animal studies. The testicular findings from the animal studies are described in the Carcinogenesis, Mutagenesis and Impairment of Fertility subsection within the Precautions section of the label. Mycamine is labeled as Pregnancy Category C.

The Clinical Pharmacology of Mycamine is described in Dr. Jang-Ik Lee's Clinical Pharmacology and Biopharmaceutics Review. Micafungin is highly protein bound (>99%). It is metabolized to M-1 by arylsulfatase, followed by further metabolism to M-2 by catechol-O-methyltransferase and subsequent hydroxylation. Based upon preclinical studies, the enzymatic activities responsible for metabolism to M-1 and M-2 are found in liver, kidney, adrenals, and other organs. Micafungin is a substrate for and a weak inhibitor of CYP3A, but CYP3A is not a major mechanism of metabolism in vitro. Mass balance studies show that more than 70% of micafungin is eliminated in the feces.

Dose adjustment in patients with renal impairment is not required. In patients with moderate hepatic impairment, no dosage adjustment is required; patients with severe hepatic impairment have not been evaluated. As noted in the Dr. Jang-Ik Lee's review, with regards to the pediatric pharmacokinetic data, there were unexplainable outliers and a number of samples were not collected at critical timepoints. Based upon these apparent methodologic problems with the study, the pharmacokinetics have not been adequately characterized in pediatric patients 2 to 16 years of age.

The microbiology of micafungin is described in Dr. Shukal Bala's microbiology Team Leader's review, Dr. Fred Marsik's microbiologist's review for NDA 21-506 and Dr. Bala and Dr. Kalavati Suvarna's microbiologist's review for _____

_____ Micafungin is a semisynthetic lipopeptide of the echinocandin class of antifungal agents. Its mechanism of action is inhibition of synthesis of 1,3- β -D-glucan; 1,3- β -D-glucan is an essential component of fungal cell walls and is not present in mammalian cells. As noted in the microbiologist's review, micafungin's metabolite M-2 has activity *in vitro* similar to the parent compound, the metabolite M-1 has 4 to 16-fold less activity than the parent compound, and M-5 has only a small fraction of the activity of the parent compound. The metabolites M-1 and M-2 are present in plasma only at very low levels, while M-5 is the predominate metabolite found in plasma.

The results of the clinical trials providing safety and efficacy data for micafungin have been thoroughly discussed in the Medical Officer reviews by Drs. Singer, Ibia, and Meyer; the statistical reviews by Dr. Tracy; and the Division Director and Team Leader Review by Drs. Albrecht and Navarro. For a detailed review of the findings of the clinical studies, the reader is referred to their reviews.

Treatment of patients with esophageal candidiasis - Efficacy

For the indication of esophageal candidiasis the applicant provided data from three studies of micafungin in the treatment of esophageal candidiasis and data from a non-comparative study of micafungin for the treatment of candidemia or invasive candidiasis. The three studies available at the time of submission of NDA 21-754 and that formed the basis for filing the NDA for the esophageal candidiasis indication were two phase 2 dose ranging studies examining the effectiveness of micafungin in the treatment of patients with esophageal candidiasis and a non-comparative study of micafungin for candidemia or invasive candidiasis. At the time of the 120-day safety update, the applicant submitted the study report and data from a randomized, double-blind comparative phase 3 study examining the effectiveness of micafungin 150 mg/day intravenously compared to fluconazole 200 mg/day. These four studies are briefly summarized in the paragraphs that follow.

Study 97-7-003 was a phase 2 dose de-escalation study examining the effectiveness of micafungin at doses of 12.5, 25, 50, 75, 100 mg/day intravenously for 14 days that enrolled a total of 120 HIV-positive patients with esophageal candidiasis by clinical signs and symptoms with endoscopic confirmation. The number of patients enrolled by dosage regimen was distributed approximately equally between the five study groups. The primary efficacy endpoint, clinical response at the end of therapy found the

following clinical response rates for patients in the clinical response category of “cleared” by dose group for the per protocol population: 12.5 mg/day 33% (6/18); 25 mg/day 54% (7/13); 50 mg/day 87% (13/15); 75 mg/day 84% (16/19); 100 mg/day 95% (18/19). The findings for the secondary endpoints, endoscopic response, mycological response, and overall treatment response, supported the findings for the primary efficacy endpoint of clinical response at end of therapy. The study showed a dose response for micafungin.

Study FG463-21-09 was a phase 2 randomized, double-blind, dose ranging study with an active control arm (fluconazole 200 mg/day). Patients were randomized 1:1:1:1 to one of the four treatment groups; micafungin at 50 mg/day, 100 mg/day, or 150 mg/day or fluconazole 200 mg/day. The primary endpoint was endoscopic response (proportion of patients with endoscopic grade 0) at end of therapy. Included among the secondary endpoints were clinical response, mycologic response, overall therapeutic success, and relapse at 2-weeks post-therapy. The study enrolled HIV-positive patients ≥ 18 years of age with clinical signs and symptoms of esophageal candidiasis and endoscopic and microbiological/histological confirmation. A total of 251 patients were randomized to one of the four treatment groups as follows: 65 patients to micafungin 50 mg/day; 65 patients to micafungin 100 mg/day; 60 patients to micafungin 150 mg/day; and 62 patients to fluconazole 200 mg/day. The duration of therapy as specified in the protocol was 14 days with an option to extend to 21 days. The endoscopic cure rates at end of therapy by treatment group were 67% (44/64) for micafungin 50 mg/day; 77% (48/62) for micafungin 100 mg/day; 90% (53/59) for micafungin 150 mg/day; and 87% (52/60) for fluconazole 200 mg/day. The findings for the primary endpoint were supported by the findings from the secondary endpoints. The study found a dose-response for micafungin and similar response rates for micafungin 150 mg/day compared to fluconazole 200 mg/day. Rates for Total Relapse by treatment group at the 2-week follow-up visit were as follows 33% (13/39) micafungin 50 mg/day; 27% (13/48) for micafungin 100 mg/day; 20% (10/50) for micafungin 150 mg/day; and 16% (8/51) for fluconazole 200 mg/day. The category of Total Relapse included patients with relapse, missing data, or patients receiving systemic antifungal treatment after study therapy was completed.

Study 03-7-005 was a pivotal phase 3 randomized (1:1), double-blind, active controlled trial comparing the efficacy and safety of micafungin 150 mg intravenously daily or fluconazole 200 mg intravenously daily for a minimum of 14 days and a maximum of 42 days. The primary efficacy endpoint was endoscopic response at end-of-therapy. Included among the secondary endpoints were clinical response, relapse at 2-weeks and 4-weeks post-therapy, and changes in clinical symptoms. The protocol also included criteria for assessing mycological response. The entry criteria required confirmed esophageal candidiasis based upon endoscopy with microbiological/histological criteria. The study enrolled 523 patients within the age range of 17 to 87 years of age; 260 were randomized to micafungin 150 mg/day and 258 were randomized to fluconazole 200 mg/day. Most patients were HIV-positive with CD₄ cell counts < 100 cells/mm³. Approximately 90% had a positive culture at baseline and almost all had *C. albicans*. Non-albicans isolates occurred very infrequently and were

often co-isolates along with *C. albicans*. The outcomes for the study in the modified full analysis set [or modified intent-to-treat population (mITT) - patients who received at least one dose of study drug and had positive histology or cytology at baseline] are summarized in table 1.

Table 1. Endoscopic, Clinical, and Mycological Outcomes for Esophageal Candidiasis at End-of Treatment - Study 03-7-005

Treatment Outcome*	Micafungin 150 mg/day N=260	Fluconazole 200 mg/day N=258	% Difference† (95% CI)
Endoscopic Cure	228 (87.7%)	227 (88.0%)	-0.3% (-5.9, +5.3)
Clinical Cure	239 (91.9%)	237 (91.9%)	0.06% (-4.6, +4.8)
Overall Therapeutic Cure	223 (85.8%)	220 (85.3%)	0.5% (-5.6, +6.6)
Mycological Eradication	141/189 (74.6%)	149/192 (77.6%)	-3.0% (-11.6, +5.6)

*Endoscopic and clinical outcome were measured in the modified intent-to-treat population, including all randomized patients who received ≥ 1 dose of study treatment. Mycological outcome was determined in the per protocol (evaluatable) population, including patients with confirmed esophageal candidiasis who received at least 10 doses of study drug, and had no major protocol violations.

†calculated as micafungin – fluconazole

Micafungin 150 mg/day was found to be non-inferior to fluconazole 200 mg/day. Additional analyses in the other analysis populations (e.g., ITT and per protocol populations) supported the results of the analyses in the mITT population.

Relapse at 2- and 4-weeks post-therapy was assessed in patients who achieved overall therapeutic success at end of therapy. Relapse was defined as a recurrence of clinical symptoms or endoscopic lesions (endoscopic grade > 0). The relapse rates by treatment group are summarized in table 2.

Table 2. Relapse of Esophageal Candidiasis at Week 2 and through Week 4 Post-Treatment in Patients with Overall Therapeutic Cure at the End of Treatment - Study 03-7-005

Relapse	Micafungin 150 mg/day N=223	Fluconazole 200 mg/day N=220	% Difference* (95% CI)
Relapse† at Week 2	40 (17.9%)	30 (13.6%)	4.3% (-2.5, 11.1)
Relapse† Through Week 4 (cumulative)	73 (32.7%)	62 (28.2%)	4.6% (-4.0, 13.1)

*calculated as micafungin – fluconazole;

N=number of patients with overall therapeutic cure (both clinical and endoscopic cure at end-of-treatment);

†Relapse included patients who died or were lost to follow-up, and those who received systemic anti-fungal therapy in the post-treatment period

Most patients (89%) in Study 03-7-005 had concurrent oropharyngeal candidiasis (OPC) along with their esophageal candidiasis (EC). In the subgroup of patients with concurrent OPC along with their EC the response rate for resolution of signs and symptoms of OPC at the end of therapy was 192/230 (84%) in micafungin-treated patients and 188/229 (82%) of fluconazole-treated patients. In the subgroup of patients

with resolution of their EC and OPC at end of therapy, 32% of the micafungin-treated patients and 18% of the fluconazole-treated patients had Relapse of OPC at 2-weeks post-treatment. [The category of Relapse included relapse (OPC grade>0), patients who died or were lost to follow-up, and those who received systemic antifungal therapy during the post-treatment period]. The cumulative Relapse by treatment group at 4-weeks post-treatment was 52% in the micafungin group and 39% in the fluconazole group.

Study 98-0-047 was an open-label, non-comparative study that enrolled patients with candidemia and invasive candidiasis. This study included 288 evaluable patients of whom 99 had esophageal candidiasis. Most patients received micafungin therapy alone at doses between 50 to 100 mg/day. The response rate for success based upon the investigator's global assessment was 92% (91/99) [92% success = 65% complete response and 27% partial response].

The Applicant has provided two adequate and well-controlled studies, the phase 3 study (Study 03-7-005) that examines micafungin at a dose of 150 mg/day and the phase 2 dose ranging active controlled study (Study FG463-21-09) for the indication of treatment of esophageal candidiasis. Additional supportive data from Study 97-7-003 and Study 98-0-047 have also been provided. The evidence from these studies supports the efficacy of micafungin 150 mg/day intravenously for the indication of treatment of esophageal candidiasis.

Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation - Efficacy

For the indication of prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation data is provided from Study 98-0-050, a phase 3 prophylaxis study in hematopoietic stem cell transplant recipients, data supporting the efficacy of micafungin in the treatment of established infections due to *Candida* spp. derived from the pivotal and supportive studies for the indication of treatment of esophageal candidiasis, and the data in *Candida*

Study 98-0-050 was a phase 3, randomized (1:1), double-blind study of micafungin compared to fluconazole for prophylaxis of fungal infections in patients undergoing hematopoietic stem cell transplant (HSCT). Patients received micafungin 50 mg/day or fluconazole 400 mg/day. Prophylaxis with study drug was to continue until one of following occurred: the patient experienced neutrophil recovery to a post-nadir ANC of ≥ 500 cells/mm³ (study drug could be continued for up to 5 days post-neutrophil recovery at the investigator's discretion); the patient developed a proven, probable, or suspected fungal infection; the patient developed unacceptable toxicity; the investigator decided that it was in the best interest of the patient to discontinue; the patient declined further study participation; death occurred; or the patient received prophylactic treatment to a maximum of 42 days after transplant (day +42 after transplant). The

study enrolled 882 patients undergoing an autologous or syngeneic (46%) or allogeneic (54%) stem cell transplant. The average duration of drug administration was 18 days (range 1 to 51 days). Successful prophylaxis was defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy, and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-therapy period. The results for Study 98-0-050 are summarized in Table 3. The rate of Success by treatment groups were micafungin 80.7% (343/425) compared to 73.7% (337/457) for fluconazole; difference (micafungin – fluconazole): +7.0% [95% CI=1.5%, 12.5%].

Table 3. Results from Clinical Study of Prophylaxis of *Candida* Infections in Stem Cell Transplant Recipients – Study 98-0-050

Outcome	Micafungin 50 mg/day (n=425)	Fluconazole 400 mg/day (n=457)
Success*	343 (80.7%)	337 (73.7%)
Failure	82 (19.3%)	120 (26.3%)
All Deaths ¹	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	3 (0.7%)
Proven/Probable fungal infection (not resulting in death) ¹	6 (1.4%)	8 (1.8%)
Suspected fungal infection ²	53 (12.5%)	83 (18.2%)
Lost to follow-up	5 (1.2%)	3 (0.7%)

* Treatment difference (micafungin - fluconazole): +7.0% [95% CI=1.5%, 12.5%]

¹ Through end-of-study (4 weeks post-therapy)

² Through end-of-therapy

Although not a protocol endpoint, examination of the rates of proven or probable *Candida* infections show similar rates between the micafungin and fluconazole arms of the study. There were 4/425 (0.9%) proven or probable *Candida* infections in the micafungin arm and 2/457 (0.4%) in the fluconazole arm. In addition, although not counted in the endpoint, the use of systemic antifungal products was examined. In the post-treatment period (end of treatment through the 4-week end of study time point), antifungal therapy was used in 42% of the patients in each of the treatment arms.

A discussion of the dose for prophylaxis is provided in the Drs. Albrecht's and Navarro's review.

The Applicant has provided evidence that is sufficient to support that micafungin 50 mg/day intravenously is effective in the prophylaxis of *Candida* infections in hematopoietic stem cell transplant recipients. The efficacy data that support this conclusion are derived from the following:

- the findings from the phase 3 prophylaxis study, Study 98-0-050
- the demonstration of the efficacy of micafungin in the treatment of esophageal candidiasis (an established infection due to *Candida* spp.)

- the clinical data supporting the activity of the 50 mg/day dose in EC
- the data derived from the studies of *Candida*

These data collectively support the conclusion that micafungin 50 mg/day intravenously is effective in prophylaxis of *Candida* infections.

Safety

The Medical Officer review of the original NDA 21-506 concluded a favorable risk profile for micafungin, based on the data available from the 1368 subjects in the original micafungin NDA submission, the majority of whom received the 50-mg dose of micafungin. The current total safety database is comprised of 2402 subjects (patients and volunteers) who received micafungin. The aggregate safety information evaluated in the current review incorporates updated safety data from the original NDA 21-506 (prophylaxis of *Candida* infections in hematopoietic stem cell transplant recipients), new safety data from the esophageal candidiasis in NDA 21-754 (esophageal candidiasis), new clinical data contained in the 120-day safety update, and postmarketing data from Japan. A total of 726 (30%) subjects received ≥ 150 mg of micafungin, and of these, the majority (606/726 or 83.5%) received this dose for at least 10 days. The mean duration of treatment for all subjects was 20.1 days (range 1-681 days).

The review team analyzed data from all of these submissions. The safety of micafungin is reviewed in detail in Dr. Singer's Medical Officer Review and summarized in Dr. Albrecht's and Navarro's review. As part of the safety review, the division also consulted the Office of Drug Safety for review of the micafungin postmarketing data available from Japan and Dr. John Senior for a consult on the hepatic safety profile of micafungin. The consults from ODS and Dr. Senior provided an assessment on the safety issues that were the respective focus of the consultations along with suggestions for specific safety information for inclusion in product labeling.

Serious allergic reactions have been reported in the Japanese postmarketing experience including serious skin and vascular reactions with anaphylactic shock. A Warning in the Mycamine product label describes these reactions. Also of note, in the Adverse Reactions section of the label, information is provided describing adverse reactions involving histamine mediated symptoms.

The hepatic safety profile includes findings from preclinical studies that the liver was one of the target organs for toxicity. In the animal species tested, laboratory and histopathologic evidence of dose-related hepatotoxicity was noted, including single cell necrosis at 3-5X the human equivalent dose (HED). Transient increases in transaminases developed in normal volunteers most of which were mild (<3 X ULN) and fully reversible. In comparative studies where the comparator was fluconazole, the incidence of hepatic adverse events was 19.0% (177/932) in the micafungin-treated group, compared to 21.0% (165/787) in the fluconazole-treated group. Serious adverse events were observed in 1.1% (10/932) of the micafungin and 1.4% (11/787) of the fluconazole treated group. The proportion of micafungin treated patients with significant

(>3X ULN) conjoint elevation of transaminases and bilirubin was similar to those observed in patients who received fluconazole. The Mycamine product label will include a statement in the Precautions section describing the hepatic effects of Mycamine.

Based upon the occurrence of serious postmarketing renal events including renal failure, the Japanese label for micafungin was revised to include renal failure as a clinically significant adverse event. In comparative studies where the comparator was fluconazole, serious renal adverse events including renal failure occurred in 12/932 (1.3%) micafungin-treated and 19/787 (2.4%) fluconazole-treated patients. The Mycamine product label will include a Precaution describing the renal effects of micafungin. A Precaution on hematologic effects is included to inform and describe the adverse hematologic effects that have been observed including hemolysis and hemolytic anemia.

Information regarding the drug interaction studies performed is included in the Precautions section of the label. The section informs the reader that patients receiving sirolimus or nifedipine in combination with micafungin should be monitored for toxicity and the dose of sirolimus or nifedipine should be reduced if necessary.

The Adverse Reactions section of the label Mycamine product label includes a description of injection site reactions ranging from pain to phlebitis and deep thrombophlebitis have been observed in patients receiving micafungin. Also described within this section are the data available from the postmarketing adverse event data from Japan[†] along with a summary of the adverse reactions from the clinical trial in the NDA.

With regards to effect on cardiac repolarization, micafungin does not suppress the I_{Kr} channel current in hERG transfected cells nor does it prolong the duration of action potentials in a microelectrode study examining the effect on action potential. Preclinical studies reveal no increase in the QT interval in chronically dosed beagle dogs. No significant QTc prolongation was observed in normal volunteer studies, and no clinical cardiac events related to QT prolongation have been documented in patients who received micafungin.

The safety data on micafungin are derived from the database of 2402 subjects (patients and volunteers). Within the overall safety database a total of 726 (30%) subjects received \geq 150 mg of micafungin (most for at least 10 days). We also have data from postmarketing experience from use of micafungin in Japan. This information provides sufficient data characterizing the safety profile to achieve a risk-benefit profile that supports the safety of micafungin in the proposed indications of (1) treatment of patients with esophageal candidiasis and (2) prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

[†] Micafungin was approved in Japan in October 2002. The Japanese label describes doses of 50 to 150 mg and also includes a proviso for doses of up to 300 mg/day in selected circumstances.

Product Name and Clinical Inspections

The proprietary name, Mycamine, was reviewed by the Division of Medication Errors and Technical Support and found to be acceptable. The Division of Scientific Investigation inspections of selected clinical study sites were completed and the results of the site audits were that the data appear to be acceptable for review.

Phase IV

The pediatric studies required under PREA for the indications being approved in these NDAs are deferred. Other than the pediatric studies which are being deferred there are no phase 4 postmarketing commitments.

Recommendation

The applicant should be issued an **Approval** letter for the following indications:

- Treatment of patients with esophageal candidiasis (NDA 21-754)
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (NDA 21-506)

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/s/

Edward Cox
3/16/05 12:35:24 PM
MEDICAL OFFICER

Medical Team Leader and Division Director Review

APPLICANT: Fujisawa Healthcare, Inc.

DRUG: Micafungin sodium for injection

Trade Name: Mycamine®

NDA/Indication: 21-506/Prophylaxis of candida infections in HSCT
21-754/Esophageal Candidiasis

DATE OF SUBMISSION: April 29, 2002 -- NDAs 21-506 (_____)
Resubmission: August 24, 2004 -- NDA 21-506

DATE OF SUBMISSION: April 23, 2004 -- NDA 21-754
Major Amendment: January 31, 2005 – NDA 21-506, NDA 21-754

PDUFA GOAL DATE: May 24, 2005

FORMULATION: Lyophilized powder for intravenous injection (50 mg)

RELATED NDAs: / / / / /

RECOMMENDATIONS:

The applicant should be issued an approval letter for the following indications:

- Esophageal Candidiasis
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation _____ (HSCT)

There are no Phase 4 post-marketing commitments for these two applications, with the exception of deferral of pediatric studies for the indications of esophageal candidiasis and prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation _____ (HSCT).

During this review cycle, the applicant requested _____ in the labeling. _____

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EXECUTIVE SUMMARY

A. Drug Product Summary

MYCAMINE (micafungin sodium) is an echinocandin antifungal that inhibits the synthesis of 1,3-β-D-glucan, an essential component of the cell wall of susceptible fungi but not mammalian cells. It is active *in vitro* against *Candida albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*. Micafungin has shown activity in both mucosal and disseminated murine models of candidiasis. Micafungin, administered to immunosuppressed mice in models of disseminated candidiasis prolonged survival and/or decreased the mycological burden.

The pharmacokinetics of micafungin were evaluated in healthy subjects, hematopoietic stem cell transplant recipients, and patients with esophageal candidiasis. The area under the concentration-time curve (AUC) was proportional to micafungin dose from 50 mg to 150 mg and 3 mg/kg to 8 mg/kg. Steady-state pharmacokinetic parameters are presented below.

Table 1: Pharmacokinetic Parameters of Micafungin in Adult Patients

Population	N	Dose (mg)	Pharmacokinetic Parameters (Mean ± Standard Deviation)			
			C _{max} (mcg/mL)	AUC ₀₋₂₄ (mcg·h/mL)	t _{1/2} (h)	Cl (mL/min/kg)
HIV- Positive Patients with EC [Day 14 or 21]	20	50	5.1±1.0	54±13	15.6±2.8	0.300±0.063
	20	100	10.1±2.6	115±25	16.9±4.4	0.301±0.086
	14	150	16.4±6.5	167±40	15.2±2.2	0.297±0.081
		<i>Per kg</i>				
HSCT Recipients [Day 7]	8	3	21.1±2.8	234±34	14.0±1.4	0.214±0.031
	10	4	29.2±6.2	339±72	14.2±3.2	0.204±0.036
	8	6	38.4±6.9	479±157	14.9±2.6	0.224±0.064
	8	8	60.8±26.9	663±212	17.2±2.3	0.223±0.081

EC = esophageal candidiasis; HSCT = hematopoietic stem cell transplant

Micafungin is highly (>99%) protein bound. It is metabolized to M-1 (catechol form), M-2 (methoxy form), and M-5 (hydroxylation at the side chain (ω-1 position)). Even though micafungin is a substrate for and a weak inhibitor of CYP3A *in vitro*, CYP3A is not a major micafungin metabolism enzyme *in vivo*. Drug interaction studies with immunosuppressants do not show significant pharmacokinetic interaction. Micafungin is neither a P-glycoprotein substrate nor inhibitor *in vitro*. Fecal excretion is the major route of elimination, accounting for 71% of the dose by 28 days, urinary recovery accounts for an additional 10-15% of the administered dose.

MYCAMINE does not require dose adjustment in patients with renal impairment or patients with moderate hepatic dysfunction (Child-Pugh score 7-9). The pharmacokinetics of MYCAMINE have not been studied in patients with severe hepatic impairment. Since micafungin is highly protein bound, it is not dialyzable.

C. Efficacy

1. Esophageal Candidiasis Efficacy, NDA 21-754

Fujisawa submitted four clinical studies in support of this indication, three in the original application and the fourth at the time of the 120-day update as summarized in the table below.

Study	Study Design	Number of Patients: age range Treatment Regimens	Study Sites and Location	Duration of Therapy	Time of Relapse Evaluation
03-7-005	Phase 3, randomized, double-blind, comparative	523 patients: ≥ 16 years old micafungin 150mg/day (N=260); fluconazole 200 mg/day (N=258)	35 sites in South Africa, Brazil, and Peru	14-21 days	2- and 4-weeks post-treatment
FG463-21-09	Phase 2, randomized, double-blind, comparative, dose ranging	251 patients: > 18 years old micafungin 50 mg/day (N=65); micafungin 100 mg/day (N=64); micafungin 150 mg/day (n=60); fluconazole 200 mg/day (n=62)	24 sites in Brazil, Peru, and South Africa	14-21 days	2-weeks post-treatment
97-7-003	Phase 2, open-label, non-comparative dose de-escalation study to determine minimum effective dose	120 patients: ≥ 18 years old micafungin 12.5 mg/day (N=26); micafungin 25 mg /day (N=22); micafungin 50 mg/day (N=26); micafungin 75 mg/day (N=22); micafungin 100 mg/day (N=24)	9 sites in South Africa	14 days	2-weeks post-treatment
98-0-047†	Phase 2, non-comparative study for candidemia or invasive candidiasis	357 patients (99 patients with EC) Adults and children	62 sites world-wide	5 days to 6 weeks	6-weeks post-treatment

† Study 98-0-047 was submitted previously with NDA 21-534

The original NDA 21-754 submission contained results of studies FG463-21-09 and 97-7-003 that provided dose ranging and comparative data adequate for review and on the surface able to support approval. Study 98-0-047 was a non-comparative study previously reviewed and served to expand the safety database. Fujisawa submitted the results of study 03-7-005 in their 120-day safety update. The review of this study placed added responsibility on the review team, necessitated additional requests for analysis of data late in the course of review regarding safety information, and led to the need to extend the PDUFA due date based on major analyses coming in during the later part of the cycle. Study 03-7-005 was a robust Phase 3 study that increased the efficacy and the safety database and insured that the indication could be approved during the first review cycle.

The primary endpoint in the esophageal candidiasis trials was endoscopic appearance of the esophageal mucosa at the end of treatment. Endoscopic cure was defined as a score of 0 based on the following scale:

Esophageal Mucosal grade	Description
0	No evidence of EC-associated plaques
1	Individual, raised plaques, each 2 mm in size or less
2	Multiple raised plaques more than 2 mm in size
3	Confluent plaques combined with ulceration

The clinical response was a secondary endpoint, evaluated at end of treatment as well as at 2 weeks (and in study 03-7-005 at 4 weeks) after completing treatment. Clinical cure was defined as achieving a score of 0 based on the following symptoms:

Parameter	Grade 0	Grade 1	Grade 2	Grade 3
Dysphagia	Swallows food normally	Swallows solid food with difficulty	Can swallow soft food or liquid only	Can swallow small amounts of liquid or cannot swallow
Odynophagia	None	Food causes pain; little or no pain with liquids	Liquids cause pain; will not eat solids	Small sips of liquids only; or will not swallow; spits
Retrosternal pain	None	Low grade intermittent or continuous pain	Continuous pain, soreness or burning; may require pain medication	Very painful; requires pain medication

In the agency's analysis, therapeutic success was defined as score of 0 (endoscopic cure and clinical cure). This differed from the applicant's approach where outcomes of "success" were considered for patients who had amelioration of endoscopic score or clinical score without complete resolution (i.e., improved). In the comparative and dose ranging studies evaluating the 150 mg/day regimen, in fact most of the patients were cured, and only a minor percentage were considered improved.

Mycological outcome was assessed by biopsy and culture, and interpreted by a fairly complex algorithm that consideration absent results as failures. In fact in study 03-7-005, more than 98% of patients had *Candida albicans* isolated at baseline, with the vast majority having *C. albicans* isolated in the absence of other non-*Candida* species. Very few patients had *Candida* species other than *C. albicans* isolated at baseline and non-*Candida* isolates were often found in the presence of *C. albicans*.

Phase 3 study 03-7-005 serves as the cornerstone for the approval of this indication. In study -005, approximately 90% of patients had HIV/AIDS as their underlying disease most with CD4 counts <100, 70% were black, average age was 37, genders were represented equally. This was the first episode of EC for 85% of patients. The infection was considered severe in 30% of patients. Concomitant medications included antibacterials 50%, TB therapy 20% and antiretrovirals 10%. The study population demographic and disease characteristics were balanced across study arms. The mean and median duration of therapy was 14 days. Efficacy in all categories showed micafungin to be non-inferior to fluconazole at end of treatment and at 2 weeks and 4 weeks after completing treatment, as shown in both of the tables below.

Phase 3 study 03-7-005: Endoscopic, Clinical, Therapeutic and Mycological Outcomes in Esophageal Candidiasis at End-of-Treatment

Outcome in study 03-7-05*	MYCAMINE 150 mg/day IV N=260	Fluconazole 200 mg/day IV N=258	% Difference (95% CI) †
Endoscopic Cure	228 (87.7%)	227 (88.0%)	-0.3% (-5.9, +5.3%)
Clinical Cure	239 (91.9%)	237 (91.9%)	0.06% (-4.6, +4.8%)
Overall Therapeutic Cure	223 (85.7%)	220 (85.3%)	0.5% (-5.6, +6.6%)
Mycological Eradication	141/189 (74.6%)	149/192 (77.6%)	-3.0 % (-11.6, +5.6)

*Endoscopic and clinical outcomes were measured in modified intent-to-treat population, including all randomized patients who received ≥ 1 dose of study treatment. Mycological outcome was determined in evaluable population, including patients with confirmed esophageal candidiasis who received at least 10 doses of study drug, and had no major protocol violations.

†calculated as MYCAMINE - fluconazole

Phase 3 study 03-7-005: Relapse of Esophageal Candidiasis at Week 2 and through Week 4 Post-Treatment in Patients who Were Therapeutic Cure at the End of Treatment

	MYCAMINE 150 mg/day IV N=223	Fluconazole 200 mg/day IV N=220	% Difference (95% CI) *
Relapse† at Week 2	40 (17.9%)	30 (13.6%)	4.3 % (-2.5, 11.1)
Relapse† Through Week 4 (cumulative)	73 (32.7%)	62 (28.2%)	4.6 % (-4.0, 13.1)

*calculated as MYCAMINE – fluconazole

N= number of patients with overall therapeutic success (both clinical and endoscopic cure at end-of-treatment)

†Relapse included patients who died or were lost to follow-up, and those who received systemic antifungal therapy in the post-treatment period.

Phase 2 study FG463-21-09 was a four arm, dose ranging study comparing 3 doses of micafungin to fluconazole 200 mg/d. The population was predominantly patients with HIV/AIDS, median age mid-30s, balanced for gender, about 50% black. HIV was confirmed in about 60% of patients; the mean CD4 count was 68 cells/mm³ and median count was 29 cells/mm³ indicating a significantly immunocompromised population. Approximately one-third of the patients were receiving concomitant antiretroviral therapy, 30% were receiving anti-tuberculous therapy, and 70% were receiving Bactrim, presumably for *Pneumocystis* prophylaxis. Bactrim has known potential for renal and hepatic toxicity and many of the antituberculous medications are associated with adverse events, including hepatotoxicity. These characteristics were taken into consideration during the review of the safety database for these applications.

The results of this study show a clear dose response in endoscopic clearance between 50 mg and 150 mg/day of micafungin, the 95% CI around the point estimates do not overlap. The clinical cure rates were consistent, but there was an unexpected decline in mycological eradication in the 150 mg/day arm. There was an unexpected increase in the number of adverse events in the 100 mg/day arm, there were numerically more deaths in the micafungin arms (see table below). Therefore, it was important that results of the Phase 3 trial 03-7-005 were available for review.

Study FG463-21-09 was not designed to test for non-inferiority to fluconazole, although the 95% CI is (-8.4, +14.7) for the endoscopic outcome. This study supports the results of the Phase 3 study.

Phase 2 study FG463-21-09: Summary of Outcome in Patients with Esophageal Candidiasis

Population	Micafungin 50 mg/day	Micafungin 100 mg/day	Micafungin 150 mg/day	Fluconazole 200 mg/day
Randomized	N = 65	N=64	N=60	N=62
SAFETY				
Adverse event during treatment	3	8	3	4
Death during and after treatment	3	3	4	1
OUTCOME				
FAS (ITT)	N=64	N=62	N=59	N=60
Endoscopic Cure (score = 0) EOT	44/64 (66.8%) [57.4, 80.1]*	48/62 (77.4%) [67.0, 87.9]*	53/59 (89.9%) [82.1, 97.5]*	52/60 (86.7%) [78.1, 95.3]*
Clinical Cure (score = 0)	47/64 (73.4%)	52/62 (83.9%)	51/59 (86.4%)	53/60 (88.3%)
Therapeutic Cure EOT **	39/64 (60.9%)	48/62 (77.4%)	50/59 (84.7%)	51/60 (85%)
Mycological eradication EOT	20/64 (31.3%)	36/62 (58.1%)	28/59 (47.7%)	35/60 (58.3%)
Relapse at 2 weeks ***	13/39 (33.3%)	13/48 (27.1%)	10/50 (20.0%)	8/51 (15.7%)

N= number of patients in specified population

* 95% confidence interval around the point estimate

** Therapeutic Cure = patients classified as both endoscopic cure and clinical cure

***Mycological eradication: Patients with missing values were counted as persistence/failure

Relapse at 2 weeks: Patients with missing values or who receiving systemic antifungal drug during the 2 week follow up are tabulated under relapse.

In summary, two adequate and well controlled studies were submitted for this indication. The results of the Phase 3 study are robust and supported by the results of the Phase 2 study. The other Phase 2 studies provide some supportive information, particularly regarding activity of lower doses of micafungin. It should be noted that the Division's acceptance of the results of the Phase 3 study 03-7-005 at the time of the 120-day safety update, significantly augmented the data for the indication of esophageal candidiasis within NDA 21-754. Inclusion of this data greatly enhanced the likelihood that the application would contain a sufficient experience in esophageal candidiasis to support a successful application for the treatment of esophageal candidiasis during this review cycle.

2. Oropharyngeal Candidiasis Efficacy

Although this indication was not requested, the applicant systematically collected this information for the patients enrolled in study 03-7-005 and FG463-21-09, and evaluated clinical signs and symptoms using the following scale:

OPC Clinical Signs and Symptom Grades

Parameter	Grade 0	Grade 1	Grade 2	Grade 3
Plaques	No evidence of OPC-associated plaques	Individual raised plaques, each 2 mm in size or less	Multiple raised white plaques more than 2 mm in size	Confluent plaques
Inflammation	None	Slightly red	Very red	Dark red/scarlet
Fissures	None	Just visible	Prominent	Deep fissure/ulcers
Mouth pain	None	Slight discomfort	Can still eat	Unable to eat

Analysis of data from 03-7-005 by FDA and the applicant showed that efficacy was comparable to fluconazole at the end of treatment, but relapse rates at both 2 weeks and 4 weeks were higher in the micafungin arm. Specifically, the following information is to be included in the package insert to reflect this information:

In this study, 459 of 518 (88.4%) patients had oropharyngeal candidiasis in addition to esophageal candidiasis at baseline. At the end of treatment 192/230 (83.5%) MYCAMINE treated patients and 188/229 (82.1%) of fluconazole treated patients experienced resolution of signs and symptoms of oropharyngeal candidiasis. Of these, 32.3% in the MYCAMINE group, and 18.1% in the fluconazole group (treatment difference = 14.2%; 95% confidence interval [5.6, 22.8]) had symptomatic relapse at 2 weeks post-treatment. Relapse included patients who died or were lost to follow-up, and those who received systemic antifungal therapy during the post-treatment period. Cumulative relapse at 4 weeks post-treatment was 52.1% in the MYCAMINE group and 39.4% in the fluconazole group (treatment difference 12.7%, 95% confidence interval [2.8, 22.7]).

Analysis of data from FG463-21-09 also shows that most patients had OPC concomitantly with EC, efficacy appears to have a dose-related pattern, and relapse rates are higher on micafungin than fluconazole:

Time of Assessment	Micafungin 50 mg/day N=64	Micafungin 100 mg/day N=62	Micafungin 150 mg/day N=59	Fluconazole 200 mg/day N=60
OPC at baseline	61/64 (95.3%)	59/62 (95.2%)	53/59 (89.8%)	57/60 (95.0%)
OPC and EC grade 0 at EOT	38/64 (59.4%)	45/62 (72.6%)	46/59 (78.0%)	50/60 (83.3%)
Total OPC Relapse at 2 weeks	18/38 (47.4%)	21/45 (46.7%)	17/46 (40.0%)	13/50 (26.0%)

Relapse rates include patients with missing values and systemic antifungal during 2 week follow up period.

The information on oropharyngeal candidiasis is important to include in labeling because these results indicate that while patient who have both esophageal and oropharyngeal candidiasis respond well in this case to 150 mg/kg/day of micafungin intravenously at the end of treatment, patients who have oropharyngeal candidiasis have a much higher chance of relapse after echinocandin treatment compared to azole treatment and this information is important for clinicians in managing these patients.

This finding is not unique to micafungin, and may represent a class effect for the echinocandin drug class. Wording reflecting significantly higher relapse rates is also included in the caspofungin labeling.

3. Prophylaxis Of *Candida* Infections In Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT) - Efficacy, NDA 21-506

Phase 3 Study 98-0-050 compared micafungin 50 mg/day IV to fluconazole 400 mg/day IV given as a 1-hour infusion in HSCT recipients. The study alone could not support approval for this indication and evidence of antifungal activity is provided from the esophageal candidiasis studies and non-comparative information on *Candida*. A summary of the regulatory guidance provided to Fujisawa is summarized by Dr. Meyer in her review.

Patients were treated up to a maximum of 42 days after transplant and considered to fail prophylaxis if they developed proven, probable, or suspected infection.

Definitions of Infections

- Proven fungal infection: (a) patients with biopsy-proved (with or without culture) invasive (sinus, lung, liver, brain, etc) or disseminated infection (positive culture). Proven pulmonary fungal infection needed presence of compatible radiographic and clinical findings of infection. (b) Immunocompromised patients with sinusitis or a pulmonary infiltrate and an acceptable positive culture of *Aspergillus* or *Fusarium* or the agents of mucor (zygomycosis) from the upper respiratory tract.
- Probable fungal infection: Immunocompromised patients (neutropenia, chronic steroid therapy, etc) with the characteristic clinical and radiographic (chest x-ray, CT scan, other) picture of pulmonary aspergillosis or chronic disseminated candidiasis.
- Suspected systemic fungal infection: patient who met all three of the following criteria for at least 96 hours: neutropenia (ANC < 500 cells/mm³); persistent or recurrent fever ($\geq 100.4^{\circ}\text{F}$, $\geq 38.0^{\circ}\text{C}$) for which there was no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy.

Approximately half the patients had allogeneic BMT and half had autologous or syngeneic BMT. Most patients had ANC < 200 cells/mm³, nearly 90% of patients were Caucasian, nearly half were female, and about a quarter of patients had GVHD during study. Based on the applicant's original analysis, micafungin was marginally superior to fluconazole in preventing fungal infections. Although not a protocol endpoint, examination of the difference between the rates of proven or probably candida infections shows the two products are similar. Micafungin is effective in allogeneic and autologous HSCT. The rates for the outcome of "Absence of Fungal Infection" younger patients are lower than in older patients across both treatment arms. Given the lower rate in the younger patients in both treatment arms, the question is raised whether these differences are due to host factors and/or is the dosage regimen has been sufficiently optimized in this age group. The information is tabulated below.

Phase 3 study Study 98-0-050: Prophylaxis of *Candida* infections in Patients Undergoing Hematopoietic Stem Cell Transplant, applicant's analysis

	MYCAMINE 50 mg/day IV	Fluconazole 400 mg/day IV	
Number of Patients	N=425	N=457	
Absence of Fungal Infection,	340/425 (80%)	336/457 (73.5%)	+6.5%, 95% CI (0.9%, 12%)
All Proven and Probable Breakthrough Systemic Fungal Infection	7 (1.6%)	11 (2.4%)	
<i>Candida</i> infections only	4 (0.9%)	2 (0.4%)	+0.5%, 95% CI (-0.6, 1.6%)
Use of Empirical Antifungal Therapy for Suspected Fungal Infection	64 (15.1%)	98 (21.4%)	
Outcome (Absence of Fungal Infection) by type of HSCT			
Allogeneic	157/220 (71.4%)	175/256 (68.4%)	
Autologous or Syngeneic	181/203 (89.2%)	161/201 (80.1%)	
None	2/2	-	
Outcome (Absence of Fungal Infection) by Age			
< 16 Years	27/39 (69.2%)	24/45 (53.3%)	
≥ 16 Years	313/386 (81.1%)	312/412 (75.7%)	
≥ 65 Years of Age	32/33 (97%)	16/23 (69.6%)	
< 65 Years	308/392 (78.6%)	320/434 (73.7%)	

During the review, it was recognized that there was some confusion between patients classified as having suspected fungal infection and on further review, the following numbers were determined to represent the protocol specified primary endpoint.

Phase 3 study Study 98-0-050: Results from Clinical Study of Prophylaxis of *Candida* Infections in Stem Cell Transplant Recipients

	Micafungin 50 mg/day (n=425)	Fluconazole 400 mg/day (n=457)
Success	343 (80.7%)	337 (73.7%)
+7.0% difference (micafungin – fluconazole) [95% CI=1.5%, 12.5%]		
Failure	82 (19.3%)	120 (26.3%)
All Deaths ¹	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	3 (0.7%)
Proven/Probable fungal infection (not resulting in death) ¹	6 (1.4%)	8 (1.8%)
Suspected fungal infection ²	53 (12.5%)	83 (18.2%)
Lost to follow-up ¹	5 (1.2%)	3 (0.7%)

¹ Through end-of-study (4 weeks post-therapy)

² Through end-of-therapy

In addition, although not counted in the endpoint, the use of systemic antifungal products was examined. In the post treatment period (end of treatment through the 4 week end of study time point), antifungals were used in 42% of the patients, and this use was balanced between the arms as seen in the table below.

Use of systemic antifungal therapy post-treatment	178 (41.9%)	192 (42.0%)
Reason for use post-treatment ¹		
Prophylaxis	160 (89.9%)	174 (90.6%)
Empirical	19 (10.7%)	27 (14.1%)
Treatment	9 (5.1%)	6 (3.2%)
Maintenance	3 (1.7%)	1 (0.5%)

1: patients could have received more than one antifungal agent post-treatment; included use beginning on day of last dose of study drug

As has been documented in the literature, patients undergoing BMT/HSCT benefit from prophylaxis against *Candida* infection and fluconazole has been demonstrated to be superior to placebo in attaining this goal. Therefore, the requested indication was revised from “prophylaxis to “prophylaxis of *Candida* infections”. In order to provide support for this indication, the applicant needs to demonstrate that micafungin is non-inferior to fluconazole (along with the other requested data) and this would be supportive of approval. The primary endpoint of the trial actually evaluated all fungal infections, including suspected ones. By the applicant’s and FDA analysis, mycafungin was marginally superior to fluconazole in attaining this goal.

..... In considering just patients with breakthrough proven and probably systemic *Candida* infections, there were 4 *Candida* infections in the mycafungin arm and 2 in the fluconazole arm. The incidence of *Candida* infections was presented in comparison to *Candida* infections from published studies by Goodman and Slavin. These studies were analyzed to justify the lower limit of the confidence interval that would be acceptable, in a study or breakthrough *Candida* infections. This analysis suggested that the proposed lower bound of the margin (fluconazole-micafungin) would be -4% and the applicant calculated that both the 95% CI and 99% CI would fall within than margin thereby meeting the definition of non-inferiority (further described in the applicant’s February 18, 2004 submission for March 8, 2004 meeting with the Agency). Thus, the primary endpoint in this trial met its designated margin of 10% and actually showed micafungin to be marginally superior to fluconazole. In addition, though not a designated endpoint, the rate of *Candida* infections in the micafungin arm was shown to be similar to fluconazole.

In the prophylaxis trial, 50 mg/day was shown to be effective while in the EC studies, the 150 mg/day dose was demonstrated to be effective. However, micafungin activity was seen at lower doses in phase 2 studies of EC 97-7-003, FG463-21-09 as well as in noncomparative data from patients with candidemia and invasive candidiasis in study 98-0-047. In these studies, 50 mg/day demonstrated some activity and this finding supports the 50 mg/day dose demonstrated to be non-inferior (statistically superior) to fluconazole. Other factors considered with regards to the 50 mg dose for the prophylaxis of *Candida* infections indication include the following:

- In general, doses needed for prophylaxis are not necessarily the same as doses needed for treatment
- Echinocandins are parenteral agents and doses that are effective systemically are not always equally effective for mucosal oropharyngeal and esophageal infections.
- Plasma concentrations following a 50 mg dose of micafungin are above the concentrations considered effective in murine models of pulmonary aspergillosis and disseminated candidiasis over a 24-hour period.
- Endoscopic cure of esophageal candidiasis shows a clear dose-response and while cure rates with micafungin at 50 mg/day are lower than 150 mg/day, the 60% cure rate observed with the 50 mg/day regimen is higher than the placebo-response rate.
- Non-comparative data in candidemia shows an overall success rate of 74% (ITT) and 86% (PP) with 50 mg/day of micafungin.
- *Candidemia* and disseminated candidiasis can be prevented with lower doses of micafungin because micafungin is readily available in blood or interstitial fluid of the target organ (supported by PK and murine studies).
- Esophageal candidiasis (EC) is a mucosal disease. It may be more difficult for micafungin to penetrate the keratinized mucosal layer. Therefore, higher doses of micafungin may be required to achieve a clinical cure in EC.

The totality of the evidence supports the conclusion that micafungin 50 mg/day is effective in prophylaxis of *Candida* infections.

D. SAFETY

MYCAMINE is a member of the echinocandin drug class that inhibits fungal cell wall glucan synthesis. Due to the absence of a mammalian structural analogue for the fungal cell wall, the applicant proposes that adverse events are unlikely to occur with MYCAMINE. The review of safety finds that MYCAMINE has a safety profile similar to other echinocandin antifungals, including adverse events such as phlebitis and histamine associated reaction. In addition, some adverse events associated with non-cell wall acting antifungal agents, such as hemolysis and hepatic adverse events also occur with MYCAMINE.

The Medical Officer review of the original NDA concluded a favorable risk profile for MYCAMINE, based on 1368 subjects, the majority of whom received the 50-mg dose of MYCAMINE. The aggregate safety information evaluated in the current review incorporates updated safety data from the original NDA 21-506 (prophylaxis of *Candida* infections in hematopoietic stem cell transplant recipients), new safety data from the esophageal candidiasis in NDA 21-754 (esophageal candidiasis), several new clinical studies contained in the 120-day safety update, and postmarketing data from Japan. The review team analyzed data from all these submissions, and also consulted with the Office of Drug Safety and Dr. John Senior during the review process. The safety of the 150 mg/day dose of MYCAMINE was more fully characterized in the safety update, consistent with the finding that this was the efficacious dose for the treatment of esophageal candidiasis.

Safety Evaluable Population from the various submissions to NDA 21-506 and 21-754

Duration (Days)	MYCA 50 mg	MYCA 75 mg	MYCA 100 mg	MYCA 150 mg	MYCA 200 mg	Total
Original submission (from Dr. Ibia's review)						
N	974	319	217	111	85	1368
Total	14732	5083	2912	2163	2362	27252
Range	1-135	1-126	1-253	1-127	1-267	1-346
Mean	15.1	15.9	13.4	19.5	27.8	19.9
Re-submission (from ISS NDA 21-754)						
N	1043	269	303	271	197	2085
Total	19920	6819	6575	7599	3238	44151
Range	1-495	1-173	1-490	1-681	2-340	1-681
Mean	19.1	25.3	21.7	28.0	16.4	21.2
120-day Safety Update						
N	1049	270	357	529	197	2402
Total	19926	6846	774	112958	3238	48379
Range	1-495	1-173	1-490	1-681	2-340	1-681
Mean	19.0	25.4	19.8	21.4	16.4	20.1

A total of 726 (30%) subjects received ≥ 150 mg of MYCAMINE, and of these, the majority (606/726 or 83.5%) received this dose for at least 10 days. The mean duration of treatment for all subjects was 20.1 days (range 1-681 days).

Overall, 2028 of 2402 (84.4%) of subjects (patients and volunteers) who received MYCAMINE experienced an adverse event. Adverse events considered to be drug related were reported in 717 (29.9%) subjects. A comparison of the adverse event profile for MYCAMINE across studies shows that adverse event rates in each category varied widely across the different patient populations studied, highlighting the confounding influence of underlying disease and other factors in evaluating drug safety in severely ill patients. Patients with systemic fungal infections (invasive aspergillosis and candidiasis) represented approximately a third (679/2402 or 28.3%) of the MYCAMINE safety database.

Comparative profile of adverse events in the various populations that received MYCAMINE

AE classification	MYCAMINE				FLUCONAZOLE	
	Study 046 Invasive Aspergillus 75-200 mg (N=326) (%)	Study 047 Invasive candidiasis 75-150 mg (N=353) (%)	Study 050 Prophylaxis In HSCTR 50 mg (N=425) (%)	Study 005 Esophageal candidiasis 150 mg (N=260) (%)	Study 050 Prophylaxis In HSCTR 400 mg (N=457) (%)	Study 005 Esophageal Candidiasis 200 mg (N=258) (%)
All Adverse Events (AE)	99.7	96.9	100.0	77.7	100.0	72.1
Serious AEs	75.5	39.9	18.8	13.5	16.2	19.3
Drug-Related AEs	31.9	42.5	15.1	27.7	16.8	21.3
Serious Drug-Related AEs	22.1*	6.2	0.9	1.2	2.2	0.3
Discontinuations (D/C)	28.1	20.1	4.2	6.2	7.2	3.9
DRAEs* w/ D/C	2.8	6.8	2.6	2.3	3.5	0.8
Deaths	56.1	29.7	4.2	11.5	5.7	10.9
Hepatic DRAEs*	9.5	16.1	5.2	3.8	6.8	3.1
Renal DRAEs*	3.7	1.7	0.7	0.4	1.3	0
Allergic/histamine DRAEs*	4.3	7.1	3.5	9.2	3.9	3.1
Phlebitis/injection site AEs	0.6	7.2	2.1	3.8	2.2	2.3

* from the original NDA 21-506 submission

The safety of MYCAMINE was compared to fluconazole in two large pivotal studies (Study 03-7-005 and Study 98-0-050) and from supportive studies 97-0-041 (prophylaxis) and FG-463-21-09 (esophageal candidiasis). The overall incidence of treatment emergent adverse events were similar; 91.6% (854/932) in the MYCAMINE-treated group and 90.3% (711/787) in the fluconazole-treated group. The more common adverse events in the studies utilizing fluconazole as a comparator found the following rates for the for the aggregate MYCAMINE treatment group versus the aggregate fluconazole group were diarrhea (41.8% MYCAMINE versus 50.4% fluconazole), mucositis (39.3% versus 47.8%), leukopenia (41.2% versus 46.6%), nausea (38.9% versus 44.6%), vomiting (35.9% versus 42.8%), and thrombocytopenia (38.4% versus 42.8%), respectively.

In the pivotal prophylaxis study (Study 98-0-050) (data shown as in the lightly shaded columns in the above table), the overall event rates in the categories of serious drug AEs, deaths, discontinuations, related hepatic and renal adverse events were numerically more frequent with fluconazole compared to MYCAMINE. By contrast, the dose of MYCAMINE (150 mg) used in the treatment of esophageal candidiasis (data shown as in the lightly shaded columns in the above table) more closely matched that of the comparator fluconazole (200 mg/day). At these dose levels, all AEs, drug related AEs, deaths, discontinuations, related hepatic, renal, injection site and histamine mediated reactions were numerically more frequent with MYCAMINE than fluconazole. A smaller proportion of the adverse events observed in these studies were attributed to drug, compared to patients in the invasive candidiasis or aspergillosis studies, which may indicate a greater tendency to attribute adverse events to the study drug in the less severely ill. For consistency with other antifungal labels, the Division proposes that the label present the common (>0.5%) drug related adverse events in the entire safety database and in the pivotal studies for the esophageal candidiasis and the prophylaxis studies.

Common Drug-Related* Adverse Events in Subjects[†] who received MYCAMINE in Clinical Trials

Number of Patients ⁽¹⁾	MYCAMINE N=2402
All system	421 (17.5%)
Blood and Lymphatic System Disorders	
Leukopenia	38 (1.6%)
Neutropenia	29 (1.2%)
Gastrointestinal Disorders	
Nausea	67 (2.8%)
Vomiting	58 (2.4%)
Diarrhea	38 (1.6%)
General Disorders and Administration Site Conditions	
Pyrexia	37 (1.5%)
Laboratory Tests	
Aspartate aminotransferase increased	64 (2.7%)
Alanine aminotransferase increased	62 (2.6%)
Blood alkaline phosphatase increased	48 (2.0%)
Liver function tests abnormal	36 (1.5%)
Metabolism and Nutrition Disorders	
Hypokalaemia	28 (1.2%)
Hypocalcemia	27 (1.1%)
Hypomagnesemia	27 (1.1%)
Nervous System Disorders	
Headache	57 (2.4%)
Vascular Disorders	
Phlebitis	39 (1.6%)
Skin and Subcutaneous Tissue Disorders	
Rash	38 (1.6%)

⁽¹⁾Within a body system, patients may experience more than 1 adverse event

*Determined by the investigator to be possibly, probably, or definitely drug-related

[†]Subjects included patients and volunteers MedDRA Version 5.0.

Other clinically significant adverse events to include in the product label are the following adverse events:

_____ and Lymphatic System:
 pancytopenia, hemolysis, thrombotic thrombocytopenic purpura
Respiratory System: dyspnea, hypoxia, pulmonary embolism, apnea
Cardiovascular System: _____, hypertension,
 tachycardia, arrhythmia, myocardial infarct, _____
 _____ hepatomegaly
Nervous System: convulsion, intracranial hemorrhage, encephalopathy.
Metabolic and Nutritional Disorders: _____, acidosis,
 _____, hyponatremia
Urogenital System: acute kidney failure, oliguria, anuria, kidney tubular necrosis
Skin: skin necrosis, urticaria, erythema multiforme
Musculoskeletal System: arthralgia

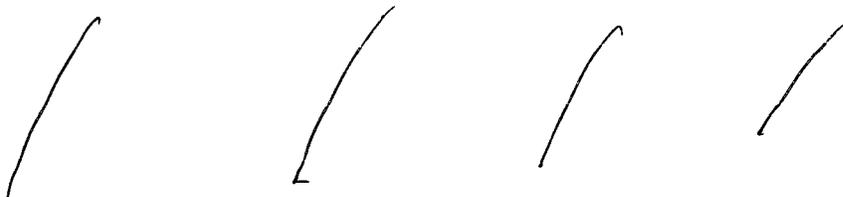
The following postmarketing adverse events reviewed by Dr. Singer and by the Office of Drug Safety review team (Drs Melissa Truffa and Adrienne Rothstein) are also proposed for inclusion in the label:[†]

Hepatic: hyperbilirubinemia, hepatic function abnormal, hepatic disorder, hepatocellular damage

Renal: acute renal failure and renal impairment

Hematologic: white blood cell count decreased, hemolytic anemia

Vascular: shock



Safety issues with special labeling

ANAPHYLAXIS

Serious events from the postmarketing Japanese experience included 7 cases of allergy, 5 serious skin reactions and 5 vascular reactions (including anaphylactic shock). Anaphylaxis was not observed to occur in the clinical studies of MYCAMINE, however anaphylactic shock and other anaphylactoid reactions in the postmarketing experience were considered to be at least possibly MYCAMINE related. A WARNING about the possibility of anaphylactoid or anaphylactic reactions during MYCAMINE infusion, is proposed in the label.

“WARNINGS:

Isolated cases of serious hypersensitivity (anaphylaxis and anaphylactoid) reactions (including shock) have been reported in patients receiving MYCAMINE. If these reactions occur, MYCAMINE infusion should be discontinued and appropriate treatment administered. “

HISTAMINE MEDIATED and OTHER ALLERGIC EVENTS

Dose-related histamine release were observed in preclinical studies in rats that received 32 - 100mg/kg of MYCAMINE, but not in rats that received 10 mg/kg. A dose relationships for these events was not established at the doses chosen for the clinical studies. Rashes and vasodilatation were observed in normal volunteers and patients; some of these reactions were serious and required MYCAMINE discontinuation. One event each of erythema multiforme and toxic epidermal necrolysis developed in the clinical studies and postmarketing events, respectively. These adverse events should be described in the Adverse Reactions section of the label as follows:

General

Possible histamine-mediated symptoms have been reported with MYCAMINE, including rash, pruritis, facial swelling, and vasodilatation.

[†] Note: there is available postmarketing experience derived from micafungin use in Japan. Micafungin was approved in Japan in October 2002. The Japanese label describes doses of 50 to 150 mg and also includes a proviso for doses of up to 300 mg/day in selected circumstances.

HEPATIC SAFETY

In *ex-vivo* studies, clinically relevant concentrations of MYCAMINE caused leakage of intracellular enzymes and loss of hepatocyte viability; these effects were intermediate between those observed with amphotericin B and fluconazole. Preclinical studies confirm that the primary target of MYCAMINE toxicity is the liver. In all animal species tested, laboratory and histopathologic evidence of dose-related hepatotoxicity was noted, including single cell necrosis at 3-5X the human equivalent dose (HED).

Dr. Singer's review of the hepatic safety finds that transient increases in hepatic laboratory function developed in normal volunteers who received MYCAMINE. Most of these transaminase elevations were mild (<3X ULN) and fully reversible. Dr Singer also notes that increases in AST, ALT, alkaline phosphatase and bilirubin were common in MYCAMINE-treated patients; and that the proportion of patients with significant (>3X ULN) conjoint elevation of transaminases and bilirubin was similar in patients who received MYCAMINE or fluconazole.

The applicant's analysis finds no dose- or duration-relationship to the liver function test elevations or the hepatic adverse events that developed in MYCAMINE treated patients, based on multiple analyses of laboratory and clinical hepatic events performed per the FDA-Pharma white paper and in response to requests for additional analyses made by the Agency. On the other hand, the Division notes that while no dose relationship was seen with absolute increases in individual hepatic analytes, a trend suggestive of a dose response was seen with transaminase elevations $\geq 3X$ ULN in patients with esophageal candidiasis although these were too infrequent to be statistically significant (see Biopharmaceutics consult by Dr. Dakshina Chilukuri). Some hepatic events were serious, such as the development of hepatic failure or liver damage. These patients had serious underlying illnesses and were receiving concomitant medications along with MYCAMINE. The applicant's panel of hepatic experts concluded that certain serious hepatic events were possibly related to MYCAMINE, a conclusion shared by the Agency's internal expert, Dr. John Senior of the ODS. Similar MYCAMINE related serious hepatic adverse events were noted in the Japanese postmarketing database. The Division's strategy to managing this risk is to propose a HEPATIC PRECAUTION statement, and to plan for postmarketing surveillance in coordination with the ODS. The following wording is proposed for the label:

PRECAUTIONS:

Hepatic Effects

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with MYCAMINE. In some patients with serious underlying conditions who were receiving MYCAMINE along with multiple concomitant medications, clinical hepatic abnormalities have occurred, and isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported. Patients who develop abnormal liver function tests during MYCAMINE therapy should be monitored for evidence of worsening hepatic function and evaluated for the risk/benefit of continuing MYCAMINE therapy.

Safety of concomitant immunosuppressant therapy

The applicant performed several steady-state drug interaction studies with the calcineurin inhibitors (cyclosporine, tacrolimus, sirolimus) and prednisolone in normal volunteers and

finding no drug interaction, proceeded to evaluate the safety of patients receiving concomitant cyclosporine, tacrolimus, sirolimus and prednisolone in the clinical studies of MYCAMINE. In the prophylaxis study, 475 of 882 (53.9%) patients received immunosuppressive medications for treatment or prophylaxis of graft-versus-host disease; of these, 198 of 882 (22.4%) patients had documented proven graft-versus-host disease during the study.

Normal volunteers in drug interaction studies that received MYCAMINE with multiple doses of ritonavir, fluconazole, nifedipine, cyclosporine and tacrolimus developed transaminase elevations >3XULN and some that received a single dose of mycophenolate developed transaminase elevations >8-10X ULN. However, the incidence of serious hepatic adverse events in patients who received concomitant MYCAMINE and mycophenolate mofetil was similar to that observed in patients who received MYCAMINE alone. Similar conclusions were derived when the patients that received MYCAMINE with other immunosuppressants were compared to patients that received MYCAMINE or fluconazole alone. The population that required concomitant immunosuppressant therapy was distinct from the group that received MYCAMINE alone, confounding an assessment of attributability. Nonetheless, clinical reviewers were reassured that no serious hepatic events requiring treatment discontinuation occurred in this prospectively evaluated randomized blinded study, with adequate laboratory and clinical documentation of adverse events.

RENAL Adverse Events

Increased BUN and creatinine and decreased creatinine clearance were observed in clinical trials of micafungin completed in Japan. Similar postmarketing renal events supported the listing of serious renal disorders as "Clinically significant adverse reactions" sub-section within the Japanese label. The label further states that renal function should be monitored in patients receiving micafungin and that treatment discontinuation should be considered if abnormalities develop. Dr. Singer performed a careful review of the individual patient data from the NDA and the postmarketing safety database. She notes that while several of these renal adverse events are confounded, there were rare events that appeared to be drug related. She notes that these events were seen at a frequency similar to that of Fluconazole. She also points out that 4 MYCAMINE-treated patients (0.4%) and 4 fluconazole-treated patients (0.5%) had renal adverse events judged to be drug-related by the investigator. To characterize these events, the following wording is proposed in the MYCAMINE label:

Renal Effects

Elevations in BUN and creatinine, and isolated cases of significant renal dysfunction or acute renal failure have been reported in patients who received MYCAMINE. In controlled trials, the incidence of drug-related _____ was 0.4% for MYCAMINE treated patients and 0.5% for fluconazole treated patients. Patients who develop abnormal renal function tests during MYCAMINE therapy should be monitored for evidence of worsening renal function.

HEMATOLOGIC

An *in vitro* assay found that MYCAMINE can induce hemolysis of red cells at clinically relevant drug concentrations. One normal volunteer developed acute hemolysis and hemoglobinuria following an infusional event characterized by shortness of breath, diaphoresis and hypotension. In addition, rare events of hemolysis have occurred in patients enrolled in MYCAMINE clinical

trials. The Japanese label lists several hematologic events including neutropenia (1.5%), thrombocytopenia or hemolytic anemia in its “Clinically significant adverse reactions” subsection and recommends that monitoring for these events be undertaken while on treatment with micafungin. The following wording is proposed for the US product label:

Hematologic Effects

Acute intravascular hemolysis and hemoglobinuria was seen in a healthy volunteer during infusion of MYCAMINE (200 mg) and oral prednisolone (20 mg). This event was transient, and the subject did not develop significant anemia. Isolated cases of significant hemolysis and hemolytic anemia have also been reported in patients treated with MYCAMINE. Patients who develop clinical or laboratory evidence of hemolysis or hemolytic anemia during MYCAMINE therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing MYCAMINE therapy.

OTHER SAFETY ISSUES:

Cardiovascular safety

Micafungin does not suppress I_{Kr} channel current in hERG transfected cells nor prolong action potential duration. Preclinical studies likewise reveal no increase in QT interval in chronically dosed beagle dogs. Finally, no significant QTc prolongation was observed in normal volunteer studies and no clinical cardiac events related to QT prolongation has been documented in patients who received MYCAMINE.

Drug Interactions

A total of 11 clinical drug-drug interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between MYCAMINE and mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin. In these studies, no interaction that altered the pharmacokinetics of MYCAMINE was observed. There was no effect of single dose or multiple dose MYCAMINE on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics.

Sirolimus AUC was increased by 21% with no effect on C_{max} in the presence of steady-state MYCAMINE compared with sirolimus alone. Nifedipine AUC and C_{max} were increased by 18% and 42%, respectively, in the presence of steady-state MYCAMINE compared with nifedipine alone. The label should note that patients receiving sirolimus or nifedipine in combination with MYCAMINE be monitored for sirolimus or nifedipine toxicity and doses of sirolimus or nifedipine be reduced if necessary.

MYCAMINE is not an inhibitor of P-glycoprotein and, therefore, would not be expected to alter P-glycoprotein-mediated drug transport activity.

Pregnancy, Lactation

Dr. McMaster concludes that MYCAMINE is a pregnancy category C drug based on the finding of visceral abnormalities in the offspring of the rabbit studies. The following wording is proposed for the label:

Pregnancy Category C

MYCAMINE administration to pregnant rabbits resulted in visceral abnormalities and abortion at 32 mg/kg, a dose equivalent to about four times the recommended dose. Visceral abnormalities included abnormal lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian artery, and dilatation of the ureter. Animal studies are not always predictive of human response; therefore, MYCAMINE should be used during pregnancy only if clearly needed.

Nursing Mothers

MYCAMINE sodium was found in the milk of lactating, drug-treated rats. It is not known whether MYCAMINE is excreted in human milk. Caution should be exercised when MYCAMINE is administered to a nursing woman.

Pediatric Use

Pediatric safety data was available from 244 pediatric subjects (<16 years of age) in the entire database, including data from 39 patients who received 1mg/kg of MYCAMINE as prophylaxis for *Candida* infections, and 4 patients who received 3mg/kg of MYCAMINE for the treatment of esophageal candidiasis. A comparison of adverse events occurring in the 244 pediatric patients to those observed in adults (≥ 16 years of age) indicates that reported events were numerically more frequent in pediatric patients. The applicant attributes the difference in adverse event rates to the severity of the underlying disease and the fungal infections in pediatric patients. Nonetheless, age-related efficacy analysis also appears to show a treatment difference favoring adults in the prophylaxis study. These safety and efficacy concerns, compounded by the limitations of the pharmacokinetic data in pediatric patients, support the recommendation to limit the approved indications to the adult populations.

Geriatric Use

No differences in safety or effectiveness were observed between the 186 subjects 65 years of age or older and those under 65 years of age in the clinical studies of MYCAMINE.

Summary and Recommendation

Safety

Upon review of the resubmission of NDA 21-506 (MYCAMINE 50 mg in the prophylaxis of *Candida* infections in the hematopoietic stem cell transplant recipients) and the new NDA 21-754 (MYCAMINE 150 mg for the treatment of esophageal candidiasis) the Agency's findings include the following with regards to safety:

- rare but serious events of anaphylaxis with MYCAMINE
- a signal for hepatic toxicity with MYCAMINE at a rate similar to that seen with fluconazole, which bears a hepatic warning in its label
- the adverse events of histamine mediated toxicity, infusion related toxicity and phlebitis, especially when MYCAMINE is infused via a peripheral line; events which can be described in the product label for MYCAMINE.
- the adverse events of hemolysis, _____, and rare renal events considered to be related to MYCAMINE therapy; events which can be described in the product label for MYCAMINE.

- no multi-dose interaction between MYCAMINE and cyclosporine, tacrolimus, sirolimus, prednisolone, mycophenolate mofetil and MYCAMINE that would require dose adjustment for MYCAMINE.
- insufficient information to conclude that a safe dose has been characterized in pediatric patients.

The applicant's submission, which includes *in vitro* studies on hemolysis, hepatic toxicity, action potential and hERG channel assays, as well as the preclinical and normal volunteer safety information, strengthens the validity of the signals identified in the clinical studies and provides a plausible link for drug attribution in evaluating the clinical safety data derived largely from patients with serious underlying illness(es) and usually receiving multiple concomitant medications. The independent assessment by the Office of Drug Safety, the detailed clinical review by Dr. Singer and the availability of postmarketing data strengthens the safety conclusions derived. We address these risks in the label with the addition of a Warning section on anaphylaxis, a precautions statement on hepatic events, statements on hemolysis and renal events. The ODS will monitor these events following the market availability of MYCAMINE.

The applicant has adequately characterized the safety of MYCAMINE in adults and provides valuable information regarding its safe use with several drugs of interest in relation to the approved indications. For esophageal candidiasis, the applicant has performed antiretroviral – MYCAMINE drug interaction studies and for the prophylaxis indication the applicant has evaluated the interaction and safety of concurrent immunosuppressant and MYCAMINE therapy. This information will be useful in the clinical use of MYCAMINE and allow for a risk-benefit evaluation for the individual patient.

Efficacy

In this resubmission, the applicant has successfully demonstrated the efficacy of micafungin in the treatment of esophageal candidiasis at a dose of 150 mg/day intravenously in adult patients. Based upon the satisfactory demonstration of efficacy in the treatment of esophageal candidiasis (a type of established infection due to *Candida* spp.) in NDA 21-754, the result from the prophylaxis study (Study 98-0-050) and the other supportive evidence derived from the aforementioned micafungin NDAs and the related micafungin NDAs, sufficient evidence has been provided to support the efficacy of micafungin in the prophylaxis of *Candida* infection in patients undergoing hematopoietic stem cell transplantation at a dose of 50 mg/day intravenously in adult patients.

Recommendation

The applicant should be issued an approval letter for the following indications:

- Esophageal Candidiasis (NDA 21-754)
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (HSCT) (NDA 21-506)

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

/s/

Renata Albrecht
3/16/05 12:27:41 PM
MEDICAL OFFICER
NDA 21-754, NDA 21-506

Eileen Navarro
3/16/05 12:37:51 PM
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Micafungin sodium for Esophageal Candidiasis
Mycamine (Micafungin sodium)

CLINICAL REVIEW

Application Type	NDA
Submission Number	N21-754
Submission Code	N-000
Letter Date	4/23/04
Stamp Date	4/26/04
PDUFA Goal Date	2/25/05; and 5/25/05 extension
Reviewer Name	Mary Singer, M.D., Ph.D.
Review Completion Date	3/14/05
Established Name:	Micafungin sodium
(Proposed) Trade Name	Mycamine™
Therapeutic Class	Antifungal Agent
Applicant	Fujisawa Healthcare, Inc.
Priority Designation	S
Formulation	Intravenous
Dosing Regimen	150 mg/day
Indication	Esophageal candidiasis
Intended Population	Adults with Esophageal candidiasis

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EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Recommendation: We recommend APPROVAL of micafungin sodium (MYCAMINE™) for the treatment of esophageal candidiasis in adults.

Efficacy of Micafungin in Treatment of Esophageal Candidiasis

The efficacy of micafungin in the treatment of esophageal candidiasis was demonstrated in the pivotal phase 3 study, 03-7-005, in which micafungin (150 mg/day) was shown to be non-inferior to fluconazole for the primary endpoint, endoscopic cure at the end-of-therapy, which was achieved in 87.7% (228/260) patients treated with micafungin and in 88% (227/258) patients treated with fluconazole. In addition, micafungin was non-inferior to fluconazole for the secondary study endpoints, clinical cure (91.9% for both micafungin and fluconazole), overall therapeutic cure (85.7% for micafungin and 85.3% for fluconazole), and mycological eradication (74.6% for micafungin and 77.6% for fluconazole), as well as relapse at 2 weeks (17.9% for micafungin and 13.6% for fluconazole), and cumulative relapse at 4 weeks post-treatment (32.7% for micafungin and 28.2% for fluconazole).

Micafungin efficacy in the treatment of esophageal candidiasis was also demonstrated in the pivotal phase 2 dose-ranging study, FG463-21-09, with a clear micafungin dose-response demonstrated for the primary study endpoint (endoscopic cure at the end-of-therapy). Endoscopic cure rates were 66.8% (44/64) for 50 mg/day micafungin, 77.4% (48/62) for 100 mg/day micafungin, and 89.9% (53/59) for 150 mg/day micafungin in comparison to 86.7% (52/60) for 200 mg/day fluconazole. Results of the secondary study endpoints, clinical response, overall therapeutic response, mycological response, and relapse at 2 weeks post-treatment supported the conclusions drawn by analysis of the primary endpoint.

Two additional studies were submitted in support of this NDA. The first was study 97-7-003, a phase 2 dose ranging study to evaluate micafungin doses of 12.5, 25, 50, 75 and 100 mg/day for treatment of esophageal candidiasis. A micafungin dose-response was observed for the primary endpoint, clinical response at the end-of-therapy. Clinical clearing (symptomatic cure) of esophageal candidiasis was observed in 33.3% (6/18) patients who received 12.5 mg/day, in 53.8% (7/13) patients who received 25 mg/day, in 86.7% (13/15) patients who received 50 mg/day, in 84.2% (16/19) patients who received 75 mg/day, and in 94.7% (18/19) patients who received 100 mg/day micafungin. The secondary endpoints, endoscopic response, mycological response, and overall treatment response, all supported the conclusions drawn using the primary study outcome. Thus, this study supports the use of micafungin for treatment of esophageal candidiasis.

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The second supportive study, 98-0-047, was an open-label, non-comparative study conducted to evaluate efficacy of micafungin in the treatment of invasive candidiasis and candidemia

— This study included 99 evaluable patients with esophageal candidiasis (34.3 % of the 288 evaluable patients in the study). Most patients with esophageal candidiasis received micafungin alone at doses between 50 and 100 mg/day. Treatment success (investigator assessment of global response to therapy) was reported in 91/99 (91.9%) patients with esophageal candidiasis. This included complete response in 64.6%, and partial response in 27.3% patients. Although the study design, micafungin dosing and study endpoint differed from those studies described above, these results generally support the use of micafungin for treatment of esophageal candidiasis.

The applicant did not request an indication for the treatment of oropharyngeal candidiasis, which frequently occurs concomitantly with esophageal candidiasis in patients with HIV/AIDS. However, in study 03-7-005, data regarding symptoms of oropharyngeal candidiasis was collected systematically, and was analyzed by the Division of Special Pathogens and Immunologic Drug Products. In this study, 88.6% (459/518) patients had oropharyngeal candidiasis at baseline. At the end-of-therapy, 83.5% (192/230) micafungin-treated patients, and 82.1% (188/229) fluconazole-treated patients had resolution of oropharyngeal candidiasis signs and symptoms. Symptomatic relapse occurred in 32.3% of those in the micafungin group and in 18.1% of those in the fluconazole group. At 4-weeks post-treatment, the cumulative relapse rates for oropharyngeal candidiasis were 52.1% in the micafungin group, and 39.4% in the fluconazole group. These differences in relapse rates between treatment groups were statistically significant. Although micafungin appears effective in the primary treatment of oropharyngeal candidiasis, a treatment indication is not justified because of the high relapse rates observed post-treatment in comparison to fluconazole.

Safety of Micafungin for Treatment of Esophageal Candidiasis

The safety of micafungin was evaluated in the individual esophageal candidiasis studies submitted for this NDA (see individual reviews for studies 03-7-005, FG463-21-09, and 97-7-003 in Appendix 10), and in the micafungin safety database, which included subjects (1980 patients and 422 volunteers) from 32 clinical studies. Of these subjects, a total of 606 individuals received at least 150 mg/day micafungin for a minimum of 10 days. Overall, 2028 of 2404 (84.4%) of subjects who received micafungin experienced an adverse event. The more common adverse events were diarrhea (26.0%), nausea, (25.7%), vomiting (24.4%), fever (23.6%), and leukopenia (20.9%). Adverse events considered at least possibly related to micafungin were reported in 717/2402 (29.9%) subjects. The more common drug-related adverse events were nausea (2.9%), increased AST (2.7%), increased ALT (2.6%), leukopenia (2.5%), vomiting (2.4%), headache (2.3%), rash (2.3%), increased alkaline phosphatase (2.0%), and diarrhea (2.0%). Overall a total of 383 of 1980 (19.3%) patients died during study participation. Two deaths were considered possibly related to study drug by the investigator (one due to pulmonary hemorrhage and pancytopenia in a patient with pulmonary aspergillosis, and the second

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due to progression of HIV in a patient with advanced AIDS), but on review by the medical officer, a relationship of these deaths to study drug seemed unlikely. Serious adverse events occurred in 554/1980 (28.0%) patients, but in no volunteers. The most common serious adverse events in these studies were sepsis (4.2%), respiratory failure (3.8%), shock (2.4%), pneumonia (2.2%), fever (2.0%), hypotension (2.0%), dyspnea (1.9%), infection (1.5%), and kidney failure (1.4%). Serious adverse events considered at least possibly related to study drug occurred in 72/1980 (3.6%) patients. Adverse events resulting in micafungin discontinuation were reported in 251/2402 (10.4%) subjects. Drug-related adverse events that led to study drug discontinuation occurred in 73/2402 (3.0%) subjects. The most common drug-related reactions resulting in study drug discontinuation were rash (0.5%), allergic reaction (0.3%), and abnormal liver function tests (0.3%), and bilirubinemia (0.2%).

Safety concerns with micafungin identified in this review include:

Anaphylaxis

In clinical studies, anaphylactoid reactions were reported with micafungin infusion; while anaphylaxis and anaphylactic shock considered possibly related to micafungin were reported in the Japanese postmarketing surveillance data. A WARNING concerning possible anaphylactic or anaphylactoid reactions with micafungin in the proposed label is recommended, as shown below:

“Isolated cases of serious hypersensitivity (anaphylaxis and anaphylactoid) reactions (including shock) have been reported in patients receiving MYCAMINE™. If these reactions occur, MYCAMINE™ infusion should be discontinued and appropriate treatment administered.”

Histamine-mediated reactions

Preclinical studies demonstrated histamine release in dogs and rats, and histamine-mediated reactions including hypotension and tachycardia were observed in rats. The overall incidence of allergic or histamine-type reactions (including rash, maculopapular rash, vesiculobullous rash, pruritus, vasodilatation, urticaria, eosinophilia, anaphylactoid reaction, and allergic reaction) was 28.1% (647/2402 subjects) in the clinical studies. Those adverse events considered at least possibly drug-related occurred in 5.0% (119/2402) of all subjects. The most common events considered drug-related were rash (2.3%), pruritus (1.0%), vasodilatation (0.8%), and maculopapular rash (0.7%). Serious adverse events included rash or maculopapular rash in 5 of 1980 patients (0.3%); allergic reaction in 5 (0.3%) patients; anaphylactoid reactions in 2 (0.1%); vasodilatation in 1 (0.15) patient; and urticaria in 1 (0.1%) patient. One case of erythema multiforme was reported in the clinical safety database for micafungin, and a number of cases of serious skin reactions, including toxic epidermal necrolysis were reported as postmarketing adverse events in Japan. Although anaphylaxis and anaphylactoid reactions could be included in this category of adverse events, a separate WARNING section for those reactions is proposed, as discussed above. A statement regarding potential histamine

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reactions with micafungin in the ADVERSE REACTIONS section of the micafungin label is proposed, as follows:

“Possible histamine-mediated symptoms have been reported with MYCAMINE™, including rash, pruritus, facial swelling, and vasodilatation.”

Hepatic safety

The liver was identified as a major target organ for micafungin toxicity in the preclinical studies (animal and *in vitro* studies). In healthy volunteers, transient increases in hepatic transaminases were observed, usually in the range of 2-3 times the upper limit of normal. However, in one drug interaction study (micafungin- mycophenolate mofetil) in healthy volunteers, ALT elevation to approximately 8 times the upper limit of normal occurred in 2 normal subjects. In patients who received mycophenolate mofetil concomitantly with micafungin, in study 98-0-050, and in the larger safety database of 1980 patients, the incidence of serious hepatic adverse events was similar to that observed in patients who did not receive this drug combination. In patients enrolled in the fluconazole-controlled studies (03-7-005, FG463-21-09, 97-7-003, and 97-0-041), the incidence of all hepatic adverse events was 19.0% (177/932) for patients who received micafungin and 21.0% (165/787) in those who received fluconazole. Drug-related hepatic adverse events occurred in 51/932 (5.5%) micafungin- and 44/787 (5.6%) fluconazole-treated patients. Serious hepatic adverse events were reported in 10/932 (1.1%) micafungin- and 11/787 (1.4%) fluconazole-treated patients. Some of these were considered at least possibly drug-related, including cases of hepatic failure or liver damage, as determined by an expert panel of hepatologists consulted by the applicant, with concurrence by Dr. John Senior in the Office of Drug Safety. Similar serious hepatic adverse events considered possibly related to micafungin were reported in the Japanese postmarketing database. Increases in AST, ALT, alkaline phosphatase and bilirubin were common in micafungin-treated patients, and occurred at rates similar to those observed in patients who received fluconazole. There was no statistically significant dose relationship between micafungin and clinically significant elevations in AST, ALT, and alkaline phosphatase or bilirubin; however, a trend toward increased incidence of AST, ALT, and alkaline phosphatase elevation was observed with the 150 mg/day dose of micafungin (see Biopharmaceutics Review by Dr. Dakshina Chilukuri). The ODS plans to perform surveillance for serious hepatic adverse events following micafungin approval in the U.S. In addition, a PRECAUTION statement regarding the potential hepatic effects of micafungin is proposed for the micafungin label, as follows:

Hepatic Effects

“Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with MYCAMINE™. In some patients with serious underlying conditions who were receiving MYCAMINE™ along with multiple concomitant medications, clinical hepatic abnormalities have occurred; and isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have also been reported. Patients who develop abnormal liver function tests during

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MYCAMINE therapy should be monitored for evidence of worsening hepatic function and evaluated for the risk/benefit of continuing MYCAMINE™ therapy.”

Renal safety

In the fluconazole-controlled studies (03-7-005, FG463-21-09, 97-7-003, and 97-0-041), renal adverse events were reported in 74/932 (7.9%) patients who received micafungin and in 85/787 (10.8%) patients who received fluconazole. The more common renal adverse events in micafungin-treated patients included increased creatinine (3.9%), and increased BUN (2.1%). Drug-related adverse events occurred in 4/932 (0.4%) micafungin-treated and 4/787 (0.5%) fluconazole-treated patients. Serious renal adverse events including acute renal failure, occurred in 12/932 (1.3%) micafungin-treated and 19/787 (2.4%) fluconazole-treated patients. Micafungin discontinuation due to increased creatinine was reported in 3/1980 (0.1%) patients; and due to kidney failure in 5/1980 (2.5%) patients in the micafungin safety database.

Serious renal adverse events, including renal failure or impairment, some of which were considered possibly related to micafungin by the ODS consultant, were reported in the Japanese postmarketing database. The Japanese micafungin label was recently revised to include acute renal failure as a clinically significant adverse event. ODS plans to perform postmarketing surveillance for serious renal failure or impairment once micafungin is approved in the U.S. A PRECAUTION is proposed for the final micafungin label regarding the potential renal effects of micafungin, as follows:

Renal Effects

“Elevations in BUN and creatinine, and isolated cases of significant renal dysfunction or acute renal failure have been reported in patients who received MYCAMINE™. In controlled trials, the incidence of drug related renal adverse events was 0.4% for MYCAMINE™ treated patients and 0.5% for fluconazole treated patients. Patients who develop abnormal renal function tests during MYCAMINE™ therapy should be monitored for evidence of worsening renal function”.

Hematologic safety

A total of 927/2402 (38.6%) subjects experienced at least one hematological adverse reaction. These events were considered at least possibly related to micafungin in 117 (4.9%) subjects. The more common drug-related adverse hematological adverse events included leukopenia (2.5%), anemia (1.2%), and thrombocytopenia (1.0%). The incidence of drug-related hematological adverse events was similar in patients treated with micafungin (5.2%) and fluconazole (3.7%) in the fluconazole-controlled studies.

Evidence of hemolysis and hemolytic anemia was observed in rats and dogs in the preclinical studies. Additionally, acute intravascular hemolysis was seen in a healthy volunteer who received concomitant micafungin and oral prednisolone in a drug interaction study. In that subject, the event was transient, and no evidence of hemolytic anemia was observed. In the micafungin safety databases, 7/2402 (0.3%) subjects

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experienced hemolysis, hemolytic anemia, or abnormal erythrocytes. Hematological adverse events possibly related to micafungin, including hemolysis, hemolytic anemia, and thrombotic thrombocytopenic purpura, were also reported in the Japanese postmarketing database. ODS plans to perform postmarketing surveillance for these serious adverse events after micafungin approval in the U.S. A PRECAUTION is proposed for the final micafungin label regarding hemolysis and hemolytic anemia, as follows:

Hematological Effects

“Acute intravascular hemolysis and hemoglobinuria was seen in a healthy volunteer during infusion of MYCAMINE™ (200 mg) and oral prednisolone (20 mg). This event was transient, and the subject did not develop significant anemia. Isolated cases of significant hemolysis and hemolytic anemia have also been reported in patients treated with MYCAMINE™. Patients who develop clinical or laboratory evidence of hemolysis or hemolytic anemia during MYCAMINE therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing MYCAMINE therapy”.

Injection site reactions

A total of 199/2402 (8.3%) subjects experienced at least one injection site reaction. These reactions included phlebitis, thrombophlebitis, deep thrombophlebitis, injection site inflammations, pain, edema, reaction or hemorrhage. The incidence of injection site reactions in fluconazole-controlled studies was 9.9% for micafungin-treated and 4.4% for fluconazole-treated patients. In the esophageal candidiasis study, 03-7-005, the incidence of injection site reactions in patients who received micafungin (150 mg/day) was 19.2% (50/260) in comparison to patients who received 200 mg/day intravenous fluconazole (5.0%, 13/258). The majority of patients in study 98-0-050 received micafungin by a peripheral intravenous catheter, and the increased incidence of injection site reactions with micafungin in this study, in comparison to that reported in study FG463-21-09, was attributed to the mode of micafungin administration. Most patients in the other clinical studies reportedly received micafungin via a central venous catheter. In the phase 2 esophageal candidiasis study, FG463-21-09, there was no obvious relationship between micafungin dose (50-150 mg/day) and injection site reactions, and the overall incidence of these reactions was 11.4% for the combined micafungin groups compared to 20.0% in the fluconazole group. A statement regarding potential injection site reactions is proposed for the final micafungin label, as follows:

“Injection site reactions, including phlebitis and thrombophlebitis have been reported, at MYCAMINE™ doses of 50-150 mg/day. These events tended to occur more often in patients receiving MYCAMINE™ via peripheral intravenous administration.”

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Additional Safety Issues

Cardiovascular Safety

At clinically relevant doses, micafungin did not suppress I_{kr} channel current in hERG-transfected cells, nor did it prolong the duration of action potential. In preclinical studies, changes in blood pressure and heart rate, attributed to histamine release were noted in rats, but not in dogs. No changes in the QT interval were noted in dogs who received micafungin for 4-, 13-, and 39 weeks. Additionally, several pharmacokinetic studies in healthy volunteers also evaluated the influence of micafungin on cardiac repolarization, and found no evidence of significant QT prolongation, consistent with the preclinical study data.

Pediatric Safety

In pediatric patients (< age 16), the overall incidence of adverse events (93/4%, 228/244) was higher than that observed in adults between the ages of 16 and 65 years old (83.5%, 1647/1972), and that observed in adults > 65 years old (82.3%, 153/186). Because of safety concerns in this age group (see section 8.4 of this review), because only 4 pediatric patients with esophageal candidiasis were included in these studies, and because pharmacokinetic data was not adequate to establish bioequivalence with adults in order to establish an effective pediatric dose, micafungin will not be labeled for pediatric use at this time. Pediatric studies for efficacy of micafungin in treatment of esophageal candidiasis (and for prophylaxis of *Candida* infections in HSCT recipients) in children from 0-16 years old, will be deferred.

Intrinsic Factors as related to Safety: Age, Race, and Gender

No overall significant differences in micafungin safety were observed in elderly patients (> 65 years old) and younger adults; and no significant differences in safety were observed between male and female subjects. The overall incidence of adverse events was higher in Caucasian subjects (90.1%, 1369/1519) than in blacks (79.5%, 422/531), or in subjects of other racial origins (67.3%, 237/352), but this was attributed to differences in underlying disease (more Caucasians had underlying hematological malignancy and/or HSCT), and no differences were seen in the incidence of drug-related adverse events in patients regardless of racial/ethnic origin.

Pregnancy

We recommend that micafungin be labeled as pregnancy category C because of embryotoxicity observed in rabbit studies.

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Risk/Benefit of Micafungin for Treatment of Esophageal Candidiasis

In patients with esophageal candidiasis, micafungin provides an alternative to other approved antifungal agents, including fluconazole, voriconazole, itraconazole oral solution, and caspofungin, the only echinocandin currently licensed for use in the U.S. The azole derivatives (except for itraconazole, for which only the oral solution has been approved for this indication) provide the advantage of availability in both oral and intravenous formulations; while the echinocandins are available only for intravenous use. Amphotericin B and its liposomal derivatives, sometimes used for treatment of esophageal candidiasis, are currently available for intravenous use only in the U.S. Patients with severe esophageal candidiasis often require intravenous administration of antifungal medications.

The safety profile of micafungin is generally similar to that of caspofungin; while the azole antifungal agents have a significant potential for hepatotoxicity, and amphotericin B, and lipid formulations of amphotericin B have the potential for nephrotoxicity. The azole antifungal agents also have a number of clinically significant drug interactions, and alone, or in combination with certain other drugs may cause prolongation of the QT interval. The echinocandins (both caspofungin and micafungin) have shown no evidence for QT prolongation in preclinical and clinical studies. No significant pharmacokinetic interactions resulting in increased micafungin exposure were observed with concomitant micafungin and steady state cyclosporine or tacrolimus, or with mycophenolate mofetil, nifedipine, prednisolone, sirolimus, fluconazole, ritonavir and rifampin. Micafungin had no effect on the pharmacokinetics of mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics, but did increase sirolimus and nifedipine AUC; while the effect of micafungin on ritonavir and rifampin pharmacokinetics was not studied. By comparison, a pharmacokinetic interaction between caspofungin and cyclosporine, resulting in increased caspofungin exposure has been demonstrated, and was associated with elevation of hepatic transaminases in healthy volunteers, and a WARNING against concomitant use of caspofungin and cyclosporine is included in the Cancidas® label. In a drug interaction study with mycophenolate mofetil and micafungin, transient ALT elevation to approximately 8 times the upper limit of normal range was demonstrated in two of thirty healthy volunteers, despite the lack of pharmacokinetic interaction between these two drugs. However, the incidence of serious hepatic adverse events was not increased in patients who received concomitant micafungin and mycophenolate mofetil in comparison to those who received micafungin alone in clinical studies. Thus, a separate precaution or warning regarding transaminase elevations in this study, other than the hepatic precaution, was not included in the micafungin label.

The studies submitted for this NDA did not assess the efficacy of micafungin in the setting of refractory esophageal candidiasis in patients who have failed other antifungal therapies. Theoretically, micafungin could be useful in that setting. Micafungin exhibited *in vitro* activity against a number of other *Candida* species other than *C. albicans*, including *C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*. However, the studies submitted for this NDA included only a limited number of patients with non-*C. albicans*

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strains, and patients with azole-resistant isolates were excluded, so micafungin efficacy for non- *C. albicans* or azole-resistant *Candida* sp. has not been established in clinical studies.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Office of Drug Safety (ODS) was consulted for review of the Japanese postmarketing surveillance experience with micafungin. The ODS reviewers recommended postmarketing surveillance for serious hepatic adverse events, including hepatic failure, liver damage, hepatocellular damage, hemolysis, hemolytic anemia; serious skin reactions, including Stevens Johnson syndrome and toxic epidermal necrolysis; serious renal adverse events including acute renal failure or renal impairment; and serious allergic reactions including anaphylaxis, and anaphylactoid reactions, as well as for prolongation of QT interval, hemolytic uremic syndrome, and hyponatremia. The Division met with ODS pre-approval of micafungin to review the risk management plan, which is outlined in section 8.7 of this review.

1.2.2 Required Phase 4 Commitments

No phase 4 commitments will be required.

1.2.3. Other Phase 4 Requests

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1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Micafungin sodium (MYCAMINE) is a semisynthetic lipopeptide (echinocandin) synthesized by chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin is an antifungal agent which inhibits synthesis of the β -D-glucan component of the fungal cell wall. Micafungin sodium is for intravenous use only.

NDA 21-754 was submitted for the use of micafungin for the treatment of esophageal candidiasis, and is the focus of this review. NDA 21-506 was re-submitted for the

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indication of prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplants (HSCT), and was reviewed separately by Dr. Joette Meyer.

For NDA 21-754, the applicant submitted studies 03-7-005, FG463-21-09, which were considered the pivotal studies for the esophageal candidiasis indication, and the supportive studies, 97-7-003, and 98-0-047. Study 03-7-005 was a phase 3 randomized, double-blinded, non-inferiority study comparing micafungin at the proposed dose, 150 mg/day to fluconazole 200 mg/day for treatment of esophageal candidiasis in a patient population that was predominantly HIV-positive. In study 03-7-005, 260 patients were treated with micafungin and 258 with fluconazole. FG463-21-09 was a randomized, double-blinded dose-ranging study to compare micafungin at doses of 50, 100, and 150 mg/day micafungin with fluconazole 200 mg/day for treatment of esophageal candidiasis in patients with HIV disease. In study FG463-21-09, 185 patients were treated with micafungin (combined treatment groups), and 60 patients, with fluconazole.

Study 97-7-003 was a phase 2 dose-ranging study (12.5, 25, 50, 75 and 100 mg/day) to determine the minimal effective dose of micafungin for treatment of esophageal candidiasis in HIV-positive patients. In study 97-7-003, a total of 120 patients received micafungin. Study 98-0-047 was an open-label non-comparative study of FK463 (micafungin) for treatment of candidemia and invasive candidiasis. In that study, HIV disease was the most common underlying condition, and 34.3% (99/288) evaluable patients in the study had esophageal candidiasis at baseline.

The micafungin safety database included 2402 subjects (422 volunteers and 1980 patients) from 32 different clinical studies, including those submitted for this NDA. A total of 674 patients in the four clinical studies described above, received micafungin for treatment of esophageal candidiasis. A total of 606 patients in all the clinical studies received a micafungin dose of at least 150 mg/day for a minimum of 10 days. The mean duration of micafungin treatment was 23.1 days (range 1-681 days) for patients, and 6.4 days (range 1-15 days) for volunteers.

Data sources used in this review included the NDA 21-754 electronic submission of 23 April, 2004, and the 120-day safety update of 24 August, 2004. The latter contained the report and data for one of the pivotal studies, 03-7-005, in addition to the safety update and the periodic safety update report, which included postmarketing surveillance data from Japan, where micafungin is currently marketed. Additional data sources included information received at the request of the Division from September, 2004 to February, 2005.

1.3.2 Efficacy

For the two pivotal trials conducted to determine the efficacy of micafungin for the treatment of esophageal candidiasis, studies 03-7-005 and FG463-21-09, the primary endpoint was endoscopic response at the end-of-treatment (EOT). For study 03-7-005, secondary endpoints included: clinical response at EOT, mucosal response at EOT, overall therapeutic response at EOT, relapse at 2- and 4- weeks post treatment, changes in

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endoscopic assessment of EC at EOT, changes in clinical symptoms of EC at EOT compared to baseline, and changes in clinical signs and symptoms of oropharyngeal candidiasis (OPC) at EOT compared to baseline. For study FG463-21-09, the secondary study endpoints included: endoscopic grade on day 14 of treatment, mycological response at EOT, clinical response at EOT, changes in endoscopic grade of EC at EOT compared to baseline, changes in clinical assessment of EC at EOT compared to baseline, changes in the clinical assessment of OPC at EOT compared to baseline, incidence of disease progression at EOT compared to baseline, relapse of EC at 2 weeks post-treatment, and overall therapeutic success.

These two clinical studies were adequate, well-controlled studies to evaluate efficacy of micafungin in treatment of esophageal candidiasis. No problems were identified in this review regarding the choice of endpoints, choice of control arms, adequacy of blinding, conduct of the studies, or statistical analyses.

We have concluded from study 03-7-005 that micafungin (150 mg/day) was non-inferior to fluconazole (200 mg/day) for the treatment of esophageal candidiasis for both primary and secondary endpoints, clinical response, overall therapeutic response, and relapse of EC at 2- and 4-weeks post-treatment. These conclusions are supported by the second pivotal study, FG463-21-09, in which a clear dose-response for micafungin was noted for the primary endpoint, endoscopic response at the end-of-therapy. Although not designed as a non-inferiority study, micafungin 150 mg/day was similar in efficacy to fluconazole 200 mg/day as measured by endoscopic response, clinical response, overall therapeutic response and relapse at 2-weeks post-treatment.

Treatment of OPC was a secondary outcome for these studies, but was important to evaluate because most patients with EC also have OPC. In study 03-7-005, the rate of OPC cure was similar in patients who received either micafungin or fluconazole, but relapse rates were higher at 2- and cumulatively, at 4- weeks in patients who received micafungin. These studies do not support OPC as a treatment indication for micafungin (and this indication was not requested by the applicant).

The supportive study 97-7-003 was a dose-ranging, non-comparative study to evaluate efficacy of micafungin for treatment of EC in patients with HIV. The primary endpoint was positive clinical response at the end-of-treatment. A positive clinical response as defined by the Applicant (cleared or improved) was reported in 66.7% (12/18) patients who received 12.5 mg/day, in 92.3% (12/13) patients who received 25 mg/day, in (93.3%) 14/15 patients who received 50 mg/day, in (100%) 19/19 patients who received 75 mg/day, and in (100%) 19/19 patients who received 100 mg/day micafungin/day. For patients who had clinical "clearing" of EC symptoms (clinical cure), response rates were 33.3%, 53.8%, 86.7%, 84.2%, and 94.7%, for micafungin doses of 12.5, 25, 50, 75, and 100 mg/day, respectively, showing a clear dose-response relationship for micafungin, and supporting the pivotal studies for the esophageal candidiasis indication.

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The supportive study 98-0-047 was an open-label non-comparative study of micafungin for treatment of candidemia or invasive candidiasis. Of the 288 evaluable patients, 99 (34.4%) had esophageal candidiasis. The primary endpoint, global response to therapy (partial or complete response as determined by the investigator) was achieved in 91/99 (91.9%) of patients with EC. Patients in this study received a starting dose of micafungin of 50 to 100 mg/day, but the dose could be increased in 50 mg/day increments as necessary (the maximum micafungin dose received by these patients was 150 mg/day). This study supports the pivotal studies, showing efficacy of micafungin in the treatment of esophageal candidiasis.

A number of other antifungal agents are currently approved for treatment of esophageal candidiasis, including caspofungin (intravenous), the only currently approved echinocandin, fluconazole (oral and intravenous), itraconazole (oral solution), and voriconazole (oral and intravenous). Amphotericin B, and liposomal amphotericin derivatives are also widely used for this indication when intravenous treatment is required (although EC is not an approved indication). Patients with severe esophageal candidiasis frequently require intravenous therapy because symptoms (odynophagia, dysphagia, and retrosternal pain), may preclude swallowing of solids and liquids. The azole antifungal agents, however, offer the advantage of oral therapy in patients with mild-moderate EC, or in continuation of treatment when intravenous therapy is no longer required. The efficacy of caspofungin for treatment of EC was 82% in comparison to 85% for fluconazole (Villanueva, et al., 2002). Micafungin efficacy for treatment of EC was similar to fluconazole, as shown in the pivotal studies for this NDA, and similar to caspofungin based on the published studies. Thus, micafungin will provide an effective alternative to caspofungin for patients with esophageal candidiasis who require intravenous therapy. Additionally, micafungin can be used in patients who require concomitant immunosuppressive agents, including cyclosporine.

1.3.3. Safety

The micafungin safety database included 2402 subjects (1980 patients and 422) volunteers in 32 clinical studies. Safety testing including monitoring of adverse events during treatment and within 72 hours of the last study drug administration, routine laboratory testing, and routine measurement of vital signs during treatment. In these studies, a total of 606 subjects received a minimum dose of 150 mg/day micafungin for at least 10 days. For all 2402 subjects, micafungin was received for a mean duration of 20.1 days, ranging from 1 to 681 days; and the total subject-days of micafungin exposure was 45,759 days. For the two pivotal studies for esophageal candidiasis, 260 patients received micafungin for a mean of 14.3 ± 3.68 days (range 1-33 days) in study 03-7-005; and 185 patients received micafungin for a mean of 14.6 ± 4.27 days (1-22 days) in study FG463-21-09. The maximum dose of micafungin received in an adult in maximum tolerated dose study (FG463-21-03) was 8.0 mg/kg/day (896 mg/day), and the maximum tolerated dose was not reached.

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Overall, 2028 of 2402 (84.4%) subjects experienced at least one adverse event. The more common adverse events were diarrhea (26.0%), nausea (25.7%), vomiting (24.4%), fever (23.6%), and leukopenia (20.9%). Adverse events considered at least possibly related to study drug were reported in 717 of 2402 (29.9%) subjects. The more common drug-related adverse events were nausea (2.9%), increased AST (2.7%), increased ALT (2.6%), leukopenia (2.5%), vomiting (2.4%), headache (2.3%), rash (2.3%), increased alkaline phosphatase (2.0%), and diarrhea (2.0%). Serious adverse events occurred in 554/1980 (28.0%) patients, and serious drug-related adverse events were reported in 3.6% (72/1980) patients. The more common serious adverse events, regardless of relationship to micafungin included sepsis (4.2%), respiratory failure (3.8%), shock (2.4%), pneumonia (2.2%), fever (2.0%), hypotension (2.0%), dyspnea (1.9%), infection (1.5%), and kidney failure (1.4%).

Important safety issues with micafungin identified in this review from the clinical studies and the Japanese postmarketing safety database include the occurrence of anaphylaxis and anaphylactoid reactions; other allergic or histamine-mediated reactions; hepatic adverse effects, including transaminase, total bilirubin, and alkaline phosphatase elevation, as well as serious hepatic adverse events such as jaundice, hepatic failure, hepatocellular damage; renal adverse events, including increases in serum creatinine and BUN, and acute renal failure; hematological adverse events including leukopenia, anemia, and thrombocytopenia, as well as hemolysis and hemolytic anemia; and injection site reactions, including phlebitis and thrombophlebitis.

Specific areas identified for continued safety monitoring in the postmarketing period for micafungin include serious hepatic and renal adverse events, serious hematological adverse events, particularly pancytopenia, hemolysis, hemolytic anemia, and thrombotic thrombocytopenic purpura, serious allergic reactions including anaphylaxis, anaphylactoid reactions, and serious skin effects, including toxic epidermal necrolysis, and erythema multiforme, and serious vascular reactions potentially resulting from local phlebitis or thrombophlebitis, such as deep thrombophlebitis and pulmonary embolism, or other vascular events such as myocardial or cerebral infarction which could potentially result from vascular injury.

As discussed above, micafungin will provide an alternative to caspofungin, fluconazole, voriconazole, and itraconazole as an approved antifungal agent to treatment of esophageal candidiasis. The azole antifungal agents all carry a WARNING regarding hepatotoxicity, and their use may be limited due to cytochrome P450-mediated drug interactions with a significant number of their mediations. Additionally, some azoles have been associated with QT prolongation, particularly in the setting of drug interactions. The azoles have been classified as pregnancy category C (fluconazole and itraconazole), and D (voriconazole).

Micafungin appears similar to caspofungin in the overall safety profile, with hepatic effects listed as a PRECAUTION in the labeling for both. Like micafungin, caspofungin has been associated with histamine-mediated reactions, infusion-related reactions,

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including anaphylaxis, and injection site reactions. Both drugs are classified as pregnancy category C, and neither drug appears to affect the QT interval in preclinical or in clinical studies. Micafungin appears to have one advantage over caspofungin, in that there was no pharmacokinetic interaction reported which resulted in increased micafungin or cyclosporine exposure, with the combination of micafungin plus cyclosporine. Additionally, in a study of micafungin- cyclosporine (steady state) in healthy volunteers, no clinically significant transaminase elevations were observed; while caspofungin carries a labeled warning regarding concomitant use of cyclosporine and caspofungin because of the potential drug interaction, with transaminase elevations observed in healthy volunteers who received the two drugs. In general, the echinocandins appear to be associated with less overall nephrotoxicity than amphotericin B, or its liposomal derivatives.

1.3.4 Dosing Regimen and Administration

The proposed micafungin dose for the indication of esophageal candidiasis is 150 mg/day. This appears to be an appropriate dose of micafungin for EC, based on efficacy and safety evaluations. In the dose-ranging study, FG463-21-09, a clear dose-response was observed with micafungin, with the highest rates of endoscopic cure, clinical cure, overall therapeutic response, and lowest relapse rate at 2-weeks post-treatment, observed at 150 mg/day micafungin. Although the incidence of drug-related adverse events was somewhat higher among subjects who received a minimum of 150 mg/day micafungin for at least 10 days (36.6%, 222/606 subjects), to those that received a lower dose or duration of micafungin therapy (27.6%, 495/1796), this could be attributed to differences in underlying disease (for example, drug-related adverse events were reported in 27.7% of 260 patients with esophageal candidiasis in 03-7-005 study, 42.5% of 353 patients with invasive candidiasis in study 98-0-047, and 31.9% of 326 patients with invasive aspergillosis in study 98-0-046).

1.3.5 Drug-Drug Interactions

Eleven (11) clinical drug-drug interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between MYCAMINE™ and mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin. In these studies, no interaction that altered the pharmacokinetics of micafungin was observed. Additionally, there was no effect of single dose or multiple doses of MYCAMINE™ on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics. Sirolimus AUC was increased by 21% with no effect on C_{max} in the presence of steady-state MYCAMINE™ compared with sirolimus alone. Nifedipine AUC and C_{max} were increased by 18% and 42%, respectively, in the presence of steady-state MYCAMINE™ compared with nifedipine alone. Patients receiving sirolimus or nifedipine in combination with MYCAMINE™ should be monitored for sirolimus or nifedipine toxicity and sirolimus or nifedipine

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dosage should be reduced if necessary. The effect of MYCAMINE™ on pharmacokinetics of ritonavir and rifampin was not evaluated.

In the mycophenolate mofetil-micafungin interaction study, ALT elevation to approximately 8 times the upper range of normal was observed in 2 of 30 healthy volunteers. This effect was transient, and could not be definitively attributed to micafungin or to the combination of micafungin plus mycophenolate. In patients who received mycophenolate mofetil concomitantly with micafungin, in study 98-0-050, and in the larger safety database of 1980 patients, the incidence of serious hepatic adverse events was similar to that observed in patients who did not receive this drug combination.

No clinically significant transaminase elevations were observed in healthy volunteers who received micafungin plus steady state tacrolimus or cyclosporine, or nifedipine, prednisolone, and rifampin. One healthy volunteer (of 24 subjects) in the micafungin-ritonavir interaction study, and one of 24 subjects in the micafungin-fluconazole interaction study, developed transient ALT elevations to more than 5 times the upper limit of normal range. However, unlike mycophenolate mofetil, both ritonavir and fluconazole alone have known potential for hepatotoxicity.

In our judgement, a specific PRECAUTION against concomitant use of micafungin and mycophenolate mofetil (or ritonavir or fluconazole) is not warranted at this time; but the general PRECAUTION included in the proposed label regarding the potential hepatic effects of micafungin, with recommendations regarding liver function test monitoring, should be sufficient.

1.3.6 Special Populations

Geriatrics

A total of 186 subjects > 65 years old (including 41 subjects 75 years of age and older) were included in the micafungin safety database of 2402 subjects. The incidence of adverse events in these subjects was similar to that observed in those between the ages of 16 and 65 years old (82.3%, and 83.5%, respectively). Additionally, the incidence of drug-related adverse events was somewhat lower in the elderly (24.2%), than in adults 16 to 65 years old (31.0%).

In the pivotal studies for esophageal candidiasis, 03-7-005 and FG463-21-09, only 5, and 2 patients, respectively were \geq 65 years old, so efficacy of micafungin for esophageal candidiasis in elderly patients can only be extrapolated from the data with younger adults. Pharmacokinetic studies in 10 healthy subjects who were between 66 and 78 years old showed no significant difference in micafungin exposure than in 10 healthy subjects between the ages of 20 and 24 years old, and no dose adjustment was recommended for elderly patients. Thus, the data on micafungin efficacy in younger adults can be extrapolated to those ages 65 and older.

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Pediatrics

A total of 244 pediatric patients (under 16 years old) were included in the micafungin safety database. The overall incidence of adverse events was higher in this age group (93.4%, 228/244), than in subjects between the ages of 16 and 65 (83.5%, 1647/1972), and those 65 years and older (82.3%), 153/186). No pediatric patients were enrolled in the pivotal studies submitted for this NDA, study 03-7-005, and FG463-21-09, and only 4 children enrolled in the supportive study, 98-0-047, had esophageal candidiasis at baseline. Thus, efficacy of micafungin in children was not established. Theoretically, if bioequivalence to adult patients could be shown, the efficacy data from adults could be extrapolated to children. However, the pediatric pharmacokinetic data submitted for this NDA was not adequate to characterize an effective dose of micafungin for treatment of esophageal candidiasis in children. Thus, safety and effectiveness of micafungin in pediatric patients has not been established, and a pediatric indication for micafungin is not recommended at this time.

Other Special Populations

The pharmacokinetics of micafungin (single infusion of 100 mg) were studied in 9 subjects with severe renal insufficiency (creatinine clearance < 30 mL/min) in comparison to 9 subjects with normal renal function. The pharmacokinetic parameters of micafungin were not altered significantly in patients with severe renal impairment, and no dose adjustment was recommended for patients with renal failure. Because micafungin pharmacokinetics are linear between 100 and 150 mg/day, these data can be extrapolated to the proposed dose of micafungin for esophageal candidiasis (150 mg/day).

The pharmacokinetics of micafungin (single infusion of 100 mg) were studied in 8 subjects with moderate hepatic dysfunction (Child-Pugh score 7-9) in comparison to 8 subjects with normal hepatic function. The AUC and C_{max} of micafungin were approximately 22% lower in subjects with moderate hepatic insufficiency compared to those with normal hepatic function. However, no dose adjustment was considered necessary for those with impaired hepatic function. Because micafungin pharmacokinetics are linear between 50 and 150 mg/day, these data can be extrapolated to the proposed dose of micafungin for esophageal candidiasis (150 mg/day).

The pharmacokinetics of micafungin were not studied in patients with severe hepatic insufficiency.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Micafungin sodium (Mycamine™) is a semisynthetic lipopeptide (echinocandin) synthesized by a chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin inhibits the synthesis of 1,3-β-D-glucan, a component of fungal cell walls. This is a new molecular entity, the second in the class of echinocandin antifungal agents to be approved. The first echinocandin approved for U.S. marketing in 2001, was caspofungin (Cancidas®).

The proposed indications for micafungin include esophageal candidiasis (NDA 21-754), and prophylaxis of *Candida* infections (NDA 21-506). The proposed dosing regimens are micafungin sodium 150 mg/day for esophageal candidiasis, and 50 mg/day for *Candida* prophylaxis in hematopoietic stem cell transplant (HSCT) recipients, by intravenous injection only in adults.

2.2 Currently Available Treatment for Indications

A number of antifungal agents are currently marketed for esophageal candidiasis, including fluconazole (Diflucan®), itraconazole (Sporanox® oral solution), voriconazole (Vfend®), and caspofungin (Cancidas®). Other antifungal medications are also widely used for treatment of esophageal candidiasis, include amphotericin B or lipid formulations of amphotericin B. The azoles (fluconazole, voriconazole, and itraconazole) are available in both oral and intravenous preparations; while caspofungin, amphotericin, and lipid formulations of amphotericin B are available for intravenous use only. The azole antifungal agents, although convenient, are associated with potential hepatic toxicity; while amphotericin B and its derivatives are associated with nephrotoxicity.

Fluconazole (Diflucan®) is currently the only antifungal agent approved for use in prophylaxis of *Candida* infections in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.

2.3 Availability of Proposed Active Ingredient in the United States

This new molecular entity is not currently marketed in the U.S.

2.4 Important Issues with Pharmacologically Related Products

Caspofungin, as discussed in the integrated summary of safety below, has a similar safety profile to micafungin, and a PRECAUTION regarding hepatic effects is included in the

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Additionally, the Agency requested submission of the ongoing phase 3 esophageal candidiasis study with the 120-day safety update. At that time, the applicant did not expect that submission to add more time to the review clock. However, Dr. Albrecht suggested that the Division may need to adjust the review clock if the Agency determined that the phase 3 trial was pivotal for approval.

There is currently no FDA guidance for industry regarding drug development for treatment of esophageal candidiasis, or for antifungal prophylaxis.

2.6 Other Relevant Background Information

Micafungin sodium (Fungard®) is currently marketed only in Japan. It was approved for use on 8 October, 2002 for “fungemia, respiratory mycosis, and gastrointestinal mycosis” caused by *Aspergillus* sp. and *Candida* sp. at doses of 50-150 mg/day intravenous micafungin, with increases to 300 mg/day for severe or refractory infections. The most recent Japanese label for Fungard® was submitted with this NDA, and was reviewed in the context of micafungin safety.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

A consultation to the Office of Pharmaceutical Sciences (OPS) concluded that the MYCAMINE™ product quality microbiology was acceptable.

No other issues were identified by the CMC reviewer that would impact interpretation of the data submitted in the clinical studies.

3.2 Animal Pharmacology/Toxicology

See Pharmacology/Toxicology review by Dr. Owen McMaster for full details regarding the toxicological program for micafungin. In brief, the major target organs for micafungin toxicity in animals were the liver and testes, with adverse effects also seen in the spleen, at the injection site, and in clinical chemistry and hematology profiles.

Liver toxicity included enlarged discolored livers with centrilobular hypertrophy, single cell necrosis, acidophilic bodies, nuclear hypertrophy, vacuolation, bile duct proliferation, and mitosis. High doses of micafungin (dosed at 5-10 times clinical exposure, based on body surface area comparisons), administered for prolonged periods produced irreversible changes in the liver in both rats and dogs.

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Some renal effects were noted in rats in a 26-week study of micafungin toxicity at a dose of 32 mg/kg micafungin. These changes included pigmentation in proximal tubular epithelium, dilatation of the collecting duct, swelling of the collecting duct epithelium, and increased urine volume.

Injection site reactions in rats included hemorrhage and cellular infiltration of the perivascular tissue. These reactions were less severe when micafungin was infused over 1 hour than with bolus injection. Injection site reactions were not observed in dogs, and a local tolerance study in rabbits demonstrated local tissue reactions comparable to control with several concentrations of micafungin (0.5 -4.0 mg/mL).

Histamine release and related reactions (decreased blood pressure and increased heart rate) were observed in rats who received micafungin by bolus injection of 32 mg/kg. However, repeat micafungin doses up to 32 mg/kg, administered by intravenous infusion over a longer time period did not result in the clinical signs of histamine release, suggesting that the potential effects of histamine release at high doses of micafungin could be minimized by avoiding bolus injections or rapid infusion.

Although increases in plasma histamine were observed in dogs who received high doses of micafungin (100 mg/kg), no effects on blood pressure, heart rate or electrocardiograms were reported.

Micafungin was shown to hemolyze rabbit RBCs *in vitro*, and has known surfactant activity at concentrations of 0.1 to 100 mg/mL. Laboratory changes associated with hemolysis were observed in animals including decreased erythrocytes, hemoglobin and hematocrit, as well as increased reticulocytes, potassium and bilirubin, along with splenic congestion, pigmentation, and increased weight as well as hypercellularity in the femoral bone marrow. These laboratory and histopathological changes which occurred mostly in the rat, at doses of 10-32 mg/kg micafungin are indicative of hemolysis with this drug. Signs of hemolytic anemia were also observed in dogs following a single dose of 200 mg/kg micafungin; however, splenic congestion was reported less frequently in dogs than in rats.

No evidence of QT prolongation with micafungin was observed in the 4-, 13- and 39-week studies in dogs; and *in vitro* studies at clinically relevant doses demonstrated no effect of micafungin on I_{Kr} current in transfected hERG cells, and did not prolong action potential duration. The *in vitro* studies are discussed further in the Cardiovascular Safety section of this review.

In a 39-week study in dogs, seminiferous tubular atrophy and decreased sperm count was reported at about 2 and 7 times the recommended clinical dose, based on body surface area comparisons. Rats treated with micafungin at about twice the recommended clinical dose (based on body surface area comparisons) showed increased epidymal weights and decreased sperm counts. There was no impairment of fertility, however, in the animal studies with micafungin. No impact on human reproductive system and fertility would be expected with the proposed clinical dose of micafungin used in the short term. This

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potential safety issue is discussed in the proposed micafungin label in the PRECAUTIONS section, under "Carcinogenesis, Mutagenesis and Impairment of Fertility".

Evidence of potential micafungin embryotoxicity was demonstrated in rabbits treated with high doses (32 mg/kg) micafungin, resulting in visceral abnormalities (abnormal lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian artery, and dilatation of the ureter) and abortion.

There was no evidence of mutagenicity in the Ames test for bacterial reversion, the chromosomal aberration test with cultured Chinese hamster lung cells, or the mouse micronucleus test. Carcinogenicity tests were not performed because chronic use of micafungin is not expected.

Micafungin did not induce delayed or immediate-type hypersensitivity in a skin test, active system anaphylaxis, or passive cutaneous anaphylaxis tests in rodents and guinea pigs. Additionally, a micafungin-guinea pig plasma protein complex did not induce a type I immunological reaction.

The NOAEL in rats was 2.5 to 4.0 mg/kg micafungin in 13 week repeat-dose toxicity studies; and the NOAEL in dogs was 3.2 mg/kg micafungin in a 39 week repeat-dose study, and 10 mg/kg in a 13 weeks study.

The minimum lethal dose of micafungin in rats was 125 mg/kg, equivalent to 8.1 times the recommended human clinical dose for esophageal candidiasis, based on body surface area comparisons. The minimum lethal dose in dogs was > 200 mg/kg micafungin.

Overall, none of the toxicity studies in animals indicated a safety concern at the clinically relevant doses of micafungin (50 or 150 mg/day) in humans. However, as discussed in the integrated summary of safety, potential safety concerns for human use identified in the micafungin safety database include serious allergic reactions, anaphylaxis and anaphylactoid reactions, clinical hepatic adverse events and liver function test abnormalities, hemolysis or hemolytic anemia, renal failure or impairment and abnormalities in serum BUN and creatinine, injection site reactions and allergic or histamine-type reactions.

4 DATA SOURCES, REVIEW STRATEGY AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data for this review included the clinical trials conducted by the applicant or designee in support of this application (NDA 21-754), and those submitted previously for NDA 21-506, _____ Data from the resubmission

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of NDA 21-506 (micafungin for prophylaxis of *Candida* infections), reviewed by Dr. Joette Meyer, was also consulted for this review.

Additionally, in August, 2004, the applicant submitted a 120-day safety update for NDA 21-754, which included the data for the phase 3 clinical study 03-7-005, which was subsequently determined to be a pivotal study for the demonstration of micafungin efficacy in the treatment of esophageal candidiasis. Additional sources of clinical information regarding micafungin included literature reviews provided by the applicant, and those performed by the medical reviewers.

Micafungin postmarketing safety data from Japan was provided by the applicant in periodic safety updates (PSUR-2 and PSUR-3) with the original submission, and with the 120-day safety update, respectively. A consultation with Office of Drug Safety (ODS) was obtained for additional review of this postmarketing safety data from Japan. Additionally, Dr. John Senior, a hepatologist, and reviewer in ODS, was consulted for review of the micafungin hepatic safety data provided with this submission. These consultations are appended to this review in section 10.

Additional consultations obtained within the Agency included those from DDMAC regarding the micafungin package insert, DMETS, regarding the carton and vial labeling, and Office of Pharmaceutical Sciences (OPS) for product quality microbiology.

4.2 Tables of Clinical Studies

A total of 32 clinical studies performed by the applicant were submitted for the micafungin safety database for this NDA, as summarized in the table below. Included in this table but not in the safety database, was study 04-0-193, a pharmacokinetic drug-interaction study (micafungin-voriconazole) for which safety data was appended to the 120-day safety update but a formal study report has not been submitted.

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Table 1. Clinical Studies included in the Micafungin Safety Database (Applicant's Appendix 2.7.4.7, 120-day Safety Update, August, 2004)

Type of Study	SD/RD	Country	Study	Subjects
Pharmacokinetic Studies				
Pharmacokinetic, dose-toxicity	SD	Japan	FJ-463-0001	Healthy volunteers
Pharmacokinetic ¹⁴ C-FK463	SD	US	97-0-040	Healthy volunteers
Pharmacokinetic ¹⁴ C-FK463	SD	UK	FG-463-21-14† (NEW)	Healthy volunteers
Pharmacokinetic	RD	Japan	FJ-463-0002	Healthy volunteers
Pharmacokinetic	SD & RD	Japan	FJ-463-0003	Healthy volunteers
Pharmacokinetic	SD	Japan	FJ-463-0004	Healthy elderly and non-elderly volunteers
Pharmacokinetic	SD	US	01-0-170	Healthy volunteers with renal impairment
Pharmacokinetic	SD	US	01-0-111	Healthy volunteers with hepatic impairment
Pharmacokinetic & Safety	SD	US	99-0-063	Healthy volunteers
Pharmacokinetic, FK463-prednisolone interaction	SD	UK	FG-463-21-06	Healthy volunteers
Pharmacokinetic, FK463-tacrolimus interaction	SD	UK	FG-463-21-04	Healthy volunteers
Pharmacodynamic, FK463-tetracycline interaction	RD	US	01-0-103	Healthy volunteers
Pharmacokinetic, FK463-Nesacel® interaction	SD	UK	FG-463-21-05	Healthy volunteers
Pharmacokinetic, FK463-cyclosporine interaction	RD	US	01-0-104	Healthy volunteers
Pharmacokinetic, FK463-irinotecan interaction	RD	US	03-0-173	Healthy volunteers
Pharmacokinetic, FK463-mycophenolate mofetil interaction	RD	US	03-0-176	Healthy volunteers
Pharmacokinetic, FK463-nifedipine interaction	RD	US	03-0-178	Healthy volunteers
Pharmacokinetic, FK463-ritonavir interaction	SD	UK	FG-463-21-15	Healthy volunteers
Pharmacokinetic, FK463-fluconazole interaction	RD	US	03-0-177	Healthy volunteers
Pharmacokinetic, FK463-clarithromycin interaction	SD	UK	FG-463-21-16	Healthy volunteers
Pharmacokinetic, FK463-verapamil interaction	RD	US	04-0-193†† (NEW)	Healthy volunteers

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Table 1 (continued) Clinical Studies included in the Micafungin Safety Database (Applicant's Appendix 2.7.4.7, 120-day Safety Update, August, 2004)

Type of Study	Country	Study	Subjects
Efficacy and Safety Studies			
Efficacy and safety in esophageal candidiasis versus fluconazole	S. Africa, Brazil, Peru	03-7-005† (NEW)	Adult patients with confirmed esophageal candidiasis
Efficacy, MED & safety in esophageal candidiasis	S. Africa	97-7-003‡	Adult, HIV-positive patients with confirmed esophageal candidiasis
Dose response, efficacy & safety in esophageal candidiasis	S. America, S. Africa	FG-463-21-09	Adult HIV-positive patients with confirmed esophageal candidiasis
Efficacy & safety in candidemia, invasive candidiasis	Multinational	98-0-047§ [FG-463-21-02]	Adult & pediatric patients with candidemia and invasive candidiasis
Efficacy and safety versus placebo as prophylaxis for invasive fungal infection	US, Canada	01-0-124†† (NEW)	Adult patients in the intensive care unit
Efficacy, safety, pharmacokinetics, & MTD in prophylaxis	US	97-0-041§	Adult allogeneic or autologous bone marrow or peripheral stem cell transplant recipients
Safety, pharmacokinetics, & MTD in prophylaxis	US	98-0-043§	Pediatric febrile and neutropenic patients who had one of the following: leukemia, lymphoma, bone marrow or peripheral stem cell transplant, aplastic anemia, myelodysplastic syndrome
Safety, pharmacokinetics, & MTD in prophylaxis	UK	FG-463-21-03	Adults scheduled to undergo bone marrow or peripheral stem cell transplantation
Efficacy & safety in prophylaxis	US, Canada	98-0-050 [NIAID MSG-46]	Adult & pediatric hematopoietic stem cell transplant recipients
Efficacy, safety & pharmacokinetics in invasive aspergillosis	Japan	FJ-463-0003††	Adult with deep mycoses

Table continued on next page

Type of Study	Country	Study	Subjects
Open label, non-cooperative trial in invasive aspergillosis	US/Canada/ Europe	01-0-125†† (NEW)	Adults and children with proven/probable systemic Aspergillus infection
Efficacy & safety in invasive aspergillosis	Multinational	98-0-046§ [FG-463-21-03]	Adult & pediatric patients with invasive aspergillosis

SD: Single dose micafungin; RD: Repeated dose micafungin; MTD: maximum tolerated dose; MED: minimum effective dose; US: United States; UK: United Kingdom; HIV: human immunodeficiency virus; NIAID: National Institute of Allergy and Infectious Disease

† This study is a new study submitted in the 120-Day Safety Update in NDA 21-754; a final report for Studies 03-7-005 and FG-463-21-14 are provided in Attachments 6 and 7, respectively. Final reports for Studies 01-0-124 and 01-0-125 will be submitted to IND 55,322 when available.

†† This report was resubmitted in NDA 21-754 because it is one of the primary efficacy studies in esophageal candidiasis patients.

§ Interim reports were provided in NDA 21-506; final reports were included in NDA 21-754.

¶ Pharmacokinetic data from this study were re-analyzed at the request of the Division of Special Pathogen and Immunologic Drug Products during review of NDA 21-506.

††† An English Extended Synopsis was provided in NDA 21-506; a final, complete safety report was provided in NDA 21-754.

†††† Safety data from Study 04-0-193 is included in Appendix 4 of this 120-day safety update; this study is not included in the integrated safety database. A final study report will be submitted to IND 55,322 when available.

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For this review, two clinical studies were considered pivotal for the evaluation of micafungin efficacy for treatment of EC, as summarized in the table below.

Table 2. Pivotal Clinical Studies Submitted for NDA 21-754: Micafungin for Treatment of esophageal candidiasis (EC)

Study Protocol	Study Design	Number of Patients Enrolled	Patient Age range	Study Sites and Location	Dose	Duration of Treatment	Time of Relapse Evaluation
03-7-005	Phase 3, randomized, double-blind, active-controlled non-inferiority study	523 patients: micafungin (260); fluconazole (258)	≥ 16 years old	35 sites in South Africa, Brazil, and Peru	Micafungin 150 mg/day; Fluconazole 200 mg/day	14 - 42 days	2- and 4-weeks post-treatment
FG463-21-09	Phase 2, randomized, double-blind, active controlled, dose-ranging study	251 patients: micafungin 50 mg (65); micafungin 100 mg (64); micafungin 150 mg (60); fluconazole (62)	> 18 years old	24 sites in Brazil, Peru, and South Africa	Micafungin 50, 100, and 150 mg/day; Fluconazole 200 mg/day	14-21 days	2-weeks post-treatment

In addition to the two pivotal studies described above, two additional studies were submitted for this NDA. These were considered supportive studies for this review, and are described in Table 3 below.

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Table 3. Supportive Clinical Studies Submitted for NDA 21-754: Micafungin for Treatment of esophageal candidiasis

Study Protocol	Study Design	Number of Patients Enrolled	Patient Age range	Study Sites and Location	Dose	Duration of Treatment	Time of Relapse Evaluation
97-7-003	Phase 2, open-label, non-comparative dose de-escalation study to determine minimum effective dose	120 patients: micafungin 12.5 mg/day (26); 25 mg/day (22); 50 mg/day (26); 75 mg/day (22); 100 mg/day (24)	≥ 18 years old	9 sites in South Africa	Micafungin 12.5, 25, 50, 75, and 100 mg/day	14 days	2-weeks post-treatment
98-0-047†	Phase 2, open-label, non-comparative study for candidemia or invasive candidiasis	357 patients (99 evaluable patients with EC)	Adults and children	62 sites worldwide	Initial dose 50 mg/day or 100 mg/day with dose-escalation as needed	5 days to 6 weeks	6-weeks post-treatment

4.3 Review Strategy

For the esophageal candidiasis indication, studies 03-7-005, FG463-21-09, and 97-7-003 were reviewed for both safety and efficacy; while study 98-0-047 (micafungin for treatment of invasive candidiasis and candidemia) was reviewed only in regards to efficacy in EC for this review, except as included in the micafungin safety database. The micafungin safety database included all patients and volunteers who received micafungin in the 32 clinical studies listed in Table 1 above, with the exception of study 04-0-193, as noted previously.

Additional reviews completed for this NDA (and NDA 21-506) were performed by Microbiology, Pharmacology/Toxicology, Clinical Pharmacology and Biopharmaceutics

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and Statistical reviewers in the DSPIDP. Dr. Joette Meyer, Clinical Reviewer, reviewed the NDA 21-506 resubmission for *Candida* prophylaxis, which is pending approval simultaneously with NDA 21-754.

4.4 Data Quality and Integrity

No Division of Scientific Investigations (DSI) audit was requested to review the applicant's data/analyses, and no systematic audits of case report forms were performed for this review. Dr. Ekopimo Ibia previously performed an audit of a random 10% sample of case report forms for the original NDA 21-506 submission, and found no significant data discrepancies.

4.5 Compliance with Good Clinical Practices

All studies were conducted according to Good Clinical Practice, as noted in the Applicant's overview of the clinical development program for micafungin. Informed consent was obtained from participants in the clinical studies, and the trials were conducted in accordance with acceptable ethical standards. No site-specific issues or significant protocol violations were noted on review of the clinical studies submitted for this NDA.

4.6 Financial Disclosures

The applicant (Fujisawa Healthcare, Inc.) certified (FDA form 3454) that the listed clinical investigators did not participate in a financial arrangement with the study's sponsor, whereby the value of compensation to the investigator conducting the study could be affected by the outcome of the study. Additionally, the listed clinical investigators had no proprietary interest in this product or significant equity interest in the sponsor of the study; and were not the recipients of significant payments of other sorts.

5 CLINICAL PHARMACOLOGY

Please see Clinical Pharmacology and Biopharmaceutics Review by Drs. Jang-Ik Lee, Dakshina Chilukuri, and Philip Colangelo, submitted for NDA 21-754 and 21-506 (amendment) for full details of clinical pharmacology review. A brief summary of their findings is presented below.

5.1 Pharmacokinetics

General

Micafungin pharmacokinetics were linear over the range of 50 to 150 mg/day. In adults who received 150 mg/day micafungin the C_{max} was 16.4 ± 6.5 $\mu\text{g/mL}$, the AUC was 166.5 ± 40.4 $\mu\text{g}\cdot\text{hr/mL}$, the clearance was 17.5 ± 4.8 mL/hr/kg , and the $t_{1/2}$ was 15.2 ± 2.2 hr, as measured at steady state.

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Protein Binding and Metabolism

Micafungin is highly (> 99%) protein bound (primarily albumin, and to a lesser extent alpha-1-acid glycoprotein) *in vitro*, and *in vivo*, and is sequentially metabolized by arylsulfatase, followed by catechol-*O*-methyltransferase, or by hydroxylation via cytochrome P450 (CYP) isozymes. Micafungin is a substrate for and a weak inhibitor of CYP3A *in vitro*. Additionally, micafungin is not a P-glycoprotein substrate or inhibitor *in vitro*. Three major micafungin metabolites have been identified M1, M2, and M5. The latter is the most abundant, but has no antifungal activity; while the other two less common metabolites, M1 and M2, have similar antifungal activity to the parent compound. A number of other minor micafungin metabolites have also been identified.

Excretion

Following a single intravenous infusion of ¹⁴C-micafungin 25 mg to 6 healthy subjects, total radioactivity was eliminated primarily in the feces, with 71% of total radioactivity recovered at 28 days post-dose. Urinary excretion accounted for a mean of 11.6% of the dose at the end of the 28 day collection period.

Gender Differences

Micafungin exposure is greater in adult females than males for the same administered dose, with the mean C_{max} and AUC for a micafungin dose of 150 mg/day (at steady state) were greater by 23% for females than males. However, the terminal $t_{1/2}$ was shorter by 1.5 hours in females than in males. These differences are thought to be due to a lower mean body weight in females. In HIV patients with esophageal candidiasis, the mean weight-adjusted values of micafungin C_{max} , AUC/dose and clearance were comparable for males and females. No dose adjustment based on gender was recommended for micafungin.

Racial Differences

No notable differences in micafungin pharmacokinetic parameters were observed among black, Caucasian or Hispanic subjects. However, the micafungin AUC was 26% higher in Japanese subjects than in blacks, possibly due to lower mean body weight. No dose adjustment based on racial or ethnic origin was recommended for micafungin.

Pharmacokinetics in the Elderly and in Patients with Renal or Hepatic Dysfunction

Micafungin pharmacokinetics did not differ significantly between subjects older than age 65 years, and younger adults, and no dose adjustment of micafungin was recommended for elderly patients. In addition, micafungin AUC and C_{max} were not altered significantly in patients with severe renal dysfunction (creatinine clearance < 30 mL/min), or in patients with moderate (Child-Pugh score 7-9) hepatic dysfunction, and no dosing adjustments are recommended for patients with severe renal dysfunction or mild-moderate hepatic dysfunction. The pharmacokinetics of micafungin have not been studied, however, in patients with severe hepatic insufficiency.

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Pharmacokinetics in Pediatric Patients

The pharmacokinetics of micafungin was not adequately established in studies submitted for this NDA in pediatric patients between the ages of 2-16 years old, the age group relevant to both the esophageal candidiasis and *Candida* prophylaxis indications.

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5.2 Pharmacodynamics

Drug Interaction Studies

A total of 11 drug-drug interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between micafungin and mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir and rifampin. No interactions which altered the pharmacokinetics of micafungin were observed in these studies.

Micafungin (single- or multiple-dose) had no effect on the pharmacokinetics of mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole. However, the sirolimus AUC was increased by 21% in the presence of steady state micafungin compared to sirolimus alone. Additionally, the AUC and C_{max} for nifedipine were increased by 18% and 42%, respectively, in the presence of steady-state micafungin in comparison to nifedipine alone. The effects of micafungin on the pharmacokinetics of rifampin or ritonavir were not evaluated.

5.3 Exposure-Response Relationships

Exposure-response relationships for micafungin effectiveness and toxicity are discussed in detail in the pharmacometric review by Dr. Chilukuri. In brief, the effectiveness of micafungin for treatment of esophageal candidiasis increased with micafungin dose, with comparable responses (endoscopic or clinical endpoints) seen at doses of 100 or 150 mg/day in the analyses by the applicant (study FG463-21-09) and by Dr. Chilukuri for studies 03-7-005, FG463-21-09, and 97-7-003. However, fewer relapses of EC (2 weeks post-treatment) were noted with 150 mg/day than with 100 mg/day micafungin. Thus 150 mg/day micafungin was considered the optimal dose for treatment of EC.

In the esophageal candidiasis studies, 03-7-005, FG463-21-09, and 97-7-003, the relationship between micafungin dose and liver function test (AST, ALT, alkaline phosphatase, and bilirubin) abnormalities was explored. No statistically significant effect of micafungin dose on these laboratory tests was found; however, a trend toward

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increasing incidence of AST, ALT and alkaline phosphatase elevation was observed in patients who received 150 mg/day micafungin.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for micafungin in NDA 21-754, is treatment of esophageal candidiasis (EC).

6.1.1 Methods

The applicant originally submitted two phase 2 studies which were considered the pivotal studies for this NDA, study FG463-21-09, and study 97-7-003, in addition to a supportive study, 98-0-047. In August, 2004, an additional study, 03-7-005, a phase 3 comparative study, was submitted with the 120-day safety update. In this latter study, micafungin 150 mg/day was compared to fluconazole 200 mg/day for the treatment of esophageal candidiasis. For this review, 03-7-005 and FG463-21-09 were considered the pivotal studies for evaluation of micafungin efficacy for treatment of esophageal candidiasis. These studies are described in Table 2, section 4.1 above. Individual study reports are provided in Appendix 10 for studies FG463-21-09, 97-7-003, and 03-7-005, as well as a synopsis for the supportive study, 98-0-047, with respect to treatment of esophageal candidiasis.

6.1.2 Discussion of Endpoints

Study 03-7-005

Primary Endpoint

The primary endpoint was endoscopic response at end-of-therapy (EOT). Endoscopic grade 0 was considered resolution or cure of EC. Endoscopic grading scale is shown in Table 4 below.

Table 4. Endoscopic Grading Scale for Esophageal Candidiasis

Esophageal Mucosal grade	Description
0	No evidence of EC-associated plaques
1	Individual, raised plaques, each 2 mm in size or less
2	Multiple raised plaques more than 2 mm in size
3	Confluent plaques combined with ulceration

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***Medical Officer Comments:** The studies for fluconazole, itraconazole and voriconazole approval for EC used the original Kodsi scale; and studies for caspofungin approval used the modified Kodsi scale for the assignment of endoscopic grade. These grading scales are similar to that used in this study, with grade 0 indicating no lesions seen endoscopically. Most previous studies for evaluation of antifungal agents in treatment of EC have used EOT as the time point for endoscopic assessment of cure; while the study for caspofungin licensing used 5-7 days post-treatment for endoscopic assessment of EC. There is currently no FDA guidance document for industry regarding development of antifungal drugs for the treatment of esophageal candidiasis.*

Secondary Endpoints

Secondary efficacy endpoints included the following:

- Clinical response at EOT, with success defined as cleared or improved
- Mucosal response at EOT, with success defined as cleared or improved
- Overall therapeutic response at EOT
- Incidence of relapse at 2 weeks and 4 weeks post-treatment
- Changes in endoscopic assessment of EC at EOT compared to baseline
- Changes in clinical symptoms of EC at EOT compared to baseline
- Changes in clinical signs and symptoms of oropharyngeal candidiasis (OPC) at EOT compared to baseline

Clinical Response was based on assessment of the symptoms of EC (dysphagia, odynophagia, and retrosternal pain). Each symptom was assigned a grade of 0-3 as shown in Table 5 below.

Table 5. Grading of Clinical Symptoms of Esophageal Candidiasis (from Appendix B, study 03-7-005 report)

Parameter	Grade 0	Grade 1	Grade 2	Grade 3
Dysphagia	Swallows food normally	Swallows solid food with difficulty	Can swallow soft food or liquid only	Can swallow small amounts of liquid or cannot swallow
Odynophagia	None	Food causes pain; little or no pain with liquids	Liquids cause pain; will not eat solids	Small sips of liquids only; or will not swallow; spits
Retrosternal pain	None	Low grade intermittent or continuous pain	Continuous pain, soreness or burning; may require pain medication	Very painful; requires pain medication

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Definitions of **Clinical Response**:

Cleared: complete resolution of clinical symptoms (grade 0)

Improved: Improvement in clinical symptoms from baseline by a reduction of 2 or more in total grade, and no increase in grade for any symptom

Unchanged: Not cleared or improved, and no increase in grade for any symptom

Worse: Deterioration (increase in grade) from baseline of 1 or more clinical symptoms

Not evaluable: No increase in any clinical symptom of EC, and one or more missing EOT assessments

Mucosal Response was based on endoscopic assessment (see Table 5 above) at baseline and EOT and was defined as follows:

- **Cleared:** Mucosal grade =0
- **Improved:** Reduction of mucosal grade from baseline by 2 or more grades at the EOT
- **Unchanged:** mucosal grade > 0 and \leq baseline grade, but not reduced by more than 1 grade.
- **Worse:** Mucosal grade increased from baseline
- **Not evaluable:** Patients without a baseline or EOT endoscopic mucosal examination

Overall Therapeutic Response was based on clinical response and mucosal grade at EOT compared to baseline. Overall therapeutic success was defined as a clinical response of cleared or improved, and a mucosal response of cleared or improved at the EOT.

Relapse was assessed in patients who were considered an overall therapeutic success at the EOT. Relapse was defined as the worsening of EC, based on clinical symptoms and endoscopic evaluation, at 2- and 4- weeks post-treatment.

***Medical Officer Comments:** For this study, and for study FG463-21-09, the secondary endpoint, relapse of esophageal candidiasis, was re-analyzed by the medical officer and statistical review, to evaluate relapse only in patients who had both clinical and endoscopic resolution of esophageal candidiasis at end-of-therapy. Additionally, patients who received systemic antifungal therapy during the post-treatment period were considered EC relapses.*

Changes in endoscopic assessment at EOT compared to baseline was determined by calculating the difference between the mucosal grade (Table 5 above) at baseline and EOT.

Changes in clinical symptoms of EC at EOT compared to baseline was determined by calculating the difference in the sum of the grades (see Table 5 above) for each clinical symptom.

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Changes in clinical signs and symptoms of OPC at EOT compared to baseline was determined by calculating the differences in the sum of the OPC sign/symptom grades (shown in Table 6 below) at baseline and EOT.

Table 6. OPC Clinical Signs and Symptom Grades

Parameter	Grade 0	Grade 1	Grade 2	Grade 3
Plaques	No evidence of OPC-associated plaques	Individual raised plaques, each 2 mm in size or less	Multiple raised white plaques more than 2 mm in size	Confluent plaques
Inflammation	None	Slightly red	Very red	Dark red/scarlet
Fissures	None	Just visible	Prominent	Deep fissure/ulcers
Mouth pain	None	Slight discomfort	Can still eat	Unable to eat

Medical Officer Comments: OPC cure and relapse were not specifically analyzed by applicant, but data regarding OPC signs and symptom grade was collected systematically in this study, and were analyzed by the medical and statistical reviewers.

Mycological Response was defined prospectively in the protocol as follows:

- **Eradication:** negative fungal culture and negative histology at EOT
- **Persistence (colonization):** Positive Candida culture, negative histology, and mucosal grade = 0 at EOT
- **Persistence (invasive):** Positive Candida culture and positive histology at EOT
- **Not assessable:** Patients without EOT mucosal grade, EOT fungal culture, and/or EOT histology results.

This definition was revised upon blinded review of the outcome data to decrease the number of patients who were not assessable. The definition of mycological response above did not take into account that investigators were not required to perform a biopsy when mucosal grade was 0 at EOT; while a biopsy for histology was obtained in some instances. To reconcile these differences in investigator practice, the following scheme was utilized to determine mycological response (Table 7 below):

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Table 7. Definitions for Mycological Response

Mucosal Grade	Histology Result	Culture Result	Outcome
0 (Cleared)	Negative	Negative	Eradication
0 (Cleared)	Negative	Positive	Persistence, Colonization
0 (Cleared)	Negative	Not done	Persistence, presumed Colonization
0 (Cleared)	Positive	Negative/Not done	Persistence, Invasive
0 (Cleared)	Positive	Positive	Persistence, Invasive
0 (Cleared)	Not done	Negative	Eradication
0 (Cleared)	Not done	Positive	Persistence, Colonization
0 (Cleared)	Not done	Not done	Persistence, presumed Colonization
≥1	Negative	Negative	Eradication
≥1	Negative	Positive/Not done	Persistence, Colonization
≥1	Positive	Negative/Not done	Persistence, Invasive
≥1	Positive	Positive	Persistence, Invasive
≥1	Not done	Negative	Persistence, Invasive
≥1	Not done	Positive	Persistence, Invasive
≥1	Not done	Not done	Persistence, Invasive
Unknown	Negative	Negative	Eradication
Unknown	Negative	Positive	Persistence, Colonization
Unknown	Positive	Negative/Not done	Persistence, Invasive
Unknown	Not done	Negative/Not done	Not evaluable

Study FG463-21-09

Primary Endpoint:

The primary study endpoint was the endoscopic response rate, defined as the proportion of patients with resolution of endoscopic lesions (grade 0) at EOT. Endoscopic grades were defined as shown in Table 5 above for study 03-7-005.

Medical Officer's Comments: The primary endpoints for the two pivotal studies, 03-7-005 and FG463-21-09 were the same, endoscopic cure at the end-of-therapy. Endoscopic cure could be considered a surrogate marker for cure of EC, and is generally not used in clinical practice to evaluate EC outcome except in patients who remain symptomatic. However, endoscopic cure is probably the most sensitive and specific measure of EC cure, and correlates well with clinical cure.

Secondary Efficacy Endpoints:

- Proportion of patients with endoscopic grade 0 on day 14 of treatment
- Mycological response, defined as the proportion of patients with either fungal eradication or residual colonization at day 14 and EOT. Grading for mycological response was as follows:
 - Eradication: histology, cytology, and fungal cultures were negative
 - Persistence (colonization): histology and cytology were negative, but fungal culture was positive
 - Persistence (invasive): histology and cytology were positive, and fungal culture could be positive or negative.
- Clinical response at EOT, as determined by the investigator and defined as follows:
 - Cleared: resolution of signs and symptoms (grade 0)
 - Improved: reduction in clinical signs and symptoms by 2 or more grades

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- Unchanged/worse: no change or progression of clinical signs and symptoms
- Changes in the quantitative endoscopic assessment of esophageal candidiasis compared to baseline
- Changes in the quantitative clinical assessment of esophageal candidiasis compared to baseline. For quantification, each symptom (dysphagia, odynophagia, and retrosternal pain) was assigned a grade of either 0 (no symptom), 1, 2, or 3.
- Changes in the quantitative clinical assessment of oropharyngeal candidiasis compared to baseline. For quantification, each sign or symptom (fissures, mouth pain, inflammation and plaques) was assigned a grade of either 0 (no symptom), 1, 2, or 3.
- Incidence of disease progression at EOT based on both clinical and endoscopic assessment compared to baseline:
- Incidence of relapse of esophageal candidiasis by clinical assessment at 2 weeks post-treatment. Relapse was defined as follows: For patients who had positive clinical response (cleared or improved) at EOT, relapse was considered an increase in 2 or more grades, or grade 3 in the clinical assessment, or the patient required antifungal treatment (non-prophylactic) during the 2 week follow-up period.
- Overall therapeutic success, defined as resolution or improvement in both clinical signs and endoscopic grades from baseline to EOT.

***Medical Officer Comments:** The secondary endpoints were generally similar in both studies, except for evaluation of relapse. In study 03-7-005, relapse was evaluated in patients who were considered an overall therapeutic success at the end-of-therapy (clinically cleared or improved and endoscopically cured or improved) at 2- and 4-weeks after completion of study treatment. In study FG463-21-09, relapse was evaluated in patients who had a positive clinical response (cleared or improved at end-of-therapy) at 2 weeks post-treatment. Additionally, if patients required non-prophylactic antifungal medication during the follow-up period in the latter study, they were counted as relapses. Relapse data for this study was also re-analyzed by the medical officer and statistical reviewer as described for study 03-7-005 above.*

6.1.3 Study Design

Study 03-7-005

The pivotal study for this NDA, study 03-7-005 was a multicenter, multinational, randomized, double-blind, parallel group, non-inferiority study comparing micafungin to fluconazole for the treatment of EC. As such, this study would be considered an adequate, well-controlled study for evaluation of micafungin efficacy and safety. Fluconazole is currently considered the treatment of choice for esophageal candidiasis; while voriconazole, amphotericin B, and caspofungin are used for severe and/or refractory esophageal candidiasis (Guidelines for Treatment of Candidiasis, Pappas, et al.

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CID 2004; 38:161-189). Thus, fluconazole was the appropriate choice of comparator in this study. The methods of patient randomization and blinding, the prospective statistical analysis plan and identification of endpoints were appropriate in this study.

Study 03-7-005 was adequately designed to assess the benefit of micafungin for treatment of EC. In this study, 260 patients received micafungin, and 258 patients received fluconazole. The duration of therapy was for a minimum of 14 days, and a maximum of 42 days. Published clinical guidelines recommend 14-21 days of treatment for EC (Pappas, et al. CID 2004; 38:161-189), so the duration of treatment was appropriate in this study. Additionally, EC relapse was evaluated at 2- and 4-weeks post-therapy in study 03-7-005. EC is a relapsing disease in immunocompromised AIDS patients; and has been studied previously in patients treated with caspofungin or fluconazole at 14- and 28- days post-therapy (Cancidas® package insert). Thus, the 2- and 4-week post-treatment evaluation of relapse in this study was appropriate.

The entry criteria for this study were appropriate. Male and female patients with confirmed EC (by endoscopic evaluation and microbiological/histological criteria) over 16 years old were enrolled. Most patients had HIV and AIDS (> 90%) and were severely immunocompromised at baseline. Most patients had mild to moderate EC by baseline endoscopic grade and clinical symptom grade; while approximately one-third of patients in each treatment arm had severe EC. Thus, only limited conclusions can be drawn regarding efficacy of micafungin in treatment of severe EC. Although < 10% enrolled patients with had underlying diseases other than HIV, there is no reason to suspect that these results cannot be generalized to non-HIV patients because the clinical course of EC is similar in patients with HIV or other conditions which pre-dispose to EC, such as chronic corticosteroid therapy, and malignancy. Additionally, most enrolled patients (two-thirds) were black; while one-third were Caucasian or mestizo. The clinical course of EC in patients with AIDS is not known to differ by race, so the results from this study can probably be generalized to patients of any race/ethnic background.

The dose of micafungin used in study 03-7-005 was based on previous phase 2 studies, particularly FG463-21-09, which evaluated the efficacy and safety of several doses of micafungin (50-150 mg/day) in comparison to fluconazole. In this latter smaller study, the efficacy of micafungin 150 mg/day for treatment of EC was comparable to fluconazole 200 mg/day at end-of-therapy, and at follow-up. Higher doses of micafungin (> 150 mg/day) were used in previous pharmacokinetic and clinical studies without significant safety concerns.

Study FG463-21-09

Study FG463-21-09 was a phase 2, multicenter, double-blind, randomized, parallel group study comparing 3 doses of micafungin (50, 100, and 150 mg/day) to fluconazole for efficacy and safety in the treatment of EC. Pharmacokinetic profiles were also obtained during this study. A total of 251 patients were randomized into the 4 treatment groups. Sixty five patients were randomized to receive 50 mg/day micafungin, 64 patients to receive 100 mg/day micafungin, 60 patients to receive 150 mg/day micafungin, and 62

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patients to receive fluconazole. Methods for randomization, blinding, prospective statistical analysis plan, and identification of endpoints were appropriate in this study. A data safety monitoring board was created to periodically review data and make recommendations to the sponsor regarding trial modification or termination based on interim review of blinded safety data.

Study FG463-21-09 was designed to compare 3 different doses of micafungin with fluconazole. This study was not designed to evaluate non-inferiority to fluconazole, but sample sizes were adequate to investigate a dose-response relationship of micafungin and for a descriptive comparison to fluconazole for efficacy of EC treatment. In this study, the planned treatment period was 14 days, with extension to 21 days, if needed. The duration of therapy was appropriate, as discussed for study 03-7-005 above; however relapse was evaluated only at 2 weeks post-therapy in this study.; whereas evaluation at 2 and 4 weeks post-therapy would have been ideal.

Study entry requirements included patients at least 18 years old with HIV/AIDS, and with documented EC by clinical signs and symptoms, endoscopy, and microbiological/histological confirmation. This population is appropriate for the study of EC treatment because most cases of EC occur in severely immunocompromised patients with HIV/AIDS. Most enrolled patients had mild to moderate esophageal candidiasis at baseline, somewhat limiting conclusions regarding the efficacy of micafungin for treatment of severe EC. In this study, approximately one-half of enrolled patients were black, and one-half were Caucasian or Hispanic; but as noted above, the clinical course of EC in patients with AIDS is not known to differ by race, so we can probably generalize these results to patients of any race/ethnic background. Additionally, because the clinical course of EC is similar in patients with AIDS or other underlying condition, these results can be generalized to all patients with EC, regardless of underlying condition.

The doses of micafungin used in this study were appropriately based on results from a previous phase 2 study, 97-7-003 which evaluated doses of micafungin from 12.5 mg/day to 100 mg/day for treatment of EC, and showed a clear dose-response relationship, with the highest dose of micafungin (100 mg/day), showing the highest efficacy.

6.1.4 Efficacy Findings

Conclusions from the pivotal study, 03-7-005, as well as supporting studies FG463-21-09 and 97-7-003 are summarized individually in this section. Results from the studies were not pooled because of differences in micafungin dosing and study endpoints.

Study 03-7-005

Patient Demographics

Most patients in this study were black (68.3% overall) and from South Africa (71% overall). There were no significant differences between treatment groups for race, gender, or age, shown in Table 8 below. The Full Analysis Set (FAS) included all randomized

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patients who received at least one dose of micafungin, and is analogous to an intent-to-treat (ITT) population. The FAS was the population used for primary analysis of efficacy and safety in this study.

Table 8. Demographics (Applicant's Table 6, 03-7-005 Study Report) (FAS)

Parameter	Treatment Group	
	Micafungin (n=260)	Fluconazole (n=258)
Race		
Caucasian	38 (14.6%)	35 (13.6%)
Black	176 (67.7%)	178 (69.0%)
Mestizo	32 (12.3%)	29 (11.2%)
Other	14 (5.4%)	16 (6.2%)
Gender		
Male	131 (50.4%)	116 (45.0%)
Female	129 (49.6%)	142 (55.0%)
Age (years)		
Mean ±SD	37.2 ±10.59	37.5 ±11.16
Range	17.0 to 80.0	17.0 to 87.0

Patient base: all randomized patients who received at least one dose of study drug (Full Analysis Set).

n=total number of patients in each treatment group.

SD: standard deviation.

Other includes verbatim terms of Cape Colored (4 micafungin and 2 fluconazole patients), Colored (6 micafungin and 5 fluconazole patients), Mixed/Mixed Race (2 micafungin and 2 fluconazole patients), Mulatto (1 micafungin and 7 fluconazole patients), and Multiracial (1 micafungin patient).

Most patients in the study had underlying HIV disease (94% overall); while 15/260 micafungin-treated (5.8%), and 17/258 (6.6%) fluconazole-treated patients had other baseline conditions which pre-disposed them to EC. These conditions are listed in the individual study report, Appendix, section 10, this review. For patients with HIV, the mean CD₄ count was 109 ± 191 cells/mm³ in the micafungin group and 110 ± 182 cells/mm³ in the fluconazole group. Median CD₄ count was 39 cells/mm³ (micafungin group) and 37 cells/mm³ (fluconazole group).

Baseline Esophageal Candidiasis

Most patients had mild-moderate EC (grades 1 and 2) in each of the treatment group, and the mean EC symptom grade score was also similar for the two treatments, as shown in Table 9 below. No significant difference was noted between the treatment groups.

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Table 9. Characteristics of Esophageal Candidiasis at Baseline (adapted from Applicant's Table 7, study report)

Parameter	Micafungin N=260	Fluconazole N=258
Baseline Mucosal Grade:		
1	87 (33.5)	96 (37.2)
2	98 (37.7)	99 (38.4)
3	75 (28.8)	63 (24.4)
Total EC Symptom Grade:		
Mean ± SD	4.2 ± 1.84	4.3 ± 1.98
Range	1.0 to 9.0	1.0 to 9.0
Number of Prior EC Episodes		
0	225 (86.5)	225 (87.2)
1	25 (9.6)	23 (8.9)
2	7 (2.7)	6 (2.3)

SD= standard deviation

Most patients had *Candida albicans* isolated at baseline; while non- *albicans Candida* species were infrequent, and usually co-isolated with *C. albicans*. Baseline fungal culture data is shown in Table 10 below.

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Table 10. Baseline Fungal Culture Data (Full Analysis Set)

Baseline <i>Candida</i> isolate (s)	Micafungin N=260	Fluconazole N=258
	n (%)	n (%)
No organism isolated	31 (11.9)	27 (10.5)
<i>Candida albicans</i>	222 (85.4)	218 (84.5)
<i>C. albicans</i> and <i>C. glabrata</i>	5	4
<i>C. albicans</i> , <i>C. glabrata</i> , and <i>C. krusei</i>	1	1
<i>C. albicans</i> and <i>C. inconspicua</i>	1	0
<i>C. albicans</i> and <i>C. tropicalis</i>	1	1
<i>C. albicans</i> and <i>C. krusei</i>	0	2
<i>C. albicans</i> , <i>C. glabrata</i> , <i>Candia sp.</i> , and <i>C. tropicalis</i>	0	1
<i>C. kefyr</i>	1	0
<i>Candida species</i>	3	2
<i>C. parapsilosis</i>	0	1

N= number of patients in Full Analysis Set

n (%) = number and proportion of patients with isolate or combination of isolates at baseline

Primary Endpoint: Endoscopic Response at End-of-Therapy (EOT)

As shown in Table 11 below, endoscopic cure (grade 0) was achieved in 228/260 (87.7%) patients treated with micafungin, and in 227/258 (88.0%) patients treated with fluconazole in the full analysis set (FAS). Because the lower bound of the 95% confidence interval around the treatment difference is < 10%, micafungin was shown to be non-inferior to fluconazole for treatment of EC. Similar results are shown for the modified full-analysis set (MFAS), patients who had confirmed EC at baseline (analogous to a modified-intent-to-treat population); and somewhat higher cure rates in both treatment groups in the Per Protocol Set (PPS), patients with confirmed EC who received at least 10 doses of study drug, and who had no major protocol violations (evaluable patients). For all three analyses, the lower limit of the confidence interval was within the bounds of the pre-specified non-inferiority margin of 10%.

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Table 11. Summary of the Endoscopic Cure Rate at End of Therapy (Applicant's Table 8, 03-7-005 study report)

Treatment Outcome	Treatment		Treatment Difference	95% CI for Treatment Difference
	Micafungin	Fluconazole		
Full Analysis Set	n=260	n=258		
Success	228 (87.7%)	227 (88.0%)	-0.3%	[-5.9%,5.3%]
Failure	32 (12.3%)	31 (12.0%)		
Mucosal Grade >0	7 (2.7%)	10 (3.9%)		
Not Evaluable	25 (9.6%)	21 (8.1%)		
Modified Full Analysis Set	n=220	n=215		
Success	191 (86.8%)	188 (87.4%)	-0.6%	[-6.9%, 5.7%]
Failure	29 (13.2%)	27 (12.6%)		
Mucosal Grade >0	6 (2.7%)	10 (4.7%)		
Not Evaluable	23 (10.5%)	17 (7.9%)		
Per Protocol Set	n=189	n=192		
Success	183 (96.8%)	182 (94.8%)	2.0%	[-2.0%, 6.0%]
Failure	6 (3.2%)	10 (5.2%)		
Mucosal Grade >0	6 (3.2%)	10 (5.2%)		

Full Analysis Set: all randomized patients who received at least one dose of study drug.

Modified Full Analysis Set: all randomized patients who received at least one dose of study drug and had a positive histology or cytology at baseline.

Per Protocol Set: all randomized patients who received at least 10 doses of study drug, who had confirmed esophageal candidiasis at baseline, who had a baseline and end of therapy endoscopy performed, and who did not have major protocol deviations.

Endoscopic cure: mucosal grade=0 at end of therapy.

n=total number of patients in each treatment group in each analysis set.

95% Confidence Interval: the 95% CI for the difference in success is based on the large sample normal approximation.

Medical Officer Comments: In the FAS and MFAS, most failures were due to non-evaluability, which was due primarily to premature treatment discontinuation due to adverse events.

Secondary Endpoints

Clinical Response at End-of-Therapy

Clinical success was defined as "cleared" or "improved" for symptoms of EC (odynophagia, dysphagia, and retrosternal pain). Clinical failure included "unchanged", "worse", or not-evaluable. Clinical response at EOT is shown in Table 12 below. For each analysis set, micafungin was shown to be non-inferior to fluconazole for treatment of EC, using a non-inferiority margin of 10%.

Clinical Review

Mary E. Singer, M.D., Ph.D.

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 12. Clinical Success at EOT (“Cleared” or “Improved”) (adapted from Applicant’s Table 8, study report 03-7-005)

Clinical Response	Micafungin	Fluconazole	Treatment Difference*	95% Confidence Interval
FAS	N=260	N=258		
Success	245 (94.2)	244 (94.6)	-0.3 %	[-4.3%, 3.6%]
Cleared	239 (91.9)	237 (91.9)	0	
Improved	6 (2.3)	7 (2.7)	-0.4 %	
MFAS	N=220	N=215		
Success	206 (93.6)	206 (95.8)	-2.2 %	[-6.4%, 2.0%]
Cleared	200 (90.9)	199 (92.6)	-1.7 %	
Improved	6 (2.7)	7 (3.3)	-0.6 %	
PPS	N=189	N=192		
Success	187 (98.9)	189 (98.4)	0.5 %	[-1.8%, 2.8%]
Cleared	184 (97.4)	183 (95.3)	-1.5 %	
Improved	3 (1.6)	6 (3.1)	-0.5%	

N= number of patients in analysis set

FAS=full analysis set; MFAS= modified full analysis set; PPS=Per Protocol set

Medical Officer Comments: Efficacy results using this secondary endpoint support the conclusions drawn from the primary efficacy outcome measure, endoscopic cure at EOT.

Overall Therapeutic Response at EOT

Overall therapeutic response at EOT was defined by the Applicant as clinical success (EC symptoms “cleared” or “improved”) with an endoscopic response of “cleared” or “improved” at the end of treatment. Overall therapeutic response at EOT is shown in Table 13 below. For each analysis set, micafungin was shown to be non-inferior to fluconazole for treatment of EC, using the non-inferiority margin of 10%.

Clinical Review
 Mary E. Singer, M.D., Ph.D.
 Micafungin sodium for Esophageal Candidiasis
 Mycamine (Micafungin sodium)

Table 13. Overall Therapeutic Response at EOT (adapted from Applicant’s Tables 13.4.4.1.1, 13.4.4.1.2, and 13.4.4.1.3, study report 03-7-005)

Overall Therapeutic Response	Micafungin	Fluconazole	Treatment Difference (Micafungin-Fluconazole)	95% Confidence Interval
FAS	N=260	N=258		
Success	227 (87.3%)	225 (87.2%)	0.1	[-5.6%, 5.8%]
Failure	33 (12.7%)	33 (12.8%)		
MFAS	N= 220	N=215		
Success	190 (86.4%)	187 (87.0%)	-0.6	[-7.0%, 5.8%]
Failure	30 (13.6%)	28 (13.0%)		
PPS	N=189	N=192		
Success	182 (96.3%)	181 (94.3%)	2.0%	[-2.2%, 6.3%]
Failure	7 (3.7%)	11 (5.7%)		

N= number of patients in analysis set

FAS= full analysis set; MFAS= modified full analysis set; PPS= per protocol set

Medical Officer Comments: The Applicant analyzed EC relapse in patients with overall therapeutic success. However, in the medical officer’s opinion, only patients with overall therapeutic cure, defined as those patients with an endoscopic grade of 0 and clinically “cleared” at the end-of-treatment would be more appropriate for relapse evaluation, as shown below.

These data were re-analyzed using the definition above for overall therapeutic cure, endoscopic cure (grade 0) plus clinical cure (“cleared”), as shown in the table below. These data support the conclusions drawn from the primary efficacy analysis.

Table 14. Overall Therapeutic Cure at EOT in FAS (Analysis by Medical Officer and Statistical Reviewer)

	Micafungin N=260	Fluconazole N=258	Treatment Difference (Micafungin-Fluconazole)	95% Confidence Interval
	n (%)	n (%)		
Overall Therapeutic Cure*	223 (85.8)	220 (85.3)	0.5	[-5.6, +6.6%]

* Overall therapeutic cure was defined as patients with endoscopic grade 0 and clinical “cleared” at EOT.

n (%) = number and proportion of patients with overall therapeutic cure.

Medical Officer Comments: The proportion of patients with overall therapeutic “cure” did not differ significantly from the proportion with overall therapeutic