

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Patient 033871 was a 29 year old Caucasian male with AIDS who received micafungin for 40 days starting at 50 mg/day and increased to 100 mg/day for esophageal candidiasis in study 98-0-047. Pancytopenia, possibly related to study drug, was reported on study day 27. A narrative summary was not available for this patient, and information was obtained from a patient profile provided by the applicant. Other serious adverse events reported the same day included severe anemia, hypokalemia, and increased cough. Pneumonia was reported as a serious adverse event on study day 38, and the patient died on day 44 due to progression of AIDS. Baseline conditions were reported as diarrhea, anemia, hyponatremia, fever, dehydration, alkaline phosphatase increased, back pain, allergic reaction, SIADH, pain, cachexia, arthralgia and hypocalcemia. The patient received multiple concomitant medications including procrit for anemia, azithromycin, oxandrin, rifampin, isoniazid, myambutol (for *Mycobacterium kansasii* bloodstream infection), ceftriaxone, celecoxib, fentanyl, morphine, and liposomal amphotericin B (startin day 37), G-CSF, and atovaquone. In addition, the patient required blood transfusion on study days 1 and 9. Laboratory values for this patient are shown in the table below.

**APPEARS THIS WAY
ON ORIGINAL**

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

Laboratory Values for Patient 033871*

Study Day	WBC X 10 ⁹	Hemoglobin g/dL	Hematocrit %	Platelets X 10 ⁹
Baseline	9.0	9.3	31.4	150
Day 6	4.2	7.8	25.9	192
Day 14	3.7	7.7	25.3	231
Day 21	2.4	6.5	20.9	156
Day 28	1.6	6.1	20.0	126
Day 31	1.9	6.1	18.7	80
Day 34	1.7	9.4	29.7	43
Day 38	2.4	7.1	22.5	47
Day 42	2.5	10.9	33.1	62

*Normal laboratory values are provided in the Appendix, section 10.1.5.

Medical Officer Comments: This patient had baseline anemia, and decreases in all three hematopoietic cell lines during micafungin treatment. However, he was treated at the same time for Mycobacterium kansasii, which could cause pancytopenia if the bone marrow was infected. I would agree that the pancytopenia may have been related to micafungin, but more likely due to the mycobacterial infection.

Thrombotic Thrombocytopenic Purpura (TTP)

One case of TTP was reported in the safety database, and is reviewed below:

Patient 068014 was a 41 year old Caucasian male with acute myelogenous leukemia, who received an autologous bone marrow transplant. He received micafungin 312 mg/day for 28 days in study FGMTD. A narrative summary was not available for this patient, and information was obtained from a patient profile provided by the applicant. Thrombotic thrombocytopenic purpura was reported as an adverse event on study day 29, and was considered unrelated to micafungin. Multiple other adverse events were reported during the study, but none were considered serious. The patient received multiple concomitant medications during micafungin dosing, including (but not limited to) tazocin, gentamicin, cyclosporine, methotrexate, G-CSF, pantoprazole, ciprofloxacin, heparin, amikacin, meropenem, acyclovir, vancomycin, and phenytoin, ganciclovir, and tacrolimus. The patient was leukopenic at baseline, and remained so throughout the study. Baseline platelet count was 55 x 10⁹/L and remained low throughout the study, with the lowest platelet count reported as 6 x 10⁹/L on study day 26. The patient was anemic at baseline with a hemoglobin and hematocrit of 8.5g/dL and 23.7%, respectively, at baseline. These reached a nadir on study day 12, at 6.9 g/dL and 19.9%. The patient required multiple blood transfusions. Throughout the study, bilirubin increased from 0.6 mg/dL at baseline to 9.95 mg/dL on day 28 and BUN and creatinine were 20 mg/dL and 0.9mg/dL, respectively, at baseline, and 76 mg/dL and 1.5 mg/dL on day 28. The patient profile did not contain information regarding the patient's neurologic status, or whether fragmented red blood cells were observed on a peripheral smear.

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

Medical Officer Comments: This case is very complex, the diagnosis of TTP cannot be confirmed, and insufficient information is available as to attribute TTP to micafungin.

Hemolysis or Hemolytic Anemia

As noted above, a number of micafungin-treated patients in the safety database of 2402 subjects experienced either hemolysis (2 patients), hemolytic anemia (3 patients), and 2 patients with abnormal erythrocytes. Three of these adverse events were considered serious and only one was considered drug-related. Patients with these adverse events are summarized in the following table.

**APPEARS THIS WAY
ON ORIGINAL**

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

Table 157. Patients with Hemolysis, Hemolytic Anemia or Abnormal Erythrocytes reported as Adverse Event in Safety Database

Patient Number (Age and gender)	Study Protocol and indication for micafungin	Micafungin dose and duration	Serious Adverse Event?	Adverse Event and study day of onset	Relationship to Micafungin *	Outcome
114771	98-0-046 invasive pulmonary aspergillosis	75 mg/day (30 days)	Yes	Hemolysis (day 26)	Possible	Persistent; death day 39 due to endocarditis
0323004	98-0-050	50 mg/day (15 days)	Yes	Hemolysis (day 17)	Not related	Persistent; death day 22 due to shock
0162501	98-0-050	50 mg/day (10 days)	No	Hemolytic anemia	Not related	Persistent at end of study
084784	98-0-046	75 mg/day (27 days)	No	Hemolytic anemia (day 6)	Not related	Recovered
290773	98-0-046	75-225 mg/day (108 days)	No	Hemolytic anemia (day 41)	Not related	Recovered
1412501	98-0-050	50 mg/day (28 days)	No	Erythrocytes abnormal (erythrocytopenia) (day 11)	Not related	Recovered
037874	98-0-047	100-150 mg/day (24 days)	Yes	Erythrocytes abnormal (RBC fragmentation) (day 15)	Not related	Persistent; death day 26 due to gastrointestinal hemorrhage

*investigator assessment of relationship to study drug

Medical Officer Comments: Each of the adverse events indicating hemolysis occurred in seriously ill patients with multiple concomitant medical conditions and medications. However, acute intravascular hemolysis also occurred in a healthy volunteer who received micafungin in a phase 1 study, as reviewed below.

Clinically significant hemolysis occurred in a healthy volunteer in study FG463-21-06, a phase 1, open-label drug interaction study of micafungin 200 mg and prednisolone 20 mg (subject #24). This subject experience an adverse event noted as hemoglobinuria on the case

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

report form, and was subsequently diagnosed with intravascular hemolysis. A narrative summary for this subject is provided below.

Narrative Summaries for Subjects and Patients with Serious Adverse Events of Hemolysis, Hemolytic Anemia, or Abnormal Erythrocytes

Subject 24 was a subject enrolled in study FG463-21-06, a phase 1 study to evaluate the pharmacokinetic interaction between multiple oral doses of prednisolone and single intravenous doses of micafungin in healthy male subjects, in which twenty four subjects were enrolled. Each subject received a single dose of micafungin (200 mg) administered as a one-hour infusion on day 1 and day 12, and single oral doses of prednisolone (20 mg) on days 5 through 14. This subject experienced no adverse events with first dose of micafungin, but during the second dose on day 12, he experienced transient headache, back pain, sweating, nausea and chest tightness. These symptoms were accompanied by transient tachycardia and increased blood pressure. The subject also experienced dizziness that started approximately 15 minutes after the micafungin infusion ended, and lasted for more than 8 hours. Several hours after the end of the micafungin infusion, the subject's urine was noted to be red. Subsequent testing of the urine revealed hemoglobinuria, which cleared by 6.5 hours after the micafungin infusion. Laboratory data revealed evidence of hemolysis in plasma up to 4 hours after the start of micafungin infusion, but none thereafter. No anemia was noted after the episode of hemolysis. The adverse event was initially described as hemoglobinuria. Both the investigator and a consulting hematologist considered the event to be mild and non-serious, and possibly related to micafungin.

A direct Coombs test was negative for IgG, but positive for C3D complement. The subject was further evaluated for any predisposition to intravascular hemolysis. He was of Moroccan and Caucasian descent. Glucose-6-phosphate dehydrogenase was normal, and cold agglutinin titer was negative. Immunotyping of the subject's RBCs showed normal expression of glucose-6-phosphate isomerase-linked antigens, excluding paroxysmal nocturnal hemoglobinuria. No underlying predisposition to intravascular hemolysis was identified.

Medical Officer Comments: Hemolysis has not been associated with prednisolone, and if the subject had no predisposing conditions that would make him more susceptible to hemolysis, this adverse event was almost certainly related to micafungin.

Patient 114771 was a 60 year-old black male who was receiving immunosuppressive therapy (prednisone and cyclosporine) following a heart and kidney transplant. Other baseline conditions included diabetes, mellitus, restrictive lung disease, hypertension, mitral valve regurgitation, chronic renal failure, and anemia. He received micafungin 75 mg/day for 30 days in addition to liposomal amphotericin B 400 mg/day for pulmonary aspergillosis. Hemolysis, considered possibly related to micafungin, was reported as a serious adverse event on study day 26. Other adverse events reported included

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

hyponatremia, kidney failure, depression, sepsis, (*Staphylococcus epidermidis* bacteremia on day 23), fever, hyperkalemia, hypotension, *Pseudomonas* pneumonia, respiratory failure, and thrombocytopenia. Multiple concomitant medications were administered during the study. The patient died on day 39, with fungal endocarditis listed as the primary cause of death. Pertinent laboratory data for this patient is shown in the table below.

Laboratory Values for Patient 114771*

Study Day	WBC x 10 ⁹	Hemoglobin g/dL	Hematocrit %	Platelets x 10 ⁹	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL
Baseline	8.4	8.5	25.8	169	18	1.4	0.6
Day 8	11.6	8.4	25.6	295	24	1.6	0.6
Day 14	9.1	8.7	27.1	264	24	1.9	--
Day 23	9.8	7.3	22.8	266	35	1.6	0.7
Day 26	15.1	6.6	20.1	261	--	--	--
Day 27	11.5	7.8	22.4	217	63	2.4	2.8 (day 28)
Day 31	11.3	7.8	23.6	162	90	3.0	--

*Normal laboratory values are provided in the Appendix, section 10.1.5.

Medical Officer Comments: This patient had anemia at baseline, and worsened during treatment with micafungin. No information was provided regarding how the diagnosis of hemolysis was made, but bilirubinemia in absence of significant increases in other liver enzymes, is suggestive of hemolysis. Whether micafungin was related to this adverse event is difficult to judge, because of multiple confounding factors.

Patient 323004 was a 38 year-old Caucasian female with chronic myelogenous leukemia who received micafungin 50 mg/day for 15 days as antifungal prophylaxis during conditioning for an allogeneic bone marrow transplant in study 98-0-050. Significant baseline conditions included anemia, increased cough, asthenia, hypocalcemia, and sinusitis. The bone marrow transplant was performed on study day 6. Hemolysis was reported as a serious adverse event on study day 17, but was considered related to a blood transfusion. Other serious adverse events reported at that time included sepsis, respiratory distress syndrome. Hypotension was reported the following day. This patient received multiple concomitant medications, some of which included dexamethasone, cyclophosphamide (chemotherapy), levofloxacin, acyclovir, cyclosporine, methotrexate, leucovorin, maxipime, and others. She received amphotericin B, followed by Abelcet® after discontinuation of micafungin for a suspected fungal infection. The patient did not achieve neutrophil recovery, and died on day 22 due to shock and multiorgan failure. Laboratory data for this patient is shown in the following table.

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

Laboratory Values for Patient 0323004*

Study day	WBC x 10 ⁹	Hemoglobin g/dL	Hematocrit %	Platelets x 10 ⁹	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL
Baseline	19.5	12.8	38	352	8	0.5	0.7
Day 6	4.1	10.3	30	259	10	0.5	0.7
Day 12	0.1	11.9	35	18	11	0.5	1.3
Day 16	0.2	5.6	15	26	19	0.6	19.6
Day 20	0.8	9.7	27	18	98	2.7	26.1

*Normal laboratory values are provided in the Appendix, section 10.1.5.

Medical Officer Comments: *This patient developed neutropenia and thrombocytopenia after chemotherapy which had started simultaneously with micafungin. Severe anemia was observed on study day 15, and hemolysis reported on day 17 simultaneously with sepsis and later, hypotension. No details are provided regarding how the diagnosis of hemolysis was made. Bilirubin levels increased significantly in the absence of transaminase or alkaline phosphatase elevation, as did BUN and creatinine. According to the narrative summary provided by the applicant, the hemolysis was due to a blood transfusion, but no further details are provided. Although micafungin could certainly be implicated in the development of hemolysis, insufficient information is provided to make that judgement.*

Patient 0374874 was a 49 year-old Oriental male who received an allogeneic bone marrow transplant for acute myelogenous leukemia. The patient received micafungin (100 mg/day increased to 150 mg/day) for 24 days for candidemia in protocol 98-0-047. Ambisome® was added to micafungin starting on study day 13. “Abnormal erythrocytes” was reported as a serious adverse event on study day 14, considered not related to micafungin. Other adverse events during the treatment period included *Enterococcus faecalis* bacteremia, cytomegalovirus viremia, and gastrointestinal bleeding. The patient died on study day 26 due to the latter. Significant baseline conditions included graft versus host disease (grade IV), involving the skin, liver and gastrointestinal tract, bilirubinemia, hypertension, pancytopenia, rheumatoid arthritis, thrombotic thrombocytopenic purpura (TTP), liver and renal failure. Some of the patients multiple concomitant medications included cyclosporine, mycophenolate mofetil, intravenous immunoglobulin, rabbit anti-thymocyte globulin, vincristine, nifedipine, ganciclovir, pentamidine, and others. Baseline hemoglobin was 11.8 g/dL, and hematocrit 34%, and by study day 7 was 7.5 g/dL and 21.6%, respectively.

Medical Officer Comments: *This patient had TTP at baseline which could account for abnormal erythrocytes. Additionally, the patient had received a number of blood transfusions prior to starting micafungin. There are too many confounding factors in this case to attribute “abnormal erythrocytes” to micafungin.*

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Deaths due to Hematological Adverse Events

A total of 25/2402 (1.0%) micafungin-treated subjects died due to hematologic adverse events in the safety database. Most of the deaths were due to leukemia or lymphoma (11 deaths due to AML, 4 due to leukemia, 3 due to CLL, 3 due to lymphoma, 1 due to acute leukemia, and 1 due to CML). Two deaths were not related to hematologic malignancy, including 1 due to coagulation disorder and 1 due to thrombocytopenia. One patient death due to pulmonary hemorrhage as a result of pancytopenia was considered possibly related to micafungin. See narrative summaries for these patients below.

In fluconazole-controlled studies, 2/932 (0.2%) micafungin-treated patients, and 4/787 (0.5%) fluconazole-treated patients died to hematologic adverse events, as shown in the following table.

Table 158. Deaths due to Hematological Adverse Events in Fluconazole-controlled studies* (adapted from Applicant's Table R8 1.2, November 1, 2004)

Hemic and Lymphatic System Adverse Event (COSTART Term)	Micafungin-treated (N=932)	Fluconazole-treated (N=787)
Any adverse event	2 (0.2)	4 (0.5)
Acute myeloblastic leukemia	0 (0)	1 (0.1)
Anemia	0 (0)	1 (0.1)
Leukopenia	0 (0)	1 (0.1)
Lymphoma-like reaction	0 (0)	1 (0.1)
Chronic lymphocytic leukemia	1 (0.1)	0 (0)
Thrombocytopenia	1 (0.1)	0 (0)

*studies 97-0-041, 98-0-050, 03-7-005, FG463-21-09

Medical Officer Comments: See narrative summary for patient who died due to thrombocytopenia below.

Narrative Summaries for Patients who died due to Hematological Adverse Events

One patient's death due to pulmonary hemorrhage secondary to pancytopenia was considered to be related to study drug. This death was previously reported in NDA 21-506. This death occurred in Patient Number 466171 enrolled in Study 98-0-046 who had pulmonary aspergillosis, and died on day 14 due to pancytopenia and pulmonary hemorrhage. He was previously treated with amphotericin B 0.32 mg/kg per day and 5-flucytosine 6400 mg per day, and received 10 doses of micafungin (75 mg per day) through day 6 and 150 mg per day through day 10. Although 5-flucytosine is known to cause pancytopenia, the investigator could not exclude the possibility that the pancytopenia was possibly related to micafungin administration.

Medical Officer Comments: Pancytopenia in this patient could be attributed to several factors: flucytosine, sepsis, or the investigational drug. The onset of fatal pulmonary hemorrhage could be a consequence of the pancytopenia or could be

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

due to invasive pulmonary aspergillosis. Aspergillus is an angioinvasive organism well known to cause mycotic aneurysms. Pulmonary hemorrhage can occur in patients with progressive aspergillosis or paradoxically, in patients following neutrophil recovery due to inflammatory cell infiltration at the site of infection.

Patient 3120 was a 49 year-old Hispanic male with AIDS, treated with micafungin 50 mg/day for 3 days for esophageal candidiasis in study FG463-21-09. Please see narrative summary for this patient in study FG463-21-09 review. This patient had developed Cryptococcal meningitis and intracranial hypertension during the study, micafungin was discontinued on day 3, at which time amphotericin B was started. Thrombocytopenia, which was listed as the primary cause of death, was initially reported as a serious adverse event on study day 17, and the patient died on study day 41.

Medical Officer Comments: The time course of these events does not implicate micafungin as the cause of thrombocytopenia.

Patient 5904 was a 51 year-old male with HIV who received micafungin 50-75 mg/day for 17 days for candidemia in study FJ0003. A narrative summary was not available for this patient, and information was obtained from the patient profile provided by the applicant. Baseline conditions were reported as pulmonary edema, hypoproteinemia, infection, sarcoma, and lymphoma. Coagulation disorder was reported as a serious adverse event on study day 4, and was listed as the cause of death on day 19. Neither the death nor the adverse event was considered related to study drug. Other serious adverse events reported during the study included bilirubinemia, ascites, pleural effusion, increased BUN and creatinine. Concomitant medications were not listed. On review of laboratory data, the patient was pancytopenic at baseline, with little change during micafungin treatment. Bilirubin was 2.5 mg/dL at baseline, and increased to 29 mg/dL by day 18, with moderate elevation of AST (181 U/L) and alkaline phosphatase (464 U/L). AST and alkaline phosphatase were somewhat elevated at baseline (121 /L, and 264 U/L), respectively. Prothrombin time values were not provided.

Medical Officer Comment: The coagulation disorder in this case was most likely related to liver disease, which appeared to worsen during treatment. Insufficient information was provided to assess whether any of these adverse events was related to micafungin.

Discontinuation of Micafungin due to Hematological Adverse Events

A total of 14/1980 (0.7%) micafungin-treated patients discontinued micafungin due to hematologic adverse events, 8 (0.4%) of these events were considered drug-related. Micafungin was not discontinued in any healthy volunteer due to a hematological adverse event. Adverse events in this category resulting in micafungin discontinuation are shown in the table below. The most common events resulting in micafungin discontinuation were leukopenia and thrombocytopenia.

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

Table 159. Hematologic Adverse Events Resulting in Micafungin Discontinuation
 (adapted from applicant's Appendix 9.1.2, 120-day Safety Update)

Hemic and Lymphatic System Adverse Event (COSTART Term)	Micafungin-treated Patients N=1980	Drug-related Adverse Events in Micafungin-treated Patients N=1980
Any adverse event	14 (0.7)	8 (0.4)
Leukopenia	5 (0.3)	3 (0.2)
Thrombocytopenia	4 (0.2)	3 (0.2)
Pancytopenia	2 (0.1)	2 (0.1)
Chronic lymphocytic leukemia	1 (0.1)	0
Coagulation disorder	1 (0.1)	0
Leukemia	1 (0.1)	0

Additional hematologic adverse events resulting in micafungin dose reduction or interruption occurred in 7/1980 (0.4%) patients. Those events included leukopenia in 3 patients, anemia, cyanosis, hemolysis, and thrombocytopenia, each in 1 patient.

In the fluconazole-controlled studies, 2/932 (0.2%) micafungin-treated, and 2/787 (0.3%) fluconazole-treated patients discontinued study medication due to hematologic adverse events. Among the micafungin-treated patients, 1 patient discontinued the drug due to leukopenia and 1 due to pancytopenia; while both fluconazole-treated patients discontinued the drug due to leukopenia.

Medical Officer Comments: Leukopenia and thrombocytopenia were common baseline conditions in patients enrolled in these studies, particularly those with HIV disease, hematologic malignancies, or hematopoietic stem cell transplant recipients. Thus, attributing these adverse events to micafungin alone is difficult.

The applicant also analyzed incidence of adverse events leading to micafungin discontinuation by micafungin dose and duration. There were no hematologic adverse events reported among 606 patients who received at least 150 mg for at least 10 days, in contrast to 14/1796 (0.8%) patients who received less than 150 mg/day micafungin or for a shorter duration.

Medical Officer Comments: This analysis is limited by the differences in patient populations who received micafungin at higher doses, and for longer duration. For example, many of the patients who received higher doses either had HIV or a hematologic malignancy, and in both cases hematologic abnormalities are not unexpected and may have been present at baseline. Thus, no firm conclusions can be drawn regarding a dose relationship between hematologic adverse events and micafungin.

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

Hematologic Laboratory Abnormalities

For all micafungin-treated subjects, mean and median hemoglobin values did not change significantly from baseline to end-of-therapy. The mean baseline hemoglobin was 11.0 ± 2.5 g/dL (standard deviation), and the mean at the end-of-therapy was 10.8 ± 2.42 g/dL; while the median values were 10.6 and 10.8 g/dL at baseline and end-of-therapy, respectively. In fluconazole-controlled studies, the mean and median hemoglobin at baseline and end-of-therapy were not significantly different.

The applicant analyzed the shift in hemoglobin from baseline to end-of-therapy for all patients who received micafungin, as shown in the table below. At baseline 509/1917 (26.6%) patients had normal hemoglobin (≥ 11.5 g/dL); and at the end-of-therapy, 260/509 patients (51%) had a normal hemoglobin. For the 494 patients who had baseline hemoglobin of < 11.5 to 10 g/dL, 224 patients (45.3%) had lower hemoglobin at the end-of-therapy. For those with a baseline hemoglobin of 8 to < 10 g/dL, 114/715 patients (15.9%) had a lower hemoglobin at the end of therapy; and for patients with a baseline hemoglobin of 6.5 to < 8 g/dL, 12/163 (7.4%) had a lower hemoglobin at the end-of-therapy. Overall, 223/1917 had a hemoglobin value of < 8 at the end of therapy (compared to 199/1917 (10.4%) at baseline).

Table 160. Shift in hemoglobin from baseline to end of therapy during treatment with micafungin for all subjects (adapted from appendix 12.2, safety update).

TREATMENT	LABORATORY TEST CODE=HEMOGLOBIN							
	BASELINE	END OF THERAPY						
	NORMAL	LOW1	LOW2	LOW3	LOW4	NO DATA		
PK463	NORMAL	260	131	111	5	2	0	509
	LOW1	78	122	200	23	2	0	494
	LOW2	51	173	377	101	13	0	715
	LOW3	7	19	72	43	12	0	163
	LOW4	3	2	8	14	9	0	36
	NO DATA	0	0	0	0	0	0	0
	TOTAL	399	527	768	185	38	0	1917

ANY SUBJECT WHO RECEIVED PK463 IN COMBINATION WITH ANOTHER DRUG WAS CONSIDERED BR463.
 LLN=LOWER LIMIT OF NORMAL.
 PER HEMOGLOBIN (IN g/dL):
 NORMAL = \geq LLN (11.5 g/dL)
 LOW 1 = 10 TO $<$ LLN
 LOW 2 = 8 TO $<$ 10
 LOW 3 = 6.5 TO $<$ 8
 LOW 4 = $<$ 6.5

Medical Officer Comments: This type of analysis evaluates the population shifts in laboratory values over time, but does not determine changes for individual

Best Possible Copy

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

patients. However, significant changes in hemoglobin and other hematological parameters in patients with hematologic malignancy, who are receiving chemotherapy or a HSCT are not unexpected.

Overall, in subjects who received micafungin, the WBC decreased slightly from a mean of $6.6 \pm 8.7 \times 10^9/L$ to $5.5 \pm 5.8 \times 10^9/L$ at baseline and end-of therapy, respectively; while the median WBC decreased from $5.2 \times 10^9/L$ at baseline to $4.6 \times 10^9/L$ at the end-of treatment. In fluconazole-controlled studies, the mean and median WBC at baseline and end-of therapy was not significantly different.

Medical Officer Comments: Measures of central tendency for patient populations do not take into account individual patients who have significant outlying values.

Post-Marketing Hematologic Adverse Events

Dr. Adrienne Rothstein, from the ODS, reviewed the Japanese postmarketing experience with micafungin in consultation with the DSPIDP. Fifty eight (58) serious hematological adverse events were identified in the period from April, 2003 to April, 2004. These included 10 cases of hemolysis, 7 of leukopenia, 20 of anemia, 14 of thrombocytopenia, and 7 of pancytopenia or bone marrow depression.

For the serious cases of hemolysis, 5 were reported as hemolytic anemia, 2 as intravascular hemolysis, and 3 as hemolysis. In the latter cases, all 3 were assessed as possibly related to micafungin. For the 2 cases of intravascular hemolysis, 1 case was considered probably, and the other possibly related to micafungin. For the adverse events of hemolytic anemia the relationship to micafungin was determined to be probable (1 case), possible (3 cases), and unlikely (1 case).

For the 7 cases of leukopenia reviewed, 1 was reported as neutropenia, 1 as agranulocytosis, and 5 as leukopenia. For the latter, two events were probably related, 1 possibly, and 2 were unlikely related to micafungin. In each of these cases, the total WBC recovered after discontinuation of micafungin.

A total of 20 serious cases of anemia were identified during this time frame. However, insufficient information was available to assess a relationship to micafungin.

Fourteen serious cases of thrombocytopenia were identified through August 2004 by the applicant, including 2 cases of idiopathic thrombocytopenic purpura, and 1 cases of thrombocytopenic purpura, which was possibly related to micafungin. Insufficient information was available to determine a relationship to micafungin for the other adverse events.

Pancytopenia was reported as a serious adverse event in 6 cases, and bone marrow depression in 1 case, during this postmarketing period. The event of bone marrow depression was considered to be unlikely related to micafungin; while pancytopenia was unlikely in 4 cases, and an assessment could not be made for the other 2 cases.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Dr. Rothstein concluded that the proposed U.S. labeling for micafungin, which lists anemia, leucopenia, and thrombocytopenia as common adverse events in the ADVERSE EVENTS section, was adequate, except to consider adding hemolytic anemia in the section listing Japanese postmarketing events. Additionally, unlabeled hematological adverse events, such as TTP and ITP, should be monitored by ODS after micafungin approval.

***Medical Officer Comment:** Anemia, thrombocytopenia, and leukopenia were common adverse events in the clinical studies. These events were not unexpected in the patient populations studied (patients with hematological malignancies, HIV, or HSCT recipients). Pancytopenia was reported as an adverse event less commonly in the clinical studies than decreases in individual cell lines. TTP was identified rarely in the clinical database (1/2402 subjects), but has now been reported in the postmarketing experience. ITP was also observed with micafungin in the postmarketing period in Japan, but was not reported in the clinical trials safety database.*

Hemolysis was reported postmarketing as well as during the clinical studies in patients and in a healthy volunteer. Micafungin, like other echinocandins is a large lipopeptide which has surfactant activity, and has been shown to hemolyze rabbit red blood cells in vitro, as well as to cause hemolysis in dogs and rats. Thus, the occurrence of this adverse event in patients who receive micafungin is not entirely unexpected. We have proposed adding a PRECAUTION statement in the final micafungin label regarding hemolysis.

Conclusions Regarding Hematologic Safety of Micafungin

Leukopenia, anemia and thrombocytopenia were the most common hematological adverse events reported in the clinical studies with micafungin. Although some of these events were serious and considered related to micafungin, leukopenia, anemia, and thrombocytopenia are not unexpected in the patient population studied. Pancytopenia was reported less commonly in the clinical studies. Rare hematological adverse events such as ITP and TTP were reported in the postmarketing experience in Japan with micafungin. However, ITP was not reported, and TTP was reported only once in the clinical studies.

Hemolysis or hemolytic anemia was observed in preclinical studies, in a healthy volunteer, and in a number of patients who received micafungin in the clinical studies, as well as in patients identified in Japanese postmarketing surveillance for adverse events. Echinocandins have known surfactant activity, so there is a plausible mechanism whereby micafungin could cause hemolysis.

In the final product labeling, we propose to list leukopenia, thrombocytopenia, and anemia as common drug-related adverse events in the ADVERSE EVENTS section, and additionally, to add a PRECAUTION statement regarding hemolysis and hemolytic anemia.

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

7.1.12. 8 Infections Reported as Adverse Events

Infections were frequently reported as adverse events in these studies. Serious infections are not unexpected in these patient populations, including those with HIV/AIDS, hematologic or other malignancies, and transplant recipients. However, in studies FG 463-21-09 and 03-7-005, the pivotal studies for this NDA, more tuberculosis and pneumonia were reported in patients treated with micafungin than fluconazole, prompting a concern as to whether receipt of micafungin was associated with a higher incidence of serious infections.

A retrospective study which examined the rates of documented bacteremia in febrile, neutropenic patients, found that the rates of bacteremia were higher in patients who received empirical antifungal therapy (particularly ketoconazole, fluconazole, and itraconazole) than in those who did not, after controlling for a number of potentially confounding factors (Viscoli, C., et al., Clin. Infect. Dis. 2001; 32:1532-1537). Although this was not a prospective study, and it was acknowledged that bacteremia could be a marker for other variables not accounted for in this study, the results are intriguing. Although some other retrospective studies came to similar conclusions, this hypothesis has not been tested in prospective, randomized, controlled studies.

As presented below, although infections were common adverse events in micafungin-treated patients, most were not attributed to micafungin by the investigator. When tuberculosis was evaluated further in the pooled fluconazole-controlled studies, the rates new-onset tuberculosis was similar between the two treatment groups, and the overall rates of pneumonia were similar in patients treated with micafungin or fluconazole.

Studies in Healthy Volunteers

A number of infections were reported as adverse events in healthy volunteers, as shown in the table below.

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

Table 161. Infections Reported as Adverse Events in Healthy Volunteers who received Micafungin in Single-dose and Repeat Dose Studies (adapted from applicant's Appendices 3.3 and 2.3, ISS eNDA 21-754)

Adverse Event COSTART Body System and Term*	Subjects who received Micafungin in single-dose studies N=198	Subject who received Micafungin in repeat-dose studies N=184
Body as a Whole:		
Flu syndrome	7 (3.5)	0 (0)
Cellulitis	0 (0)	1 (0.5)
Respiratory System:		
Pharyngitis	2 (1.0)	8 (4.3)
Sinusitis	0 (0)	3 (1.6)
Skin and appendages:		
Furunculosis	0 (0)	2 (1.1)
Herpes simplex	1 (0.5)	1 (0.5)
Urogenital system:		
Urinary tract infection	0 (0)	1 (0.5)
Special senses		
Conjunctivitis	0 (0)	1 (0.5)

* Subject could experience more than one adverse event within a body system

Medical Officer Comments: Most of these infections were minor, and none were considered serious adverse events. None of these infections would be unexpected in a healthy population, and the term, "flu syndrome" could apply to a symptom complex (fever, chills, myalgias, arthralgias, upper respiratory symptom) that could represent a hypersensitivity reaction, rather than a viral infection. The applicant did not calculate the overall incidence of infections in these subjects, but the number of infections does not appear to be inordinately high when considered over a 2-3 week study period.

Infections in Micafungin-Treated Patients

The overall incidence of infections reported as adverse events in these studies was not reported, because several COSTART Body system classifications include infections; however, the most common events in this category included "infection", sepsis, pneumonia, and pharyngitis. Those events considered at least possibly drug-related were uncommon, the most frequent of which was pharyngitis, as shown in the table below.

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

Table 162. Infections Reported as Adverse Events in Micafungin-Treated Patients
(adapted from Applicant's Appendix 2.7.4.3.2)

Adverse Event (COSTART Body System and Term)	All Adverse Events Micafungin-Treated Patients N=1980	Drug-Related Adverse Events Micafungin-Treated Patients N=1980
Body as a Whole:		
Infection	354 (17.9)	2 (0.1)
Sepsis	293 (14.8)	1 (0.1)
Flu syndrome	47 (2.4)	2 (0.1)
Cellulitis	31 (1.6)	1 (0.1)
Abscess	19 (1.0)	0
Tuberculosis, aggravated	18 (0.9)	0
AIDS	12 (0.6)	1 (0.1)
Peritonitis	8 (0.4)	0
Tuberculosis, reactivated	8 (0.4)	0
Infection, superimposed	1 (0.1)	0
Digestive system:		
Gastroenteritis	44 (2.2)	0
Esophagitis	33 (1.7)	1 (0.1)
Colitis	28 (1.4)	0
Enteritis	11 (0.6)	1 (0.1)
Cholecystitis	7 (0.4)	0
Enterocolitis	7 (0.4)	0
Cholangitis	1 (0.1)	0
Nervous System:		
Meningitis	7 (0.4)	1 (0.1)
Encephalitis	2 (0.1)	0
Brain abscess	1 (0.1)	0
Myelitis	1 (0.1)	0
Respiratory System:		
Pneumonia	159 (8.0)	1 (0.1)
Pharyngitis	125 (6.3)	5 (0.3)
Sinusitis	54 (2.7)	0
Bronchitis	23 (1.2)	0
Pulmonary tuberculosis, reactivated	10 (0.5)	0
Laryngitis	4 (0.2)	0
Aspiration pneumonia	3 (0.2)	0
Interstitial pneumonia	2 (0.1)	0
Pulmonary mycosis	1 (0.1)	0
Cardiovascular System:		
Endocarditis	3 (0.2)	0
Skin and appendages:		
Herpes simplex	55 (2.8)	0
Herpes zoster	16 (0.8)	0
Furunculosis	3 (0.2)	0
Skin infection	2 (0.1)	0
Urogenital System:		
Urinary tract infection	78 (3.9)	1 (0.1)
Cystitis	29 (1.5)	0
Pyelonephritis	2 (0.1)	0

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Musculoskeletal System:		
Pyogenic arthritis	1 (0.1)	0
Special senses:		
Otitis media	13 (0.7)	1 (0.1)
Otitis externa	5 (0.3)	0
Retinitis	4 (0.2)	0

*Patient could experience more than one adverse event within a body system

Medical Officer Comments: None of these infections would be unexpected in a seriously ill, patient population. Superficial infections, such as moniliasis, and conjunctivitis, were not included in the above table. Additionally, conditions which have infectious as well as non-infectious etiologies (eg. pericarditis) were not included in this analysis. Interestingly, pharyngitis was the most common infection considered drug-related among patients, and was also common among healthy volunteers. However, the actual incidence of pharyngitis in these studies may be no higher than what would be expected in the general population.

Infections Reported as Adverse Events in Fluconazole-controlled Studies

To determine if the incidence of infections with micafungin treatment exceed that in with fluconazole treatment, the incidence of adverse events indicative of an infection were compared in the fluconazole-controlled studies, as shown in the table below. Those adverse events considered at least possibly related to micafungin in these studies included enteritis (1 patient), esophagitis (1 patient), infection (2 patients), cellulitis (1 patient), AIDS (1 patient), sepsis (1 patient), pharyngitis (2 patients), pneumonia (1 patient), urinary tract infection (1 patient).

**APPEARS THIS WAY
ON ORIGINAL**

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

Table 163. Infections Reported as Adverse Events in Fluconazole-controlled Studies*

Adverse Event (COSTART body system and term)	Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787
Digestive System:		
Esophagitis	21 (2.3)	29 (3.7)
Gastroenteritis	14 (1.5)	14 (1.8)
Colitis	20 (2.1)	8 (1.0)
Enteritis	8 (0.9)	7 (0.9)
Enterocolitis	4 (0.4)	2 (0.3)
Cholecystitis	2 (0.2)	1 (0.1)
Pseudomembranous colitis	0 (0)	1 (0.1)
Body as a whole:		
Infection	183 (19.6)	167 (21.2)
Sepsis	119 (12.8)	133 (16.9)
Cellulitis	9 (1.0)	11 (1.4)
AIDS	8 (0.9)	6 (0.8)
Tuberculosis, aggravated	18 (1.9)	4 (0.5)
Abscess	3 (0.3)	3 (0.4)
Tuberculosis, reactivated	4 (0.4)	3 (0.4)
Infection, superimposed	1 (0.1)	0 (0)
Nervous system:		
Meningitis	4 (0.4)	3 (0.4)
Brain abscess	0 (0)	1 (0.1)
Encephalitis	1 (0.1)	1 (0.1)
Myelitis	1 (0.1)	0 (0)
Respiratory System:		
Pharyngitis	71 (7.6)	76 (9.7)
Pneumonia	64 (6.9)	44 (5.6)
Sinusitis	21 (2.3)	20 (2.5)
Bronchitis	15 (1.6)	9 (1.1)
Laryngitis	1 (0.1)	1 (0.1)
Pulmonary tuberculosis, reactivated	4 (0.4)	1 (0.1)
Interstitial pneumonia	1 (0.1)	0 (0)
Cardiovascular system:		
Endocarditis	1 (0.1)	1 (0.1)
Skin and appendages:		
Herpes simplex	25 (2.7)	24 (3.0)
Herpes zoster	6 (0.6)	5 (0.6)
Furunculosis	1 (0.1)	0 (0)
Urogenital system		
Urinary tract infection	34 (3.6)	29 (3.7)
Cystitis	13 (1.4)	16 (2.0)
Pyelonephritis	0 (0)	1 (0.1)
Salpingitis	0 (0)	1 (0.1)
Special senses:		
Otitis media	1 (0.1)	4 (0.5)
Retinitis	2 (0.2)	0 (0)

*studies 97-0-041, 98-0-050, FG-21-09, and 03-7-005

**Patient could experience more than one adverse event within a body system

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

Medical Officer Comments: The overall incidence of tuberculosis (reported as an adverse event) in micafungin-treated patients to be 2.8% (26/932) and 1.0% (8/787) in fluconazole-treated patients; while the overall incidence of pneumonia reported as an adverse event was 7.0% (65/932) in those who received micafungin, and 5.6% (44/787) in those who received fluconazole. Additionally, proportionately more cases of colitis were reported in micafungin-treated patients, although the type of colitis was not specified; while sepsis occurred more frequently in fluconazole-treated patients. Further analysis of the cases of tuberculosis and pneumonia is provided below.

Infections Reported as Serious Adverse Events

The overall incidence of infections considered serious adverse events in these studies was not determined. The most common serious adverse events were sepsis and pneumonia, as shown the table below. Only one of these events was considered at least possibly related to micafungin, meningitis in one patient.

APPEARS THIS WAY
ON ORIGINAL

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

Table 164. Infections in Micafungin-treated Patients Reported as Serious Adverse Events

Serious Adverse Event (COSTART Body System and Term)	Micafungin-treated Patients
Respiratory System:	
Pneumonia	44 (2.2)
Pulmonary tuberculosis, reactivated	4 (0.2)
Sinusitis	3 (0.2)
Interstitial pneumonia	2 (0.1)
Pulmonary mycosis	1 (0.1)
Body as a whole:	
Sepsis	83 (4.2)
Infection	29 (1.5)
AIDS	8 (0.4)
Abscess	6 (0.3)
Tuberculosis, reactivated	5 (0.3)
Tuberculosis, aggravated	4 (0.2)
Cellulitis	2 (0.1)
Peritonitis	1 (0.1)
Cardiovascular system:	
Endocarditis	1 (0.1)
Digestive System:	
Cholecystitis	1 (0.1)
Colitis	1 (0.1)
Enteritis	1 (0.1)
Enterocolitis	1 (0.1)
Gastroenteritis	1 (0.1)
Nervous System:	
Meningitis	6 (0.3)
Brain abscess	1 (0.1)
Urogenital system:	
Urinary tract infection	3 (0.2)
Skin and appendages:	
Herpes zoster	3 (0.2)
Furunculosis	1 (0.1)
Herpes simplex	1 (0.1)
Special senses:	
Retinitis	2 (0.1)

* Patient could have more than one adverse event within a body system

Medical Officer Comments: Serious infections are not unexpected in a very sick patient population. Tuberculosis occurred mainly in HIV patients enrolled in the esophageal candidiasis studies (03-7-005, FG463-21-09. Tuberculosis is endemic in the countries these studies took place, and many patients had active tuberculosis at baseline which worsened during the study.

Infections Reported as Serious Adverse Events in Fluconazole-controlled studies

Infections reported as serious adverse events in patients enrolled in the fluconazole-controlled studies are shown in the table below. None of these events was considered drug-related.

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

Table 165. Infections Reported as Serious Adverse Events in Fluconazole-controlled studies (adapted from Applicant's Table R9 1.2, November 1, 2004)

Serious Adverse Event COSTART Body System and Term	Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787
Body as a whole:		
Sepsis	19 (2.0)	15 (1.9)
AIDS	5 (0.5)	2 (0.3)
Tuberculosis, reactivated	2 (0.2)	1 (0.1)
Tuberculosis, aggravated	4 (0.4)	0 (0)
Digestive system:		
Gastroenteritis	0 (0)	2 (0.3)
Esophagitis	0 (0)	1 (0.1)
Pseudomembranous colitis	0 (0)	1 (0.1)
Enteritis	1 (0.1)	0 (0)
Respiratory system:		
Pneumonia	15 (1.6)	10 (1.3)
Bronchitis	0 (0)	1 (0.1)
Interstitial pneumonia	1 (0.1)	0 (0)
Pulmonary tuberculosis, reactivated	3 (0.3)	0 (0)
Sinusitis	2 (0.2)	0 (0)
Urogenital system:		
Pyelonephritis	0 (0)	1 (0.1)
Urinary tract infections	1 (0.1)	0 (0)
Nervous system:		
Meningitis	4 (0.4)	2 (0.3)
Brain abscess	0 (0)	1 (0.1)
Skin and appendages:		
Herpes simplex	1 (0.1)	0 (0)
Herpes zoster	1 (0.1)	0 (0)
Special senses:		
Retinitis	1 (0.1)	0 (0)

*studies 97-0-041, 98-0-050, 03-7-005, FG463-21-09

** patient could experience more than one adverse event within a body system

Medical Officer Comments: Tuberculosis (aggravated, reactivated, or pulmonary tuberculosis), and pneumonia were reported more frequently as serious adverse events in patients who received micafungin, than in those who received fluconazole, as further discussed below.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Tuberculosis as an Adverse Event in the Fluconazole-Controlled Studies

In the esophagitis candidiasis studies, 03-7-005 and FG463-21-09, tuberculosis was fairly common at baseline in both fluconazole and micafungin-treatment groups, and was reported as an adverse event if it were a new diagnosis, or if it worsened during the study (aggravated tuberculosis). Tuberculosis is endemic in Africa and South America, where these studies were conducted, and a relatively high incidence of tuberculosis among patients with HIV/AIDS is not unexpected. Tuberculosis at baseline and that reported as an adverse event is shown in the following table.

Table 166. Incidence of tuberculosis reported as at baseline and as an adverse event in individual Fluconazole studies

Study protocol	Micafungin-treated patients			Fluconazole-treated patients		
	Number of patients with TB at baseline	Number of adverse events reported as TB	N	Number of patients with TB at baseline	Number of adverse events reported as TB	N
03-7-005	38 (14.6)	7 (2.7)	260	36 (14.0)	4 (1.6)	258
FG463-21-09	52 (28.1)	19(10.3)	185	14 (23.3)	4 (6.7)	60
98-0-050	0	0	425	0	0	457
98-0-041	0	0	62	0	0	12
Total	90 (9.7)	26 (2.8)	932	50 (6.4)	8 (1.0)	787

Medical Officer Comments: In study FG463-21-09, the incidence of tuberculosis at baseline was somewhat higher in patients treated with micafungin, than in those treated with fluconazole for EC; while the incidence of baseline tuberculosis was similar between treatment groups in 03-6-005. A total of 26 patients in the micafungin safety database had tuberculosis reported as an adverse event. All of these cases occurred in the the esophageal candidiasis studies, 03-7-005, and FG463-21-09. In study 03-7-005, 1 of the 7 cases of tuberculosis reported as an adverse event was due to worsening of the baseline condition; while the 6 other cases among micafungin-treated patients and the 4 among fluconazole-treated patients had tuberculosis diagnosed during treatment. In study FG463-21-09, 11 of the 19 cases of TB reported in the micafungin group, had TB diagnosed at baseline; while the 8 other cases among micafungin-treated patients and the 4 cases among fluconazole-treated patients had TB diagnoses during treatment. Thus, if those cases which were actually an exacerbation of baseline TB, were not included as adverse events, similar proportions of patients in the micafungin and fluconazole groups developed new onset tuberculosis during the studies, 14/932 (1.5%) for micafungin, and 8/787 (1.0%) for fluconazole.

Pneumonia Reported as an Adverse Event in Fluconazole-controlled studies

Overall, pneumonia (including interstitial pneumonia) was reported as an adverse event in 65 of 932 (7.0%) micafungin-treated and in 44 of 787 (5.6%) fluconazole-treated

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

patients. The incidence of pneumonia reported as a serious adverse event is shown in the table below.

Table 167. Incidence of Pneumonia as a Serious Adverse Event in Fluconazole-controlled studies (03-7-005, FG463-21-09, 98-0-050, and 98-0-041) (adapted from Applicant's Table R9 1.2, 1 November, 2004)

Study Protocol	Micafungin-treated patients		Fluconazole treated patients	
	Number of patients with pneumonia reported as an adverse event	N	Number of patients with pneumonia reported as an adverse event	N
03-7-005	6 (2.3)	260	4 (1.6)	258
FG463-21-09	2 (1.1)	185	0	60
98-0-050	7 (1.6)	425	6 (1.3)	457
98-0-041	0	62	0	12
Total	15 (1.6)	932	10 (1.3)	787

Medical Officer Comments: *The overall incidence of pneumonia reported as a serious adverse event in the studies was similar in both treatment groups. Most cases of pneumonia in the esophageal candidiasis studies, 03-7-005 and FG463-21-09 were due to *Pneumocystis jiroveci* (formerly *carinii*), a finding not unexpected in this population of severely immunocompromised patients, most of whom had underlying AIDS. It is of interest that although micafungin had activity in an in vivo mouse model of *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP), it had no apparent efficacy in preventing PCP in patients in these studies.*

Deaths due to Infections in all Patients Treated with Micafungin

Infections were a relatively common cause of death in these studies. The most common infections resulting in death were sepsis, pneumonia, and pulmonary mycosis, as shown in the table below.

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

Table 168. Deaths caused by Infections in Micafungin-treated Patients

Adverse Event (COSTART Body System and Term)	Micafungin-treated Patients N=1980
Respiratory System	
Pneumonia	29 (1.5)
Pulmonary mycosis	20 (1.0)
Pulmonary tuberculosis, reactivated	6 (0.3)
Interstitial pneumonia	2 (0.1)
Sinusitis	1 (0.1)
Body as a whole:	
Sepsis	45 (2.3)
Infection	16 (0.8)
Tuberculosis, reactivated	6 (0.3)
Tuberculosis, aggravated	4 (0.2)
Moniliasis	1 (0.1)
Peritonitis	1 (0.1)
Cardiovascular system	
Endocarditis	4 (0.2)
Nervous system:	
Meningitis	2 (0.1)
Encephalitis	1 (0.1)

Medical officer Comments: Death due to a serious infection is not unexpected in this population of seriously ill patients, including those with HIV/AIDS, hematologic malignancy, and transplant recipients.

Infections resulting in Death in fluconazole-controlled studies

There did not appear to be an excess in deaths due to infection in micafungin-treated patients in comparison to fluconazole, as shown in the table below. One micafungin-treated patient died due to progressive HIV infection, which was considered possibly related to micafungin, and will be described below.

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

Table 169. Deaths due to Infection in Fluconazole-controlled Studies (FG463-21-09, 03-7-005, 98-0-050, and 97-0-041)

Adverse Event (COSTART Body System and Term)	Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787
Body as a Whole:		
AIDS	20 (2.1)	14 (1.8)
Sepsis	4 (0.4)	6 (0.8)
Tuberculosis, reactivated	4 (0.4)	1 (0.1)
Tuberculosis, aggravated	4 (0.4)	0 (0)
Respiratory system:		
Pneumonia	9 (1.0)	6 (0.8)
Pulmonary tuberculosis, reactivated	5 (0.5)	2 (0.3)
Colitis	0 (0)	1 (0.1)

Medical Officer Comments: The incidence of death due to tuberculosis, pneumonia, and worsening of AIDS, was somewhat higher in patients treated with micafungin than in patients who received fluconazole. The higher incidence of death due to tuberculosis may be related to the higher incidence of tuberculosis at baseline in the micafungin treatment groups in study FG463-21-09, as described above.

Narrative Summary for Patient whose death was considered possibly related to Micafungin

Patient 10655006 was a 33 year-old black South African male with HIV and a CD₄ count of 0 cells/mm³. He was not receiving antiretroviral therapy. He received micafungin 150 mg/day for 12 days for EC in study 03-7-005. Baseline conditions included suspected tuberculosis, cachexia, hypokalemia, oral leukoplakia, SIADH, chest pain and insomnia. At the time of study enrollment the patient was receiving metoclopramide, augmentin and cotrimoxazole, which were continued. Adverse events reported during micafungin treatment included anorexia and arthralgia. Micafungin was stopped on day 12 due to HIV progression and the patient died on day 13. The cause of death was reported as progression of HIV, and no autopsy was performed. The investigator considered the death possibly related to micafungin. Additional concomitant medications included rifabutin (isoniazid, rifampin, pyrazinamide, and ethambutol), amitriptyline, amikacin, paracetamol, potassium chloride, zolpidem, clothiapine, cyproheptadine and diclofenac (topical). The patient also received a blood transfusion on day 11 due to hemoglobin incorrectly reported as 7.4. Laboratory values obtained during the study are shown in the table below. Additionally, AST, ALT, total bilirubin and alkaline phosphatase were normal at baseline and during treatment.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Laboratory Values* for Patient 10655006

Study Day	WBC X 10 ⁹	Hemoglobin %	Platelets X 10 ⁹	BUN (mg/dL)	Creatinine (mg/dL)	Albumin g/dL
Baseline	2.7	12	174	42	1.2	1.8
Day 8	2.9	13	98	23	1.1	2.8

*normal laboratory values are shown in Appendix 10.

Medical Officer Comments: *The only significant laboratory value reported during treatment was a decreased platelet count of 98×10^9 on study day 8. No additionally laboratory values were available. Death due to HIV disease itself is uncommon, and is usually related to an opportunistic infection, malignancy, or complication related to treatment. The details provided in the case report form and narrative summary are insufficient to judge whether this death was related to micafungin or to some other event not reported.*

Infections Resulting in Micafungin discontinuation

Micafungin was not discontinued in any healthy volunteer due to infection. The following table shows infections resulting in micafungin discontinuation in patients. Additionally, several micafungin-treated patients required dose interruption or reduction for infections, including "infection", *Herpes simplex*, and pneumonia each in 1 patient.

Table 170. Micafungin Discontinuation due to Infection (from Applicant's Appendix 9.1.2)

Adverse Event (COSTART Body System and Term)	Micafungin-treated Patients N=1980
Respiratory System	
Pneumonia	17 (0.9)
Pulmonary tuberculosis, reactivated	2 (0.1)
Body as a whole:	
AIDS	4 (0.2)
Tuberculosis, reactivated	2 (0.1)
Abscess	1 (0.1)
Peritonitis	1 (0.1)
Tuberculosis, aggravated	1 (0.1)
Nervous system:	
Meningitis	4 (0.2)

Adverse events resulting in drug discontinuation in fluconazole-controlled studies are shown in the table below.

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

Table 171. Adverse Events Leading to Discontinuation of Study Drug in Fluconazole-controlled Studies (FG463-21-09, 03-7-005, 98-0-050, and 97-0-041)

Adverse Event (COSTART Body System and Term)	Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787
Nervous System:		
Meningitis	0 (0)	1 (0.1)
Respiratory System:		
Pneumonia	4 (0.4)	3 (0.4)
Pulmonary tuberculosis, reactivated	2 (0.2)	0 (0)
Body as a whole:		
Sepsis	0 (0)	2 (0.3)
Tuberculosis, reactivated	1 (0.1)	0 (0)
Tuberculosis, aggravated	1 (0.1)	0 (0)

Medical Officer Comments: A total of 4 patients who received micafungin, but none of the fluconazole-treated patients, required drug discontinuation due to tuberculosis. See additional discussion regarding tuberculosis as an adverse event in these studies above.

Portmarketing Adverse Events

A total of 11 infections reported as serious adverse events considered at least possibly related to micafungin were reported from 1 January, 1998 to 8 April 2004 in Japan. These included aspergilloma (1 case), aspergillosis (2 cases), HIV wasting syndrome (1 patient), interstitial pneumonia (1 case), bacterial pneumonia (1 case), CMV pneumonia (1 case), sepsis (2 cases), septic embolus (1 case), and systemic candida (1 case).

Conclusions Regarding Infections Reported as Adverse Events

Infections were commonly reported as adverse events in these studies, but most were not considered drug-related. Serious infections, which were a common cause of death in these studies, would not be unexpected in patients with underlying HIV/AIDS, hematological malignancies, or in transplant recipients. The higher incidence of tuberculosis reported as an adverse event and death due to tuberculosis in patients treated with micafungin than in those treated with fluconazole was likely due to a higher incidence of tuberculosis at baseline in study FG463-21-09 in those who received micafungin. None of the adverse events in this category appears to be of serious concern regarding the safety of micafungin at this time, and no special precautions are proposed in the micafungin label.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

7.1.12.9 Gastrointestinal Adverse Events

The incidence of any gastrointestinal adverse event was 58.3% (1400/2402) subjects. Those events considered to be drug-related occurred in 221 (9.2%) subjects. The most common drug-related adverse events included nausea (2.9%), vomiting (2.4%), diarrhea (2.0%), and abnormal liver function tests (1.9%). Hepatic safety is discussed separately in section 7.1.12.4. The incidence of drug-related gastrointestinal adverse events was similar in patients treated with micafungin, 8.2% (255/932) patients, or fluconazole, 8.3% (169/787 patients) in the studies which used fluconazole as a comparator.

Serious gastrointestinal adverse events occurred in 4.1% (83 of 1980) patients. None were reported in healthy volunteers. The incidence of drug-related serious adverse events was 0.4% (7/1980) patients. These events included diarrhea, liver damage, abnormal liver function tests, nausea, pancreatitis, rectal hemorrhage, and vomiting, each in one patient. Gastrointestinal adverse events resulting in micafungin discontinuation occurred in 0.9% (21/2402) subjects; events considered drug-related included abnormal liver function tests in 0.4% (7/1980) patients, and anorexia, hepatitis, liver damage, and nausea, each in one patient. Deaths due to gastrointestinal adverse events in the clinical studies occurred in 10 patients, 4 with gastrointestinal hemorrhage, 3 with veno-occlusive liver disease, 2 with hepatic failure, and 1 with gastrointestinal carcinoma. None of the deaths was considered related to micafungin.

In the Japanese postmarketing experience, 15 serious gastrointestinal adverse events, at least possibly related to micafungin, were reported in the period from 1 January, 1998 to 8 April, 2004. The most common of these events were hemorrhagic colitis, and gastrointestinal hemorrhage.

Overall, gastrointestinal adverse events were common in the clinical studies. Other than hepatic adverse events, which are discussed below, none of the gastrointestinal adverse events appear to be a major safety concern at this time.

7.1.12.10 Nervous System Adverse Events

The overall incidence of any nervous system adverse event was 43.8% (1053/2402) subjects; while adverse events considered at least possibly related to micafungin occurred in 118/2402 (4.9%) subjects. The most common drug-related event was headache, which occurred in 2.3% subjects. In fluconazole-controlled studies, the incidence of drug-related adverse events was 5.0% (47/932) for micafungin-treated patients and 3.9% (31/787) for fluconazole-treated patients.

Serious nervous system adverse events were reported in 72/1980 (3.6%) patients, most commonly convulsion, which occurred in 18/1980 (0.7%) patients. No serious adverse events occurred in healthy volunteers. Drug-related serious adverse events were uncommon, and included delirium (2 patients), and anxiety, cerebral hemorrhage,

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

confusion, dementia, meningitis, and neuropathy, each in one patient. Micafungin was discontinued in due to nervous system adverse events in 25/2402 (1.0 %) subjects. Drug-related adverse events resulting in micafungin discontinuation included delirium in 2 patients, and cerebral hemorrhage, convulsion, dementia, and headache, each in one patient. Deaths due to nervous system adverse events occurred in 24/2402 (1.0%) subjects. None of the deaths was considered related to micafungin.

In the Japanese postmarketing experience, 16 serious nervous system adverse events at least possibly related to micafungin were reported from 1 January, 1998 to 8 April, 2004. These most common serious postmarketing events were depressed level of consciousness (5 cases), and cerebral hemorrhage (4 cases).

Overall, nervous system adverse events were common in the clinical studies, but appeared to reflect the underlying disease states in the patient population. None of the adverse events in this category appear to constitute a serious safety concern at this time; and whether micafungin crosses the blood-brain barrier is unknown. Additionally, it will be important in the postmarketing period to monitor for postmarketing events such as stroke, cerebral infarction, cerebral hemorrhage, given the potential irritative effect of micafungin on blood vessels, resulting in phlebitis and thrombophlebitis, and unknown potential effects on the larger vasculature.

7.1.12.11 Metabolic and Nutritional Disorders

A total of 1198/2402 (49.9%) subjects experienced at least one metabolic abnormality. These abnormalities were considered at least possibly related to study drug in 9.7% (234/2402) subjects. The most common drug-related adverse events were increased AST (2.7%), increased alkaline phosphatase (2.5%), and increased ALT (2.4%), bilirubinemia (1.8%), hypomagnesemia (1.6%), and hypokalemia (1.4%). Hepatic laboratory abnormalities are discussed in section 7.1.12.4. In fluconazole-controlled studies, metabolic abnormalities were reported in 56.4% (526/932) patients treated with micafungin, and in 62.3% (490/787) of patients treated with fluconazole.

Serious adverse events in this category were reported in 63/1980 (3.2%) patients; while those considered drug-related occurred in 16 (0.8%) patients. These included bilirubinemia in 5 (0.3%) patients, hypokalemia in 4 (0.2%) patients, increased creatinine in 3 (0.2%) patients, increased alkaline phosphatase in 3 (0.2%) patients, increased AST in 2 (0.1%) patients, and increased BUN, hyponatremia, and increased ALT, each in one patient. None of the healthy volunteers experienced a serious metabolic abnormality. Micafungin was discontinued in 18/1980 (0.9%) patients due to a metabolic abnormality. Drug-related adverse events resulting in discontinuation included bilirubinemia in 6 (0.3%) patients, increased alkaline phosphatase in 3 (0.2%) patients, increased creatinine in 2 (0.1%) patients, and increased AST, and “enzymatic abnormality”, each in 1 patient. Two patients died due to metabolic abnormalities

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

(acidosis in both patients); however, neither adverse event was considered related to micafungin.

In the Japanese postmarketing experience, a total of 13 serious adverse events considered drug-related occurred in the period from 1 January, 1998 to 8 April, 2004. The most common of these was hyponatremia.

Although metabolic abnormalities were common in the clinical studies, this is not unexpected in this patient population, particularly those with underlying hematologic malignancies who were receiving chemotherapy, or a HSCT. None of these events appears to pose a serious safety concern with micafungin at this time; although ODS has recommended postmarketing surveillance for hyponatremia because of its relative frequency in the Japanese postmarketing database.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no reported or documented evidence of either withdrawal or rebound effects with micafungin, nor of psychological or physical dependence with micafungin. CNS adverse events have been described in the clinical studies of mycamine, including headache, confusion, obtundation, lethargy, and one case of convulsions. However, none of these have occurred in the normal volunteer studies. There is no prior experience in healthy subjects to suggest that micafungin therapy can impair mental ability. In clinical trials repeated daily doses of micafungin up to a maximum of 8 mg/kg in adults were administered with no dose-limiting toxicity. No overdose with micafungin has been reported.

7.1.14 Human Reproduction and Pregnancy Data

To assess the effect of micafungin on human reproduction and pregnancy, the applicant preformed reproductive studies in rats and rabbits, all were previously submitted in NDA 21-506. Studies in rabbits indicate that micafungin administration to pregnant rabbits resulted in visceral abnormalities and abortion at 32 mg/kg, a dose equivalent to about four times the recommended human dose. Visceral abnormalities included abnormal lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian artery, and dilatation of the ureter. As animal studies are not always predictive of human response; therefore, MYCAMINE should be used during pregnancy only if clearly needed and a pregnancy category C was negotiated in the label.

In lactating rats evaluated 8 days post-delivery, micafungin and/or metabolites were demonstrated to have been secreted into breast milk. Caution should be exercised when micafungin is administered to a nursing woman, as it is uncertain whether secretion into human breast milk also occurs.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

7.1.15 Assessment of Effect on Growth

No clinical studies were performed to assess the effect of micafungin on growth. In the clinical studies in which pediatric patients were enrolled, growth was not systematically evaluated. Long-term, chronic use micafungin is not envisioned for treatment of esophageal candidiasis; however, for antifungal prophylaxis in the setting of HSCT, micafungin could potentially be utilized for longer periods of time. In a study to evaluate micafungin toxicity in newborn rats, micafungin was administered daily for 4 weeks at doses of 0, 3.2, 10 and 32 mg/kg in 10 male and 10 female animals. The NOAEL of micafungin was determined to be 10 mg/kg in these animals. The main target organs for toxicity of micafungin in newborn rats were liver, kidney, urinary bladder, and erythrocytes.

7.1.16 Overdose Experience

No cases of MYCAMINE overdosage have been reported. Repeated doses up to 8 mg/kg have been administered in a small number of patients in clinical study without dose-limiting toxicity. The minimum lethal dose of MYCAMINE in rats is 125 mg/kg, equivalent to 8.1 times the recommended human dose for treatment of esophageal candidiasis. Review of postmarketing serious adverse events did not reveal any reports of micafungin overdosage.

7.1.17 Postmarketing Experience

Currently micafungin is marketed only in Japan, where it was approved in October, 2002 for “fungemia, respiratory mycosis, and gastrointestinal mycosis” caused by *Candida* sp. and *Aspergillus* sp. The worldwide patient exposure during the reporting period of 9 October, 2003 to 8 April, 2004, was estimated as — patient months. For this time period, there were 522 reported adverse events, which were considered related to micafungin, as shown in the table below. Hepatobiliary adverse events were the most common postmarketing events reported.

Table 172. Postmarketing Adverse Events in Japan (October, 2003 to April, 2004) (from Applicant’s 120-day Safety Update)

System Organ Class (SOC)	Non-Serious Cases	Serious Cases	Total
Investigations	108	96	204
Hepatobiliary disorders	31	43	74
Blood and lymphatic system disorders	6	31	37
Infections and infestations	1	32	33
Respiratory, thoracic and mediastinal disorders	0	25	25
Metabolism and nutrition disorders	17	7	24
General disorders and administration site conditions	4	17	21
Renal and urinary disorders	2	18	20

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

Skin and subcutaneous tissue disorders	12	4	16
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	15	15
Gastrointestinal disorders	4	10	14
Nervous system disorders	2	11	13
Cardiac disorders	1	6	7
Vascular disorders	2	5	7
Injury, poisoning and procedural complications	0	5	5
Psychiatric disorders	0	3	3
Immune system disorders	0	2	2
Ear and labyrinth disorders	1	0	1
Musculoskeletal and connective tissue disorders	1	0	1
Total	192	330	522

The most common serious adverse events reported during this time period were thrombocytopenia, and abnormal hepatic function, as shown in the table below. Postmarketing adverse events are discussed in the individual safety sections by organ system.

Table 173. Most Common Postmarketing Serious Adverse Events in Japan (Regardless of Causality), from 9 October, 2003 to 8 April, 2004) (applicant's Table 24, 120-day Safety Update)

Preferred Term (MedDRA v. 6.1)	Number of Patients Experiencing this Serious Adverse Event
Platelet Count Decreased	16
Hepatic Function Abnormal	12
Pneumonia	10
Sepsis	8
Respiratory Failure	8
White Blood Cell Count Decreased	8
Multi-organ Failure	7
Renal Impairment	7
Anaemia	6
Liver Disorder	6
Pancytopenia	5
Shock	5
Blood Bilirubin Increased	5

Medical Officer Comments: Postmarketing surveillance in the U.S., will focus on (but will not be limited to) hepatic, renal and hematologic abnormalities, as discussed in the special safety studies above.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Data sources for this review included individual study reports for the clinical studies, and the integrated summary of safety, submitted with NDA 21-754, 23 April, 2004.

Additionally, the 120-day safety update, submitted 24 August, 2004, contained the bulk of the safety information referenced in this review, as well as the study report for protocol 03-7-005, a pivotal study for treatment of esophageal candidiasis. From both sources, case report forms, narrative summaries, and electronic databases provided by the applicant for this NDA were utilized for review. In addition, reference was made to patient case report forms, narrative summaries, the electronic database, and individual study reports provided in the original NDA 21-506, submitted 29 April, 2002, and the amendment to NDA 21-506, 24 August, 2004.

7.2.1.1 Study type and design/patient enumeration

Study type, design, micafungin dosing, and treatment groups, patient populations, study location, were described in section 4.2 of this review.

7.2.1.2 Demographics

The demographic profile for all subjects who received micafungin in the pooled safety database is shown in the following table. Overall, most patients were male and Caucasian. The mean age was 38 ± 17.5 years old, (ranging from 1 week to 92 years of age). A majority of subjects had an underlying hematologic malignancy, or received a bone marrow transplant.

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

Table 174. Demographic Profile for All Micafungin-treated Subjects (Applicant's Appendix 2.7.4.2.1.1)

PARAMETER	CLASS	--TREATMENT-- PK463 (1) (N=2402)
GENDER	MALE	1489 (62.0%)
	FEMALE	913 (38.0%)
RACE	CAUCASIAN	1519 (63.2%)
	BLACK	531 (22.1%)
	ORIENTAL	177 (7.4%)
	OTHER	175 (7.3%)
PATIENT CONTINENT	NORTH AMERICA	1273 (53.0%)
	SOUTH AMERICA	304 (12.7%)
	EUROPE	240 (10.0%)
	ASIA	153 (6.4%)
	AFRICA	432 (18.0%)
AGE GROUP	<16	244 (10.2%)
	16 TO <65	1972 (82.1%)
	>=65	186 (7.7%)
UNDERLYING DISEASE	HEMATOLOGIC MALIGNANCY OR BMT	946 (39.4%)
	HIV	670 (27.9%)
	OTHER	786 (32.7%)
TRANSPLANT TYPE	ALLOGENEIC	282 (11.7%)
	ALLOGENEIC	441 (18.4%)
	NONE	1677 (69.8%)
BASELINE NEUTROPENIC STATUS	ANC >=500 CELLS/MM	1016 (42.3%)
	ANC < 500 CELLS/MM	254 (10.6%)
	NOT ASSESSED	1132 (47.2%)
AGE (YEARS)	N	2402
	MEAN	38.0
	STD	17.50
	MIN	0.0
	MEDIAN	38.0
	MAX	92.0
WEIGHT (KG)	N	2390
	MEAN	63.6
	STD	21.17
	MIN	0.6
	MEDIAN	61.1
	MAX	265.0

Best Possible Copy

Many of the adverse event tables shown in this integrated summary of safety are shown for all patients, rather than all subjects. The demographic profile for all patients who received micafungin is shown in the following table. Similar to all subjects who received micafungin, most patients were Caucasian and male. The mean patient age was 38.8 ± 18.2 years.

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

Table 175. Demographic Profile for all Micafungin-Treated Patients (Applicant's Appendix 2.7.4.2.1.2)

PARAMETER	CLASS	-- TREATMENT -- PR463 (1) (N=1980)
GENDER	MALE	1127 (56.9%)
	FEMALE	853 (43.1%)
RACE	CAUCASIAN	1228 (62.0%)
	BLACK	504 (25.5%)
	ORIENTAL	93 (4.7%)
	OTHER	155 (7.8%)
PATIENT CONTINENT	NORTH AMERICA	1061 (53.6%)
	SOUTH AMERICA	304 (15.4%)
	EUROPE	113 (5.7%)
	ASIA	70 (3.5%)
	AFRICA	432 (21.8%)
AGE GROUP	<16	244 (12.3%)
	16 TO <65	1573 (79.4%)
	>=65	163 (8.2%)
UNDERLYING DISEASE	HEMATOLOGIC MALIGNANCY OR BMT	946 (47.8%)
	HIV	670 (33.8%)
	OTHER	364 (18.4%)
TRANSPLANT TYPE	AUTOLOGOUS	382 (19.3%)
	ALLOGENEIC	443 (22.4%)
	NONE	1255 (63.4%)
BASELINE NEUTROPENIC STATUS	ANC >=500 CELL/MM	1015 (51.3%)
	ANC < 500 CELL/MM	254 (12.8%)
	NOT ASSESSED	711 (35.9%)
AGE (YEARS)	N	1980
	MEAN	38.8
	STD	18.17
	MIN	0.0
	MEDIAN	39.0
	MAX	92.0
WEIGHT (KG)	N	1960
	MEAN	61.7
	STD	24.45
	MIN	0.6
	MEDIAN	60.6
	MAX	265.0

Best Possible Copy

Additionally, in the integrated summary of safety, patients in fluconazole-controlled studies were compared to determine whether there were an excess of adverse events in micafungin-treated patients. The demographic profile for these patients is shown in the following table. Overall, the treatment groups were fairly balanced for these characteristics. There were fewer patients < 16 years old in these studies than in the overall patient population shown above.

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

Table 176. Demographic Profile for Patients in Fluconazole-Controlled Studies*

PARAMETER	CLASS	TREATMENT	
		FG463 (1) (N=912)	FLUCONAZOLE (N=787)
GENDER	MALE	493 (52.9%)	423 (53.7%)
	FEMALE	439 (47.1%)	364 (46.3%)
RACE	Caucasian	551 (59.1%)	480 (61.0%)
	Black	312 (33.5%)	247 (31.4%)
	Other	5 (0.5%)	8 (1.0%)
	Other	64 (6.9%)	52 (6.6%)
PATIENT CONTINENT	North America	487 (52.3%)	469 (59.6%)
	South America	169 (18.1%)	108 (13.7%)
	Africa	276 (29.6%)	210 (26.7%)
AGE GROUP	<16	39 (4.2%)	45 (5.7%)
	16 TO <65	852 (91.4%)	714 (90.7%)
	≥65	41 (4.4%)	28 (3.6%)
UNDERLYING DISEASE	Hematologic malignancy or BMT	487 (52.3%)	469 (59.6%)
	HTV	430 (46.1%)	301 (38.2%)
	Other	15 (1.6%)	17 (2.2%)
TRANSPLANT TYPE	Autologous	339 (36.2%)	207 (26.3%)
	Allogeneic	246 (26.4%)	262 (33.3%)
	None	447 (48.0%)	318 (40.4%)
BASELINE NEUTROPHILIC STATUS	ANC ≥500 CELL/MM	447 (48.0%)	437 (55.5%)
	ANC < 500 CELL/MM	39 (4.2%)	32 (4.1%)
	NOT ASSESSED	446 (47.9%)	318 (40.4%)
AGE (YEARS)	N	932	787
	MEAN	40.0	40.0
	STD	14.05	14.94
	MIN	0.6	0.6
	MEDIAN	39.0	40.0
	MAX	80.0	87.0
WEIGHT (KG)	N	928	787
	MEAN	65.8	67.7
	STD	21.66	21.82
	MIN	5.9	6.1
	MEDIAN	63.0	65.2
	MAX	149.7	172.7

Best Possible Copy

*Fluconazole-controlled studies included 97-0-041, 98-0-050, FG463-21-09, and 03-7-005

7.2.1.3 Extent of exposure (dose/duration)

Safety data for this review was obtained from a pooled safety database, including 32 clinical studies including 422 volunteers and 1980 patients, as shown in the following table. Safety data was also reviewed for the individual studies submitted for this NDA, studies FG463-21-09, 03-7-005, and 97-7-003 (see individual study reports in Appendix, section 10.1)

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

Table 177. Summary of Subject Population (Applicant's Table 1, Summary of Clinical Safety, July, 2004)

	Micafungin	Fluconazole	Placebo	Total
Volunteers or other subjects in the safety database†	422	0	3	425
Patients in the combined safety database ("all patients")	1980	787	51	2818
<i>Prophylaxis (BMT/HSCT)</i>	600	469	0	1069
<i>Esophageal Candidiasis (EC)</i>	674	318	0	992
TOTAL ("all subjects")	2402	787	54	3243

Subject base: all randomized/enrolled patients or healthy volunteers who received at least one dose of study drug in 32 clinical studies.

BMT: Bone marrow transplant HSCT: Hematopoetic stem cell transplant.

The following table summarizes the number of patients who received ≥ 150 mg/day micafungin for at least 10 days. A total of 606 patients in a number of clinical studies received this dose which has been proposed for treatment of esophageal candidiasis.

Table 178. Subjects who received ≥ 150 mg/day (or ≥ 3 mg/kg/day) Micafungin for at least 10 days (Applicant's Table 2, Clinical Summary of Safety, July, 2004)

Study Numbers	Population	≥ 150 mg
97-7-003 FG-463-21-09	HIV-positive patients with esophageal candidiasis	56
03-7-005	Patients with esophageal candidiasis	243
98-0-047	Patients with candidemia and invasive candidiasis	26
98-0-046	Patients with invasive aspergillosis	110
97-0-041 98-0-043 FG-463-21-03	Neutropenic patients who received micafungin as prophylaxis	47
FJ-463-0003	Patients with deep-seated mycoses	11
03-0-175 03-0-176 03-0-177 03-0-178	Healthy volunteers	113
All Studies Combined	Total number of subjects	606

The following table summarizes micafungin exposure by days of exposure and mean duration.

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

Table 179. Summary of Micafungin Treatment Duration and Days of Exposure
 (Applicant's Table 3, Clinical Summary of Safety, July, 2004)

Population	n	Total Days of Subject Exposure	Mean Duration of Treatment
All Subjects (Volunteers and Patients)	2402	45759 days	20.1 days range: 1 to 681 days 73.4% of subjects ≥10 days
All Patients	1980	43187 days	23.1 days range: 1 to 681 days 82.0% of patients ≥10 days
All Volunteers	422	2572 days	6.4 days range: 1 to 15 days 32.9% of subjects ≥10 days

Micafungin doses in these studies ranged from 12.5 mg/day to 200 mg/day; and in one study, FG463-21-03, from 3.0 to 8.0 mg/kg/day.

Medical Officer Comments: For the proposed dose of micafungin for esophageal candidiasis, 150 mg/day, adequate numbers of subjects were exposed for an adequate duration (at least 10 days) to evaluate the safety of micafungin.

Subject exposure by mean daily dose and duration of micafungin is shown in the following table.

Table 180. Drug Exposure in Subjects* by Mean Daily Dose and Duration of Micafungin
 (from Applicant's Appendix 2.7.4.1.1.2)

Mean Daily Dose of Micafungin	< 1.0 mg/kg N=822	1.0-1.9 mg/kg N=804	2.0-2.9 mg/kg N=487	3.0-3.9 mg/kg N=215	≥ 4.0 mg/kg N=62	Total N=2390
Treatment duration (days):						
1-9	197 (24.0%)	236 (29.4%)	132 (27.1%)	58 (27.0%)	9 (14.5%)	632 (26.4%)
10-20	392 (47.7%)	312 (38.8%)	275 (56.5%)	115 (53.5%)	27 (43.5%)	1121 (46.9%)
21-60	215 (26.2%)	213 (26.5%)	52 (10.7%)	30 (14.0%)	20 (32.3%)	530 (22.2%)
> 60	18 (2.2%)	43 (5.3%)	28 (5.7%)	12 (5.6%)	6 (9.7%)	107 (4.5%)
Range of treatment duration (days)	1-168	1-490	1-681	1-173	1-147	1-681
Mean of treatment duration (days)	17.1	22.1	21.9	19.0	25.4	20.1

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

*All subjects who received at least one dose of micafungin, and for whom weight was obtained

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No studies other than those submitted with the overall micafungin safety database were used as secondary clinical data sources in this review.

7.2.2.2 Postmarketing experience

The Global Periodic Safety Update Reports (PSUR) encompassing the time periods, 8 April, 2003 to 8 October, 2004 (PSUR-2), and 9 October, 2003 to 8 April, 2004 (PSUR-3) were submitted by the applicant with NDA 21-754, and the 120-day safety update, submitted in August, 2004. These reports included summaries of the postmarketing adverse events reports referenced in this safety summary.

7.2.2.3 Literature

Review of the published literature from searches by the Applicant and the medical reviewers revealed no safety concerns with micafungin in addition to those identified in clinical studies and postmarketing data from Japan.

7.2.3 Adequacy of Overall Clinical Experience

Overall, 2402 subjects received at least one dose of micafungin in the clinical studies. Of these, 606 subjects (299 of whom had esophageal candidiasis) received a dose of ≥ 150 mg/day micafungin for at least 10 days, which is an adequate number of subjects to assess safety for the esophageal candidiasis indication, for which the proposed micafungin dose is 150 mg/day. No specific duration of treatment is specified in the proposed micafungin label, but the usual course of EC treatment is 14 to 21 days. The median duration of treatment in patients enrolled in the clinical studies which evaluated esophageal candidiasis was 14 days, with a range of 1-33 days. Thus, the duration of micafungin administration appears to adequately encompass the expected time frame for treatment of esophageal candidiasis.

The two pivotal studies reviewed for the indication of esophageal candidiasis, 03-7-005, and FG463-21-09 were both randomized, double-blind, controlled studies. The former study, 03-7-005, was a phase 3 study, which enrolled an adequate number of patients in each arm to assess the non-inferiority of micafungin to fluconazole; while study FG463-21-09 was a phase 2 micafungin dose-ranging study with a fluconazole treatment arm for comparison. The latter study, however, was not statistically powered to evaluate non-inferiority of micafungin to fluconazole. Study 97-0-003 was a phase 2 micafungin dose-

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

ranging study submitted as a supportive study, as was study 98-0-047, which was an open-label study of micafungin for treatment of candidemia or invasive candidiasis, in which a large proportion of patients enrolled had esophageal candidiasis.

Potential class effects were adequately assessed by adverse event monitoring in the clinical studies, including hepatic, renal and hematological adverse events. In addition, collection of laboratory data was adequate to evaluate changes in hepatic, renal, and hematological parameters, as well as changes in other serum chemistries. Additionally, in normal volunteer studies, electrocardiographic data was obtained to evaluate any effects of micafungin on cardiac repolarization. These studies were adequate to assess any potential for QT prolongation in addition to the animal and *in vitro* data obtained in preclinical studies.

The micafungin safety database included 244 subjects < 16 years of age, 1972 subjects between the ages of 16 and 65, and 186 subjects age 65 and older (including 41 subjects who were ≥ 75 years old). In the pivotal studies for this NDA, patients with significant hepatic or renal dysfunction were excluded. Pharmacokinetics and safety of a single 1 hour infusion of 100 mg micafungin was studied in 8 volunteers with moderate hepatic dysfunction (Child-Pugh score of 7-9), and in 9 subjects with a creatinine clearance of < 30 mL/min. The pharmacokinetics of micafungin was similar in subjects with severe renal dysfunction or moderate hepatic dysfunction in comparison to normal subjects, thus micafungin safety can be extrapolated to patients with severe renal dysfunction or mild-to-moderate hepatic dysfunction. However, micafungin pharmacokinetics were not studied in patients with severe hepatic dysfunction, and thus micafungin dosing and safety cannot be directly inferred in this group.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The toxicological profile of micafungin was evaluated in a variety of animals in 46 nonclinical studies, in single-dose and repeat dose toxicity studies. See pharmacology/toxicology review by Dr. Owen McMaster for full details. These studies have adequately characterized the primary target organ for micafungin toxicity as the liver in rats and dogs, as well as other organ-specific findings, including injection site reactions and local tolerance, histamine-related events, hemolysis and splenic changes in animals. Findings from the preclinical studies are incorporated into the clinical safety sections by organ system above. *In vitro* studies to evaluate cardiac repolarization were described in the cardiovascular safety section, and *in vitro* tests to evaluate micafungin hepatotoxicity were described in the hepatic safety section.

7.2.5 Adequacy of Routine Clinical Testing

Routine laboratory tests obtained in all clinical studies included hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count, serum

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

creatinine, blood urea nitrogen, AST, ALT, total bilirubin, sodium, potassium, chloride, calcium and albumin. Additionally, absolute neutrophil count, alkaline phosphatase, total protein, phosphate, magnesium, bicarbonate, and urinalysis were performed in most of the studies. Adverse event data was collected throughout the treatment period and for 72 hours after study drug administration. Vital sign data was collected routinely in each of the clinical studies; however, electrocardiograms were obtained on a routine basis only in phase 1 studies which enrolled healthy volunteers. Overall the routine clinical testing was adequate to evaluate safety. However, it would have been useful to have electrocardiographic data available for patients who experienced arrhythmias during the study, in order to determine the type of arrhythmia, and to evaluate for evidence of QT/QTc prolongation.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Micafungin metabolism, and excretion is discussed in section 5, and in the Clinical Pharmacology Review by Dr. Jang-Ik Lee. Micafungin was determined to be a substrate for, and a weak inhibitor of cytochrome P450 (CYP3A) *in vitro*. However, micafungin metabolism by CYP3A appears to be a relatively minor pathway *in vivo*. A number of drug-interaction studies were performed in healthy volunteers to evaluate potential interaction between micafungin and mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin. The drug-interaction work-up for micafungin appears to be adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Preclinical studies identified the liver as a major target organ for micafungin toxicity in animals. Other safety signals identified in animals were hemolysis, hemolytic anemia, injection site reactions, and histamine-associated effects. Monitoring for these potential micafungin toxicities was adequately performed by routine monitoring of adverse events and clinical laboratories in the clinical studies.

Caspofungin is the only approved echinocandin to date, and the potential for hepatic toxicity and histamine-mediated effects have been identified. Additionally, a caspofungin-cyclosporine drug interaction has been identified, which results in significant increases in caspofungin exposure. In a study in healthy volunteers, in which subjects received concomitant caspofungin and cyclosporine, several subjects developed transient elevations of ALT. In a drug interaction study of micafungin plus steady-state cyclosporine, no pharmacokinetic interactions were observed which resulted in increased micafungin exposure. Transient significant ALT elevations were observed in 2 healthy volunteers in this study, but could not be clearly attributed to micafungin alone, or micafungin in combination with mycophenolate mofetil. This review further analyzed patients who received micafungin plus mycophenolate mofetil in study 98-0-050, and in

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

the overall safety database, and no differences in serious hepatic adverse events were seen in patients who received micafungin alone or in combination with mycophenolate mofetil. These data are discussed in detail in the hepatic safety section,

7.1.12.4. Additional drug interaction studies were performed with micafungin, and are discussed further in section 7.4.2.5.

7.2.8 Assessment of Quality and Completeness of Data

Safety data for 2402 subjects in 3 clinical studies was submitted. Case report forms for a number of patients with serious adverse events in several studies were reviewed and no discrepancies were found in the database for adverse events reporting or for laboratory data. Additionally, for the original submission of study 98-0-050 for NDA 21-506, Dr. Ekopimo Ibia reviewed a random sample of case report forms to examine the quality of data entry, to ascertain entry criteria and accuracy of risk assessment, to compare success rate in the random sample with the overall success rate, to assess relatedness of treatment-emergent adverse events to study drug as assigned by the investigator. Dr. Ibia concluded that findings from review of the 10% random sample were consistent with the findings of the applicant.

7.2.9 Additional Submissions, Including Safety Update

In addition to the original NDA 21-754 submission, the 120-day safety update was submitted on 24 August, 2004. This submission included the updated Clinical Summary of Safety, the final study report for protocol 03-7-005, a pivotal study for the indication of esophageal candidiasis, the final study report for FG463-21-14, a phase 1 pharmacokinetics study, and a revision of the proposed micafungin label.

Additionally, the DSPIDP requested additional information regarding micafungin efficacy and safety data on a number of different occasions to adequately address questions raised during the review process. The largest of these submissions included hepatic safety data from clinical studies in which patients received concomitant mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, nifedipine, fluconazole, and ritonavir. Data from these submissions have been incorporated into the integrated summary of safety.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Drug-relatedness of an adverse event was assessed by the investigator, and includes possibly-related, probably-related and definitely-related to study drug. The overall incidence of drug-related adverse events was 29.9% (717/2402) in subjects who received micafungin. The most common drug-related adverse events were nausea, increased AST, increased ALT, leukopenia, vomiting, headache, rash, increased alkaline phosphatase,

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

and diarrhea, below. Common drug-related adverse events tables proposed for inclusion in the final micafungin labeling are found in section 3.1.5 above.

Adverse events identified as important and treatment-related in this review include:

- **Allergic reactions:** rash, maculopapular rash, urticaria, allergic reaction, anaphylactoid reactions
- **Hematological:** leukopenia, anemia, thrombocytopenia, hemolysis, hemolytic anemia
- **Hepatic:** abnormal liver function tests, increased AST, ALT, and alkaline phosphatase bilirubinemia, liver damage, hepatic failure, jaundice
- **Injection Site Reactions:** phlebitis, thrombophlebitis, injection site inflammation
- **Histamine-mediated reactions:** vasodilatation, rash, facial edema, pruritus
- **Infusion-related reactions:** hypotension, hypertension, tachycardia, chills, fever, cyanosis vomiting, and the histamine-mediated reactions listed above
- **Renal:** renal failure or dysfunction

These adverse findings are discussed in the special safety studies section (7.1.12), by organ system.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

The applicant pooled all clinical studies into an integrated safety database which included 2402 subjects (1980 patients and 422 volunteers) who received micafungin. This pooled data thus includes both patients and healthy volunteers, pediatric and adult patients, patients with differing underlying diseases, and a wide range of micafungin dosing regimens. Because of the wide range of subjects included in this database, meaningful safety signals could be obscured; however, identification of less frequent clinically significant adverse events can be done with the larger patient population.

For this review, the pooled safety data was reviewed for the integrated summary of safety, and safety was also evaluated separately for the individual studies submitted for this NDA, 03-7-005, FG463-21-09, 97-7-003, and 98-0-047. Safety was evaluated for the study 98-0-050 by Dr. Joette Meyer, for NDA 21-506, and Dr. Ekopimo Ibia previously reviewed safety in the studies submitted with the original NDA 21-506 submission.

7.4.1.1 Pooled data vs. individual study data

The individual studies submitted for the indication of esophageal candidiasis, 03-7-05, FG463-21-09, and 97-7-003, were reviewed individually for efficacy and safety. Supporting study 98-0-047 was reviewed with regard to efficacy of micafungin in

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

esophageal candidiasis, and with regard to safety as part of the pooled micafungin safety database provided by the Applicant in the 120-day safety update.

7.4.1.2 Combining data

Efficacy data for this NDA was not combined across studies. The applicant pooled safety data from 32 clinical studies into the micafungin safety database comprised of 2402 subjects, of which 1980 were patients and 422 were volunteers. Adverse events and laboratory data were pooled across all 32 studies. Additionally, a subset of studies, the fluconazole-controlled studies was analyzed for safety, comprised of 932 patients who received micafungin and 787 patients who received fluconazole. Pooling across studies was done without regard to study drug dose or duration, except where indicated.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

A dose-response analysis was performed by the Pharmacometrics Reviewer, Dr. Dakskina Chilukuri to evaluate the effect of micafungin dose on liver enzyme abnormalities in the esophageal candidiasis studies, 03-7-005, FG463-21-09, and 97-7-003. . See Pharmacology/Biopharmaceutics Review for full details. In brief, elevations of AST, ALT, total bilirubin and alkaline phosphatase were not significantly related to dose on a statistical basis. However, the frequency of ALT, AST, and alkaline phosphatase elevation ≥ 3 times the upper limit of normal was highest with 150 mg micafungin.

Additionally, in the pooled safety database, the applicant analyzed adverse events by micafungin dose and duration. For the pooled safety database, 222/606 (36.6%) subjects who received ≥ 150 mg/day micafungin for at least 10 days experienced an adverse event, in comparison to 495/1796 (27.6%) subjects who received a lower dose or duration of micafungin. This difference was attributed to increased severity of underlying illness between subjects who received the higher doses/duration of micafungin.

***Medical Officer Comments:** It is agreed that comparison between these dosing groups across studies is fraught with error due to differences in underlying illness, and potentially to a number of other unidentified factors.*

In the dose-ranging studies for treatment of esophageal candidiasis (studies FG463-21-09 and 97-7-003) the applicant found no clinically significant differences in the incidence of adverse events by dose. In our analysis of hepatobiliary adverse events, more patients who received 150 mg/day micafungin experienced a hepatobiliary adverse event than those who received 50 or 100 mg/day micafungin in study FG463-21-09, although the numbers of events were too low to show statistical significance (see FG463-21-09 study report, Appendix 10.1.2). For other classes of adverse events in this study (hematologic, renal, cardiovascular, injection site reactions, infusion reactions) there was no obvious

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

dose-response. In study 97-7-003, no clear dose-response was observed for all adverse events (including hepatobiliary adverse events), drug-related adverse events, and serious adverse events.

7.4.2.2 Explorations for time dependency for adverse findings

There was no apparent relationship between duration of micafungin therapy and the incidence of adverse events in the pooled safety database.

**APPEARS THIS WAY
ON ORIGINAL**

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

7.4.2.3 Explorations for drug-demographic interactions

Adverse Events by Age Group

The overall incidence of all adverse events was highest in pediatric patients (< 16 years old) in comparison to adults. A total of 228/244 (93.4%) pediatric subjects, 1647/1972 (83.5%) subjects, from 16 to < 65 years old, and 153/186 (82.3%) subjects \geq 65 years old experienced at least one adverse event in the clinical studies. The incidence of drug-related adverse events was somewhat lower in pediatric subjects, 24.6% (60/244) in comparison to adult subjects between the ages of 16 and 65 years old, 31.0% (612/1972). See section 8.3 for full discussion on pediatric safety. In elderly subjects (65 years and older), adverse events were generally similar in comparison to those reported in subjects between 16 and 65 years of age.

Adverse events reported more commonly among elderly subjects included infection (15.6% versus 13.6%), asthenia (18.3% versus 13.1%), sepsis 17.2% versus 10.8%), stomatitis (4.8% versus 2.3%), dysphagia (5.9% versus 1.8%), hypokalemia (23.1% versus 17.4%), peripheral edema (12.9% versus 8.6%), hypophosphatemia (10.8% versus 5.4%), confusion (8.1% versus 5.1%), ecchymosis (5.9% versus 2.8%), leukocytosis (7.0% versus 1.4%), hypotension (13.4% versus 9.1%), shock (5.4% versus 1.9%), atrial fibrillation (4.3% versus 1.4%), thrombophlebitis (2.7% versus 1.1%), skin disorder (7.0 versus 3.4%), urinary tract infection (6.5% versus 3.0%), and oliguria (7.0% versus 2.3%).

The incidence of drug-related adverse events in the elderly was lower, 24.2%, (45/186) subjects than in subjects 16 to < 65 years old, 31.0%, (612/1972). Only a few drug-related adverse events were marginally more common among the elderly than adults under age 65, including bilirubinemia (2.7% versus 1.2%), vomiting (2.7% versus 2.5%), diarrhea (2.7% versus 2.0%), anorexia (2.2% versus 0.3%), and phlebitis (2.2% versus 1.6%).

Adverse Events by Gender

No significant differences were observed in the incidence of adverse events between male, 81.2% (1209/1489) and female, 89.7% (819/913) subjects in the pooled safety database.

Adverse Events by Race or Ethnic Background

The overall incidence of adverse events was highest in Caucasian subjects in the pooled safety database. A total of 1369/1519 (90.1%) Caucasian subjects, 422/531 (79.5%) black subjects, and 237/352 (67.3%) subjects of other races/ethnic background experienced at least one adverse event. The applicant attributed this difference in adverse events to underlying diseases. In the pooled safety database, 84 % of Caucasian patients had an underlying hematological malignancy or were HSCT recipients, and 25.1% had HIV disease; while 57% black patients had HIV disease, and 7.9% had a hematological

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

malignancy or were HSCT recipients. The incidence of adverse events considered to be drug-related, was similar, however, among Caucasian, 30.2%, (458/1519) subjects, black subjects, 27.3% (145/531), and subjects of other races, 32.4%, (114/352).

***Medical Officer Comments:** The differences observed in underlying diseases between races in these clinical studies constitutes a plausible explanation for what appears to be racial differences in adverse events, because, as shown below, patients with an underlying hematological malignancy or HSCT recipients had higher incidence of adverse events than did patients with underlying HIV disease.*

7.4.2.4 Explorations for drug-disease interactions

Adverse Events by Underlying Disease

The overall incidence of adverse events was highest in patients with an underlying hematological malignancy or who received a HSCT. In the pooled safety database, 561/670 (83.7%) of patients with HIV disease, 935/946 (98.8%) of those with hematological malignancy or HSCT, and 328/364 (90.1%) of patients with other underlying conditions, experienced at least one adverse event. When drug-related adverse events were compared, patients with HIV disease had the highest incidence of adverse events at least possibly related to micafungin, 40.7%, (273/670), compared to 23.3% (219/946) in those with hematological malignancy or HSCT, and 27.2% (99/364) patients with other underlying conditions.

***Medical Officer Comments:** Although these data appear contradictory, patients with HIV in these studies were generally not hospitalized, and were taking fewer concomitant medications than those with a hematological malignancy or HSCT, which may explain why drug attribution of adverse events was highest in the HIV population.*

7.4.2.5 Explorations for drug-drug interactions

Drug-drug interaction studies were discussed in section 5.1 Pharmacology. Additional information regarding hepatic laboratory abnormalities in healthy subjects in the drug interaction studies, and analysis of hepatic adverse events in patients in who received immunosuppressant medications with micafungin was discussed in the Hepatic Safety section, 7.1.12.4.

7.4.3 Causality Determination

All evaluations regarding causality of adverse events in the clinical studies are likely limited due to the inherent complicated nature of the patients enrolled in the treatment studies of micafungin. In the adverse events of greatest concern, the causality evaluation proceeded as follows:

- 1) in vitro and preclinical data signifying a plausible link with drug exposure
- 2) the presence of a signal in normal volunteer data

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

- 3) positive de-challenge and re-challenge information in patients
- 4) comparative event rate to drugs with an established rate for the individual event of concern in a similar patient population
- 5) expert evaluation

Nonetheless, despite these thresholds for evaluating drug attribution, the information for specific events could still be limited. The reader is referred to the specific events of concern discussed in the organ specific safety section of this review. Some limitations in information could be augmented by additional information, such as performing controlled normal volunteers studies with a control arm. For some events, the alternative option is to prospectively evaluate postmarketing rates.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

For prophylaxis of infections caused by *Candida albicans*, the proposed dose in adults is 50 mg once daily and for treatment of esophageal candidiasis, the proposed dose is 150 mg once daily in adults. In clinical studies, patients with esophageal candidiasis were treated for a median duration of 14 days (ranging from 1-33 days) and Hematopoietic Stem Cell Transplant (HSCT) recipients were treated for a median duration of 18 days (ranging from 1-51 days). Patients successfully treated for esophageal candidiasis were treated for a mean duration of 15 days (ranging from 10-30 days); while HSCT patients with successful prophylaxis received micafungin for a mean of 19 days (ranging from 6 – 51 days).

Micafungin is to be marketed only as 50 mg vials, to be given as intravenous infusion following a 2 step drug preparation process. First, micafungin powder is to be reconstituted with physiologic saline or 5% dextrose to a final concentration of 10 mg/mL. The micafungin vial is overfilled by — during the filling process to compensate for the amount of drug product retained in vial following withdrawal. The drug is then withdrawn from the vial and further diluted with any of the two solutions. The diluted infusion solution should be protected from light. It is not necessary to cover the infusion drip chamber or the tubing. Revised directions for dilution of the reconstituted solution were proposed for the micafungin label, as follows:

For prophylaxis of *Candida* infections: add 50 mg MYCAMINE reconstituted in 5 ml Sodium Chloride for Injection, USP (See Reconstitution) into 100 mL of 0.9% Sodium Chloride for Injection, USP.

For treatment of esophageal candidiasis: add 150 mg MYCAMINE (from (3) 50 mg MYCAMINE vials) reconstituted in 15 ml Sodium Chloride for Injection USP (See Reconstitution) into 100 mL of 0.9% Sodium Chloride for Injection, USP.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

MYCAMINE is preservative-free. Discard partially used vials.

Infusion Volume and Duration

Revised directions for MYCAMINE infusion in the final product label were proposed, as follows:

MYCAMINE should be administered by intravenous infusion over a period of 1 hour. More rapid infusions may result in more frequent histamine mediated reactions.

NOTE: An existing intravenous line should be flushed with 0.9% Sodium Chloride for Injection, USP, prior to infusion of MYCAMINE.

No dosing adjustments are required based on race, gender, or in patients with severe renal dysfunction or mild-to-moderate hepatic insufficiency. The effect of severe hepatic impairment on micafungin pharmacokinetics has not been studied. (See **CLINICAL PHARMACOLOGY – Special Populations**).

No dose adjustment for MYCAMINE is required with concomitant use of mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, or rifampin. (See **PRECAUTIONS – Drug Interactions**.)

A loading dose is not required; typically, 85% of the steady-state concentration is achieved after three daily micafungin doses.

Do not mix or co-infuse MYCAMINE with other medications. MYCAMINE has been shown to precipitate when mixed directly with a number of other commonly used medications.

***Medical Officer Comments:** In the esophageal candidiasis study, 03-7-005, phlebitis and thrombophlebitis were common adverse events in patients who received 150 mg/day micafungin. However, there was no evidence of a clear dose-reponse for these adverse events in studies FG463-21-09 or in the maximum tolerated dose study, FG463-21-03. Additionally, the applicant has attributed the findings in study 03-7-005 to the use of peripheral intravenous catheters. At this time, it is unclear whether phlebitis is a dose-related adverse event, or related to the type of intravenous catheter used for administration. We have negotiated a statement in the ADVERSE REACTIONS section of the label which states that injection site reactions, including phlebitis and thrombophlebitis have been reported at doses of 50-150 mg/day. These events tended to occur more often in patients receiving MYCAMINE via peripheral intravenous administration.*

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

8.2 Drug-Drug Interactions

A number of drug-drug interaction studies were performed to evaluate the pharmacokinetic interactions between micafungin and mycophenolate mofetil, cyclosporine, tacrolimus, sirolimus, nifedipine, fluconazole, ritonavir, and rifampin. No interactions that altered the pharmacokinetics of micafungin were observed. Additionally no effect of single- or multiple- dose micafungin on the pharmacokinetics of mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, or fluconazole was observed. The effect of micafungin on the pharmacokinetics of rifampin and ritonavir has not been studied.

Sirolimus AUC was increased by 21%, with no effect on C_{max} in the presence of steady state micafungin, compared to sirolimus alone. Additionally, the AUC and C_{max} of nifedipine were increased by 18%, and 42%, respectively, in the presence of steady state micafungin, in comparison to nifedipine alone. The proposed micafungin label states “Patients receiving sirolimus or nifedipine in combination with micafungin should be monitored for sirolimus or nifedipine toxicity, or the dosage of these drugs should be reduced, if necessary.

***Medical Officer Comments:** In review of safety in these drug interaction studies in healthy volunteers, significant elevations of hepatic transaminases were seen in 3 subjects who received concomitant micafungin plus mycophenolate mofetil, fluconazole, and ritonavir. Significant transaminase elevation was not observed in subjects who received steady state cyclosporine or tacrolimus with micafungin (or with non-steady state sirolimus). These studies are reviewed in the hepatic safety section of in this review, section 7.1.12.4.*

In addition, we analyzed serious hepatic adverse events and significant transaminase elevations in patients who received concomitant micafungin plus mycophenolate mofetil, cyclosporine, or tacrolimus in study 98-0-050, a patient population at high risk for graft-versus-host disease (GVHD), who received these immunosuppressive agents frequently either for prophylaxis or treatment of GVHD. Additionally, patients who received concomitant nifedipine plus micafungin in study 98-0-050 were evaluated; and patients in the pooled safety database who received concomitant fluconazole plus micafungin, and patients in study FG463-21-09 who received micafungin plus ritonavir, were evaluated for serious hepatic adverse events and transaminase elevations. See hepatic safety section, this review, section 7.1.12.4.

8.3 Special Populations

Geriatric Use

A total of 186 subjects in clinical studies of MYCAMINE were 65 years of age and older, and 41 of these subjects were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (See section 7.4.2.3 for drug-demographic relationships).

8.4 Pediatrics

A total of 244 pediatric patients under the age of 16 were enrolled in clinical studies and are included in the micafungin safety database. Sixty of these patients were under the age of 2 years, an age group not generally expected to require treatment for either esophageal candidiasis or antifungal prophylaxis after HSCT. A total of 4 pediatric patients were treated for esophageal candidiasis in the invasive candidiasis study, 98-0-047.

_____ , they received micafungin at a dose of 1.0 to 2.1 mg/kg/day, _____

_____ Thirty nine pediatric patients were enrolled in the *Candida* prophylaxis study, 98-0-050 and received micafungin 1.0 mg/kg/day, _____

Micafungin safety was evaluated in 244 pediatric patients, most of whom had underlying hematological malignancies or who were HSCT recipients. Of these, patients, 184 were between the ages of 2 and 16 years old, and only 23 patients in this age group received micafungin at doses of ≥ 3 mg/kg/day, 31 patients received ≥ 2 mg/kg/day, 100 patients received between 1.0 and 1.9 mg/kg/day, and 30 patients received less than 1.0 mg/kg/day.

Review of the pediatric safety data revealed a higher incidence of any adverse event in subjects under 16 years of age, 93.4 %, (228/244), in comparison to those between the ages of 16 and 65 years, 83.5%, (1647/1972), and those 65 years and older, 82.3%, (153/186). Those events that were considered at least possibly related to study drug, occurred in 24.6% (60/244) subjects < 16 years old, 31% (612/1972) subjects between the ages of 16 and 65 years, and in 24.2% (45/186) subjects ages 65 and above. Serious adverse events occurred in 35.2% (86/244) patients under the age of 16, 26.6% (418/1573) patients between the ages of 16 and 65, and in 30.7% (50/163) elderly patients. The incidence of mortality in pediatric patients in these studies was 20.1% (49/244), compared to 19.2% (291/1573) in patients between 16 and 65 years old, and 26.4% (43/163) in patients aged 65 years and older.

These safety data, particularly those showing a higher incidence of all adverse events and serious adverse events in pediatric patients, were concerning, and have led us to conclude that additional micafungin safety data will be recommended in children prior to receiving a pediatric indication for either *Candida* prophylaxis or esophageal candidiasis. We propose to include the following statement in the final micafungin labeling: "The safety and efficacy of MYCAMINE™ in pediatric patients has not been established in clinical studies".

An overview of the pediatric safety of micafungin is provided below.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Pharmacokinetics of Micafungin in Pediatric Patients

Please see Clinical Pharmacology review by Dr. Jang-Ik Lee, for full details. In brief, the applicant submitted pediatric pharmacokinetic data for for _____ patients between 2 and 17 years old. _____

/ / / / /

For the 2-17 year old febrile, neutropenic patients evaluated in study 98-0-043 for micafungin efficacy, safety, and pharmacokinetics, significant errors in data collection were identified, and the data was considered inadequate to fully evaluate the pharmacokinetic profile of micafungin in this age group. Thus, we have proposed that no pediatric pharmacokinetic information be included in the current micafungin labeling.

Patient Characteristics

A total of 244 patients under age 16 received micafungin in the clinical development program. Age ranges for pediatric patients are shown in the table below. Most pediatric patients were between 2 to 12 years old. Additionally, most children (68%) were recipients of a hematopoietic stem cell transplant (HSCT), or had received chemotherapy for a hematologic malignancy. The majority of pediatric patients were male (52.7%), Caucasian (76.6%), and from the United States (91.8%).

Table 181. Pediatric Age Categories for Micafungin-Treated Pediatric Patients: All Studies (Applicant's Table 2, section 5.3.5.3.2)

Age Categories	Number of Pediatric Patients in Each Category
Infants and Toddlers (0 through <24 months)	50 (20.5%)
Children (2 through <12 years)	132 (54.1%)
Adolescents (12 through <16 years)	62 (25.4%)

Patient base: all pediatric patients who received at least 1 dose of study drug.
Source: Appendix 1.4.2

Patient Disposition

Overall approximately 75% of pediatric patients completed the study in which they were enrolled, 19% died, and 3% were lost-to-follow-up. The incidence of mortality was highest in older children, 24.6% in 8-12 year olds, and 23.9% in 13-15 year olds.

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

Table 182. Summary of Patient Disposition by Age (from applicant's Appendix 1.1)

	0-2 years old N=60	3-7 years old N=76	8-12 years old N=65	13-15 years old N=46	Overall N=247
	n (%)	n (%)	n (%)	n (%)	n (%)
Full Analysis Set	60 (100)	75 (98.7)	65 (100)	46 (100)	244 (98.8%)
Per Protocol Set	51 (85)	58 (89.5)	51 (78.5)	38 (82.6)	208 (84.2)
End of Study Status:					
Completed Study	48 (80)	61 (80.3)	43 (66.2)	34 (73.9)	186 (75.3)
Death	9 (15)	12 (15.8)	16 (24.6)	11 (23.9)	48 (19.4)
Lost to follow-up	1 (1.7)	2 (2.6)	4 (6.2)	1 (2.2)	8 (3.2)
Other	2 (3.3)	1 (1.3)	2 (3.1)	0 (0)	5 (2.0)

N= number of patients enrolled

n (%) = number and percentage of patients

Full analysis set = patients who received at least one dose of micafungin

Per protocol set= patients who were evaluable in their respective studies

**APPEARS THIS WAY
 ON ORIGINAL**

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

Micafungin Exposure in Pediatric Patients

The following table shows studies in which pediatric patients were enrolled. Four patients in the invasive candidiasis study (98-0-047) were treated for esophageal candidiasis at micafungin doses ranging from 1.0 to 2.1 mg/kg/day, for 17-42 days.

Table. 183. Pediatric Studies in Micafungin Database

Study	Study Design	Indication for Micafungin	N	Micafungin Dose	Duration Range (days)
98-0-043	Open-label, sequential dose escalation (maximum tolerated dose) and PK study	Febrile neutropenia	69	0.5, 1.0, 1.5, 2.0, 3.0, or 4.0 mg/kg/day (maximum 200 mg/day)	3 days to 4 weeks
98-0-046	Open-label	Invasive aspergillosis	70	Initial dose 75 mg/day (1.5 mg/kg/day for ≤ 40 kg, could be escalated to 225 mg/day (4.5 mg/kg/day for ≤ 40 kg)	Maximum of 90 days
98-0-047	Open-label	Invasive candidiasis	53	50 mg/day or 1 mg/kg/day if ≤ 40 kg; and 100 mg/day or 2 mg/kg/day if ≤ 40 kg	Maximum 6 weeks
98-0-050	Randomized, double-blind	Antifungal prophylaxis	45	50 mg/day or 1 mg/kg/day if ≤ 50 kg vs. fluconazole 400 mg/day	Maximum of 42 days

N= number of patients who received at least 1 dose of micafungin (FAS)

Overall micafungin exposure in the pediatric age group is shown in the table below.

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

Table 184. Summary of Micafungin Treatment Duration (Days) by Mean Daily Dose

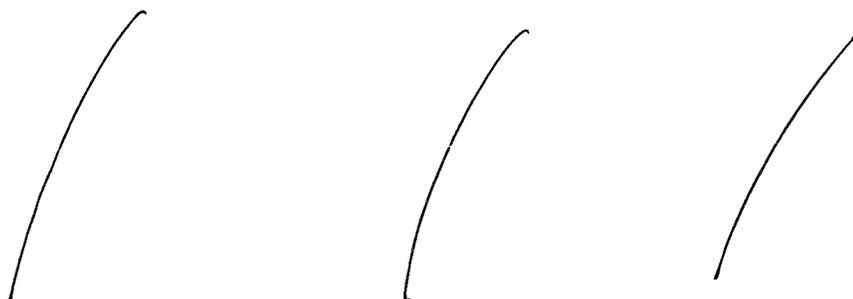
and Age Group (Applicant's Table 4, section 5.3.5.3.2)

Age Group	Micafungin Mean Daily Dose (mg/kg)				
	<1.0	1.0-1.9	2.0-2.9	3.0-3.9	≥4.0
0-23 months	(n=10)	(n=34)	(n=7)	(n=7)	(n=2)
Mean (Days)	2.4	21.7	40.4	22.0	27.5
Range (Days)	1-7	1-58	1-134	1-114	27-28
3-7 years	(n=7)	(n=42)	(n=13)	(n=7)	(n=6)
Mean (Days)	11.3	26.4	78.4	31.6	47.2
Range (Days)	3-22	2-218	3-495	2-173	4-132
8-12 years	(n=10)	(n=32)	(n=13)	(n=3)	(n=5)
Mean (Days)	17.0	24.0	29.2	3.7	64.8
Range (Days)	4-29	2-106	1-162	2-6	4-147
13-15 years	(n=13)	(n=26)	(n=5)	(n=1)	(n=1)
Mean (Days)	20.2	64.8	174	91.0	65.0
Range (Days)	3-112	2-490	5-681	91-91	65-65
Total Treatment Days of Exposure	536	4298	2552	477	727

Patient base: all pediatric patients who received at least 1 dose of study drug.

Source: Appendix 2.4.2 and 2.1.2

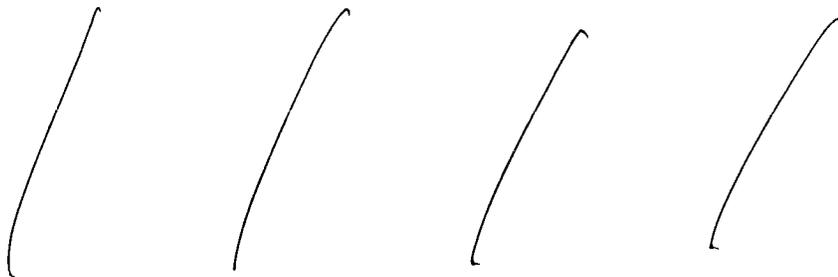
Medical Officer Comments: If patients under 2 years old are excluded, 30 patients received < 1.0 mg/kg/day, 100 patients received between 1.0 and 1.9 mg/kg/day, 31 patients received between 2.0 and 2.9 mg/kg/day, and 23 patients received ≥ 3 mg/kg/day micafungin in these studies.



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



Efficacy of Micafungin in Pediatric Patients



Safety of Micafungin in Pediatric Patients

A summary of adverse events in pediatric patients is shown in the following table.

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

Table 186. Adverse Events in Pediatric Patients who received Micafungin

	Pediatric Patients (N=244)
	n (%)
All adverse events	228 (93.4)
All drug-related adverse events	60 (24.6)
Serious adverse events	86 (35.2)
Drug-related serious adverse events	12 (4.9)
Adverse events resulting in discontinuation	30 (12.3)
Deaths	49 (20.1)

The overall incidence of adverse events in children under age 16 was 93.4% (228/244) subjects, was higher than that reported in patients between the age of 16 and 65, 83.5% (1647/1972) subjects, and than in patients older than 65 years, 82.3% (153/186). The table below, adverse compares the adverse event profile in pediatric patients and adults by age category.

Table 187. Summary of Adverse Events in Micafungin-Treated Subjects by Age Group (adapted from Applicant's Appendix 4.1.1, Safety Update)

BODY SYSTEM (1) COSTART TERM	-----AGE GROUP (YEARS)-----			TOTAL (N=2402)
	< 16 (N=244)	16 TO <65 (N=1972)	>=65 (N=186)	
ALL SYSTEMS	228(93.4%)	1647(83.5%)	153(82.3%)	2028(84.4%)
BODY AS A WHOLE ANY AE	183(75.0%)	1143(58.0%)	111(59.7%)	1437(59.8%)
ABDOMINAL PAIN	66(27.0%)	335(17.0%)	32(17.2%)	433(18.0%)
INFECTION	57(23.4%)	268(13.6%)	29(15.6%)	354(14.7%)
PROCEDURAL COMPLICATION	61(25.0%)	272(13.8%)	19(10.2%)	352(14.7%)
ALLERGIC REACTION	26(10.7%)	75(3.8%)	5(2.7%)	106(4.4%)
GRAFT VERSUS HOST DISEASE	20(8.2%)	57(2.9%)	0	77(3.2%)
FACE EDEMA	14(5.7%)	55(2.8%)	4(2.2%)	73(3.0%)
DIGESTIVE SYSTEM ANY AE	177(72.5%)	1120(56.8%)	103(55.4%)	1400(58.3%)
VOMITING	86(35.2%)	464(23.5%)	36(19.4%)	586(24.4%)
LIVER FUNCTION TESTS ABNORMAL	14(5.7%)	87(4.4%)	4(2.2%)	105(4.4%)
JAUNDICE	9(3.7%)	51(2.6%)	2(1.1%)	62(2.6%)
HEPATOMEGALY	20(8.2%)	12(0.6%)	0	32(1.3%)
HEPATIC FAILURE	2(0.8%)	7(0.4%)	1(0.5%)	10(0.4%)
HEPATOSPLENOMEGALY	3(1.2%)	6(0.3%)	0	9(0.4%)
CHOLESTATIC JAUNDICE	1(0.4%)	4(0.2%)	0	5(0.2%)
HEPATITIS, NONSPECIFIC	1(0.4%)	2(0.1%)	0	3(0.1%)
METABOLIC NUTRITIONAL ANY AE	158(64.8%)	936(47.5%)	104(55.9%)	1198(49.9%)
HYPOKALEMIA	62(25.4%)	343(17.4%)	43(23.1%)	448(18.7%)
HYPOMAGNESEMIA	38(15.6%)	324(16.4%)	25(13.4%)	387(16.1%)
EDEMA	34(13.9%)	165(8.4%)	15(8.1%)	214(8.9%)
PERIPHERAL EDEMA	10(4.1%)	170(8.6%)	24(12.9%)	204(8.5%)
HYPOCALCEMIA	22(9.0%)	137(6.9%)	14(7.5%)	173(7.2%)
BILIRUBINEMIA	29(11.9%)	123(6.2%)	10(5.4%)	162(6.7%)
SGPT INCREASED	22(9.0%)	109(5.5%)	5(2.7%)	136(5.7%)
SGOT INCREASED	17(7.0%)	112(5.7%)	6(3.2%)	135(5.6%)
ALKALINE PHOSPHATASE INCREASED	7(2.9%)	89(4.5%)	7(3.8%)	103(4.3%)
BUN INCREASED	13(5.3%)	56(2.8%)	7(3.8%)	76(3.2%)

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

ACIDOSIS	15(6.1%)	47(2.4%)	6(3.2%)	68(2.8%)
HYPERNATREMIA	15(6.1%)	36(1.8%)	7(3.8%)	58(2.4%)
ELECTROLYTE ABNORMALITY	2(0.8%)	6(0.3%)	0	8(0.3%)
CREATININE CLEARANCE DECREASED	1(0.4%)	1(0.1%)	1(0.5%)	3(0.1%)
NERVOUS SYSTEM ANY AE	106(43.4%)	878(44.5%)	69(37.1%)	1053(43.8%)
HEADACHE	43(17.6%)	397(20.1%)	23(12.4%)	463(19.3%)
INSOMNIA	13(5.3%)	243(12.3%)	20(10.8%)	276(11.5%)
AGITATION	19(7.8%)	52(2.6%)	4(2.2%)	75(3.1%)
NERVOUSNESS	13(5.3%)	47(2.4%)	5(2.7%)	65(2.7%)
CONVULSION	13(5.3%)	15(0.8%)	2(1.1%)	30(1.2%)
NEUROPATHY	3(1.2%)	15(0.8%)	1(0.5%)	19(0.8%)
CEREBROVASCULAR ACCIDENT	1(0.4%)	2(0.1%)	1(0.5%)	4(0.2%)
RESPIRATORY SYSTEM ANY AE	144(59.0%)	783(39.7%)	78(41.9%)	1005(41.8%)
COUGH INCREASED	38(15.6%)	199(10.1%)	12(6.5%)	249(10.4%)
DYSPNEA	33(13.5%)	174(8.8%)	14(7.5%)	221(9.2%)
LUNG DISORDER	27(11.1%)	126(6.4%)	9(4.8%)	162(6.7%)
RHINITIS	30(12.3%)	123(6.2%)	8(4.3%)	161(6.7%)
PNEUMONIA	15(6.1%)	134(6.8%)	10(5.4%)	159(6.6%)
EPISTAXIS	33(13.5%)	119(6.0%)	6(3.2%)	158(6.6%)
HYPOXIA	18(7.4%)	53(2.7%)	6(3.2%)	77(3.2%)
LUNG EDEMA	7(2.9%)	29(1.5%)	4(2.2%)	40(1.7%)
HEMIC/LYMPHATIC SYSTEM ANY AE	119(48.8%)	730(37.0%)	78(41.9%)	927(38.6%)
LEUKOPENIA	50(20.5%)	418(21.2%)	33(17.7%)	501(20.9%)
THROMBOCYTOPENIA	52(21.3%)	379(19.2%)	34(18.3%)	465(19.4%)
ANEMIA	40(16.4%)	253(12.8%)	20(10.8%)	313(13.0%)
PETECHIA	18(7.4%)	60(3.0%)	5(2.7%)	83(3.5%)
LEUKOCYTOSIS	7(2.9%)	28(1.4%)	13(7.0%)	48(2.0%)
CARDIOVASCULAR SYSTEM ANY AE	131(53.7%)	710(36.0%)	77(41.4%)	918(38.2%)
HYPOTENSION	34(13.9%)	180(9.1%)	25(13.4%)	239(10.0%)
TACHYCARDIA	31(12.7%)	181(9.2%)	13(7.0%)	225(9.4%)
HYPERTENSION	51(20.9%)	139(7.0%)	10(5.4%)	200(8.3%)
SHOCK	5(2.0%)	38(1.9%)	10(5.4%)	53(2.2%)
BRADYCARDIA	16(6.6%)	33(1.7%)	3(1.6%)	52(2.2%)
ARRHYTHMIA	14(5.7%)	18(0.9%)	4(2.2%)	36(1.5%)
DEEP THROMBOPHLEBITIS	4(1.6%)	19(1.0%)	1(0.5%)	24(1.0%)
PERICARDIAL EFFUSION	7(2.9%)	16(0.8%)	1(0.5%)	24(1.0%)
DERMATOLOGIC ANY AE	121(49.6%)	647(32.8%)	59(31.7%)	827(34.4%)
RASH	62(25.4%)	308(15.6%)	26(14.0%)	396(16.5%)
PRURITUS	41(16.8%)	135(6.8%)	5(2.7%)	181(7.5%)
SKIN DISORDER	25(10.2%)	68(3.4%)	13(7.0%)	106(4.4%)
MACULOPAPULAR RASH	7(2.9%)	55(2.8%)	4(2.2%)	66(2.7%)
VESICULOBULLOUS RASH	7(2.9%)	16(0.8%)	2(1.1%)	25(1.0%)
SKIN NECROSIS	1(0.4%)	0	0	1(0.0%)
UROGENITAL SYSTEM ANY AE	75(30.7%)	403(20.4%)	47(25.3%)	525(21.9%)
HEMATURIA	15(6.1%)	94(4.8%)	8(4.3%)	117(4.9%)
OLIGURIA	19(7.8%)	46(2.3%)	13(7.0%)	78(3.2%)
KIDNEY FAILURE	9(3.7%)	37(1.9%)	4(2.2%)	50(2.1%)
KIDNEY FUNCTION ABNORMAL	9(3.7%)	29(1.5%)	4(2.2%)	42(1.7%)
ACUTE KIDNEY FAILURE	4(1.6%)	16(0.8%)	2(1.1%)	22(0.9%)
HEMORRHAGIC CYSTITIS	5(2.0%)	13(0.7%)	0	18(0.7%)
ALBUMINURIA	3(1.2%)	11(0.6%)	1(0.5%)	15(0.6%)
KIDNEY TUBULAR DISORDER	1(0.4%)	1(0.1%)	0	2(0.1%)
MUSCULOSKELETAL SYSTEM ANY AE	45(18.4%)	250(12.7%)	12(6.5%)	307(12.8%)
ARTHRALGIA	23(9.4%)	106(5.4%)	7(3.8%)	136(5.7%)

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

MYASTHENIA	7(2.9%)	24(1.2%)	0	31(1.3%)
ARTHROSIS	2(0.8%)	7(0.4%)	0	9(0.4%)
SPECIAL SENSES ANY AE	45(18.4%)	234(11.9%)	15(8.1%)	294(12.2%)
EYE PAIN	8(3.3%)	20(1.0%)	2(1.1%)	30(1.2%)
ENDOCRINE SYSTEM ANY AE	5(2.0%)	10(0.5%)	0	15(0.6%)
HYPOTHYROIDISM	3(1.2%)	2(0.1%)	0	5(0.2%)
ADRENAL CORTEX INSUFFICIENCY	2(0.8%)	2(0.1%)	0	4(0.2%)

Medical Officer Comments: Some of the more common adverse events that occurred more frequently in children younger than 16 than in older patients, included abdominal pain, infection, procedural complication, sepsis, chills, pain, allergic reactions, vomiting, mucositis, anorexia, rectal disorder, stomatitis, hepatomegaly, hypokalemia, edema, hyperglycemia, bilirubinemia, hypervolemia, hypoproteinemia, hypernatremia, anxiety, agitation, nervousness, convulsion, increased cough, dyspnea, lung disorder, rhinitis, epistaxis, pharyngitis, hypoxia, hyperventilation, thrombocytopenia, anemia, petechia, hypotension, hypertension, tachycardia, bradycardia, arrhythmia, valvular heart disease, rash, skin disorder, pruritus, urinary tract infection, oliguria, and arthralgia.

The higher incidence of adverse events in the pediatric population in comparison with adults may be due to differences in underlying disease and severity of illness because most pediatric patients in the safety database had an underlying hematological malignancy, were neutropenic, or had received a HSCT in comparison to the adult population which included healthy volunteers, patients with HIV and patients with hematological malignancies or transplant.

Adverse Events by Dose

Study 98-0-043 was an open-label study in febrile, neutropenic pediatric patients, 2-17 years old, to evaluate the maximum tolerated dose of micafungin. This study was summarized by the applicant for the section on pediatric safety with this NDA submission, but was not reviewed in its entirety for this review, because it was submitted with NDA 21-506. Safety data from this study was included in the pooled micafungin safety database. This study enrolled 77 patients, 8 of whom were 16-17 years old and were not included as pediatric patients in the combined pediatric safety database. Patients received micafungin doses of 0.5, 1.0, 1.5, 2.0, 3.0 and 4.0 mg/kg in the 98-0-043 protocol. Overall, 9/77 (11.7%) patients experienced an adverse event that was at least possibly related to micafungin. The applicant concluded that there was no evidence of dose-limiting toxicity at doses up to 4 mg/kg/day in this patient population. Common adverse events are shown by micafungin dose in the table below.

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

Table 188. Common Adverse Events in Pediatric Study 98-0-043 by Micafungin Dose (Applicant's Synopsis Table 7, NDA 21-506)

Body System Preferred Term	FK463 Dose Level (mg/kg per day)					
	n (%)					
	0.5 (n=16)	1.0 (n=18)	1.5 (n=13)	2.0 (n=12)	3.0 (n=10)	4.0 (n=8)
No. with Adverse Event	15 (93.8%)	15 (83.3%)	12 (92.3%)	11 (91.7%)	7 (70.0%)	8 (100.0%)
Body As A Whole						
Abdominal Pain	2 (12.5%)	3 (16.7%)	4 (30.8%)	2 (16.7%)	1 (10.0%)	1 (12.5%)
Abdomen Enlarged	1 (6.3%)	0 (0.0%)	0 (0.0%)	3 (25.0%)	0 (0.0%)	0 (0.0%)
Chills	4 (25.0%)	3 (16.7%)	1 (7.7%)	2 (16.7%)	1 (10.0%)	1 (12.5%)
Pain	0 (0.0%)	1 (5.6%)	0 (0.0%)	3 (25.0%)	0 (0.0%)	3 (37.5%)
Procedural Complication	4 (25.0%)	2 (11.1%)	5 (38.5%)	0 (0.0%)	1 (10.0%)	1 (12.5%)
Cardiovascular System						
Tachycardia	4 (25.0%)	2 (11.1%)	1 (7.7%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Digestive System						
Diarrhea	4 (25.0%)	1 (5.6%)	5 (38.5%)	2 (16.7%)	2 (20.0%)	1 (12.5%)
Vomiting	2 (12.5%)	2 (11.1%)	4 (30.8%)	0 (0.0%)	3 (30.0%)	2 (25.0%)
Mucositis	5 (31.3%)	0 (0.0%)	3 (23.1%)	1 (8.3%)	0 (0.0%)	3 (37.5%)
Rectal Disorder	1 (6.3%)	5 (27.8%)	2 (15.4%)	1 (8.3%)	1 (10.0%)	1 (12.5%)
Hemic & Lymphatic System						
Anemia	4 (25.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	2 (20.0%)	1 (12.5%)
Thrombocytopenia	4 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)
Metabolic and Nutritional Disorders						
Hypocalcemia	4 (25.0%)	2 (11.1%)	1 (7.7%)	1 (8.3%)	1 (10.0%)	1 (12.5%)
Hypophosphatemia	4 (25.0%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	3 (37.5%)
Edema	5 (31.3%)	0 (0.0%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	0 (0.0%)
Hyperglycemia	0 (0.0%)	2 (11.1%)	0 (0.0%)	3 (25.0%)	1 (10.0%)	0 (0.0%)
Nervous System						
Headache	3 (18.8%)	6 (33.3%)	1 (7.7%)	0 (0.0%)	2 (20.0%)	1 (12.5%)
Respiratory System						
Epistaxis	5 (31.3%)	1 (5.6%)	3 (23.1%)	3 (25.0%)	1 (10.0%)	1 (12.5%)
Hyperventilation	2 (12.5%)	2 (11.1%)	0 (0.0%)	3 (25.0%)	0 (0.0%)	0 (0.0%)
Cough Increased	1 (6.3%)	1 (5.6%)	2 (15.4%)	0 (0.0%)	0 (0.0%)	2 (25.0%)
Skin and Appendages						
Rash	4 (25.0%)	2 (11.1%)	2 (15.4%)	2 (16.7%)	0 (0.0%)	1 (12.5%)

Patient base: all patients who received at least 1 dose of study drug (full analysis set). Both age groups combined.
 Procedural complications: these complications were related to central lines, Broviac catheters, or post-surgical procedures. See Appendix 14.4.17. More than 1 event may be reported for each patient. Common ≥ 25% at any dose level. Source: Table 13.5.1.1

Best Possible Copy

Medical Officer Comments: Too few patients were included in each dosing category to draw firm conclusions about dose-related adverse events in this study.

In the combined pediatric safety database, the overall incidence of adverse events was somewhat higher in pediatric patients who received ≥ 150 mg micafungin (or ≥ 3 mg/kg/day) for at least 10 days than in patients who received lower doses or durations of micafungin; and likewise, the incidence of adverse events was higher in those who received ≥ 100 mg/day (or ≥ 2 mg/kg/day) for at least 10 days in comparison to those who received lower doses or shorter duration of micafungin. Common adverse events are shown by dose in the following table.

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

Table 189. Common Adverse Events* in Pediatric Patient by Dose/Duration of Micafungin (adapted from Appendices 4.3.2.1.1 and 4.3.2.2.1, section 5.3.5.3.2)

Adverse Event COSTART Body System and Preferred Term**	Micafungin < 100 mg/day (or < 2 mg/kg/day for patient < 40 kg for <10 days) N=199	Micafungin ≥ 100 mg/day (or ≥ 2 mg/kg/day for patient < 40 kg for ≥ 10 days) N=45	Micafungin ≤ 150 mg/day (or < 3 mg/kg/day for patient < 40 kg for < 10 days) N=215	Micafungin ≥ 150 mg/day (or ≥ 3 mg/kg/day for patient < 40 kg for ≥ 10 days N=29
	n (%)	n (%)	n (%)	n (%)
All Systems	183 (92.0)	45 (100)	199 (92.6)	29 (100)
Body as a whole:				
Abdominal pain	48 (24.1)	18 (40.0)	54 (25.1)	12 (41.4)
Procedural complication	45 (22.6)	16 (35.6)	48 (22.3)	13 (44.8)
Fever	40 (20.1)	15 (33.3)	43 (20.0)	12 (41.4)
Infection	36 (18.1)	21 (46.7)	40 (18.6)	17 (58.6)
Sepsis	33 (16.6)	16 (35.6)	35 (16.3)	14 (48.3)
Pain	28 (14.1)	10 (22.2)	29 (13.5)	9 (31.0)
Chills	25 (12.6)	8 (17.8)	26 (12.1)	7 (24.1)
Allergic reaction	20 (10.1)	6 (13.3)	21 (9.8)	5 (17.2)
Abdomen enlarged	15 (7.5)	9 (20.0)	20 (9.3)	4 (13.8)
Back pain	19 (9.5)	5 (11.1)	19 (8.8)	5 (17.2)
Asthenia	11 (5.5)	7 (15.6)	13 (6.0)	5 (17.2)
Cellulitis	4 (2.0)	5 (11.1)	5 (2.3)	4 (13.8)
Accidental injury	3 (1.5)	3 (6.7)	3 (1.4)	3 (10.3)
Malaise	0 (0)	3 (6.7)	0 (0)	3 (10.3)
Digestive System:				
Vomiting	66 (33.2)	20 (44.4)	74 (34.4)	12 (41.4)
Mucositis	51 (25.6)	5 (11.1)	51 (23.7)	5 (17.2)
Nausea	47 (23.6)	13 (28.9)	51 (23.7)	9 (31.0)
Diarrhea	45 (22.6)	22 (48.9)	49 (22.8)	18 (62.1)
Anorexia	33 (16.6)	5 (11.1)	33 (15.3)	5 (17.2)
Rectal disorder	21 (10.6)	5 (11.1)	22 (10.2)	4 (13.8)
Constipation	19 (9.5)	7 (15.6)	20 (9.3)	6 (20.7)
Hepatomegaly	14 (7.0)	6 (13.3)	16 (7.4)	4 (13.8)
Stomatitis	7 (3.5)	10 (22.2)	8 (3.7)	9 (31.0)
Dyspepsia	6 (3.0)	3 (6.7)	6 (2.8)	3 (10.3)
Dry mouth/nose	3 (1.5)	4 (8.9)	4 (1.9)	3 (10.3)
Tongue disorder	3 (1.5)	3 (6.7)	3 (1.4)	3 (10.3)
Metabolic and				

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

Nutritional disorders:				
Hypokalemia	44 (22.1)	18 (40.0)	49 (22.8)	13 (44.8)
Hypomagnesemia	31 (15.6)	7 (15.6)	33 (15.3)	5 (17.2)
Edema	26 (13.1)	8 (17.8)	28 (13.0)	6 (20.7)
Hypoproteinemia	21 (10.6)	5 (11.1)	24 (11.2)	2 (6.9)
Bilirubinemia	19 (9.5)	10 (22.2)	22 (10.2)	7 (24.1)
Hypervolemia	21 (10.6)	9 (20.0)	22 (10.2)	8 (27.6)
Hyperglycemia	17 (8.5)	10 (22.2)	20 (9.3)	7 (24.1)
Hypocalcemia	16 (8.0)	6 (13.6)	17 (7.9)	5 (17.2)
ALT increased	17 (8.5)	5 (11.1)	17 (7.9)	5 (17.2)
Hypophosphatemia	15 (7.5)	4 (8.9)	15 (7.0)	4 (13.8)
Hypernatremia	9 (4.5)	6 (13.3)	12 (5.6)	3 (10.3)
Hyponatremia	11 (5.5)	5 (11.1)	12 (5.6)	4 (13.8)
AST increased	12 (6.0)	5 (11.1)	12 (5.6)	5 (17.2)
Acidosis	10 (5.0)	5 (11.1)	11 (5.1)	4 (13.8)
Hyperkalemia	7 (3.5)	7 (15.6)	11 (5.1)	3 (10.3)
Respiratory acidosis	6 (3.0)	5 (11.1)	9 (4.2)	2 (6.9)
BUN increased	7 (3.5)	6 (13.3)	8 (3.7)	5 (17.2)
Dehydration	1 (0.5)	3 (6.7)	1 (0.5)	3 (10.3)
Respiratory System:				
Cough increased	25 (12.6)	13 (28.9)	28 (13.0)	10 (34.5)
Epistaxis	21 (10.6)	12 (26.7)	24 (11.2)	9 (31.0)
Lung disorder	19 (9.5)	8 (17.8)	23 (10.7)	4 (13.8)
Dyspnea	15 (7.5)	18 (40.0)	21 (9.8)	12 (41.4)
Rhinitis	16 (8.0)	14 (31.1)	21 (9.8)	9 (31.0)
Hyperventilation	15 (7.5)	8 (17.8)	16 (7.4)	7 (24.1)
Pharyngitis	10 (5.0)	9 (20.0)	11 (5.1)	8 (27.6)
Pneumonia	9 (4.5)	6 (13.3)	11 (5.1)	4 (13.8)
Respiratory failure	7 (3.5)	4 (8.9)	8 (3.7)	3 (10.3)
Sinusitis	5 (2.5)	8 (17.8)	8 (3.7)	5 (17.2)
Respiratory disorder	6 (3.0)	4 (8.9)	7 (3.3)	3 (10.3)
Pleural effusion	6 (3.0)	7 (15.6)	6 (2.8)	7 (24.1)
Asthma	4 (2.0)	4 (8.9)	4 (1.9)	4 (13.8)
Lung edema	2 (1.0)	5 (11.1)	3 (1.4)	4 (13.8)
Cardiovascular system:				
Hypertension	34 (17.1)	17 (37.8)	38 (17.7)	13 (44.8)
Hypotension	22 (11.1)	12 (26.7)	24 (11.2)	10 (34.5)
Tachycardia	22 (11.1)	9 (20.0)	23 (10.7)	8 (27.6)
Bradycardia	7 (3.5)	9 (20.0)	12 (5.6)	4 (13.8)
Arrhythmia	9 (4.5)	5 (11.1)	10 (4.7)	4 (13.8)
Skin and appendages:				

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

Rash	46 (23.1)	16 (35.6)	51 (23.7)	11 (37.9)
Pruritis	29 (14.6)	12 (26.7)	32 (14.9)	9 (31.0)
Skin disorder	17 (8.5)	8 (17.8)	19 (8.8)	6 (20.7)
Urticaria	9 (4.5)	6 (13.3)	10 (4.7)	5 (17.2)
Maculopapular rash	4 (2.0)	3 (6.7)	4 (1.9)	3 (10.3)
Hemic and lymphatic system:				
Leukopenia	42 (21.1)	10 (22.2)	43 (20.0)	7 (24.1)
Thrombocytopenia	42 (21.1)	10 (22.2)	43 (20.0)	9 (31.0)
Anemia	35 (17.6)	5 (11.1)	36 (16.7)	4 (13.8)
Petechia	11 (5.5)	7 (15.6)	11 (5.1)	7 (24.1)
Ecchymosis	9 (4.5)	12 (26.7)	10 (4.7)	11 (37.9)
Coagulation disorder	2 (1.0)	3 (6.7)	2 (0.9)	3 (10.3)
Nervous System				
Headache	28 (14.1)	15 (33.3)	31 (14.4)	12 (41.4)
Anxiety	17 (8.5)	8 (17.8)	17 (7.9)	8 (27.6)
Agitation	14 (7.0)	5 (11.1)	14 (6.5)	5 (17.2)
Dizziness	9 (4.5)	4 (8.9)	9 (4.2)	4 (13.8)
Convulsion	6 (3.0)	7 (15.6)	8 (3.7)	5 (17.2)
Depression	3 (1.5)	4 (8.9)	3 (1.4)	4 (13.8)
Urogenital system:				
Oliguria	14 (7.0)	5 (11.1)	16 (7.4)	3 (10.3)
Hematuria	11 (5.5)	4 (8.9)	12 (5.6)	3 (10.3)
Kidney function abnormal	5 (2.5)	4 (8.9)	5 (2.3)	4 (13.8)
Special senses:				
Conjunctivitis	3 (1.5)	4 (8.9)	3 (1.4)	4 (13.8)
Conjunctival edema	2 (1.0)	3 (6.7)	2 (0.9)	3 (10.3)
Musculoskeletal system				
Arthralgia	14 (7.0)	9 (20.0)	17 (7.9)	6 (20.7)
Bone pain	5 (2.5)	3 (6.7)	5 (2.3)	3 (10.3)
Myasthenia	3 (1.5)	4 (8.9)	3 (1.4)	4 (13.8)

* Adverse events which occurred in at least 10% of patients

** Patients may have experienced more than one adverse event within a body system

Medical Officer Comments: Most of these adverse dose occurred more frequently at higher doses of micafungin. This analysis, however, may be confounded by the observation that the children who received the higher doses were probably sicker (underlying hematological malignancy with diagnosis of invasive aspergillosis) than those who received lower doses or durations of micafungin.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Drug-Related Adverse Events

Adverse events considered drug-related by the investigator occurred in 60/244 (24.6%) pediatric patients. The most common events in this category included increased ALT in 9/244 (3.7%), bilirubinemia in 8/244 (3.3%), hypokalemia in 7/244 (2.9%), abnormal liver function tests in 6/244 (2.5%), and hypertension in 6/244 (2.5%) patients. The incidence of drug-related adverse events was somewhat lower in patients < 16 years old, 24.6% (60/244), in comparison to those ages 16-< 65, 31.0% (612/1972), but was similar to that observed in those \geq 65 years of age, 24.2% (45/186).

The applicant noted that the incidence of drug-related adverse events among pediatric patients enrolled in study 98-0-050 was higher in patients who received micafungin, 28.2%, (11/39) than in those who received fluconazole, 11.1%, (5/45). The most common drug-related adverse event in pediatric patients in this study was bilirubinemia which occurred in 3/39 (7.7%) micafungin-treated, and in 1/45 (2.2%) fluconazole-treated patients. Micafungin safety in study 98-0-050 has been reviewed by Dr. Joette Meyer for the NDA 21-506 amendment.

Serious Adverse Events in Pediatric Patients

A total of 86/244 (35.2%) pediatric patients experienced at least one serious adverse event in these studies. The most common events in this category included sepsis, dyspnea, fever, and respiratory failure. Serious adverse events in this age group (< 16 years old) was higher than that observed in patients between the ages of 16 and 65 years old, 26.6%, (418/1573), and those patients aged 65 and older, 30.7%, (50/163). Events in this category that occurred in more than 2 patients are shown in the table below.

**APPEARS THIS WAY
ON ORIGINAL**

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

Table 190. Serious Adverse Events Occurring in > 2 Micafungin-treated Patients (< 16 years old). (Adapted from applicant's Appendix 4.3.1)

Adverse Event (COSTART Body System* and Preferred Term)	Micafungin-treated Patients < 16 years old N= 244
	n (%)
All Systems	86 (35.2)
Respiratory System	
Dyspnea	11 (4.5)
Respiratory failure	11 (4.5)
Hypoxia	8 (3.3)
Respiratory Distress Syndrome	7 (2.9)
Lung disorder	3 (1.2)
Lung hemorrhage	3 (1.2)
Pneumonia	3 (1.2)
Respiratory disorder	3 (1.2)
Body as a whole:	
Sepsis	20 (8.2)
Fever	11 (4.5)
Infection	7 (2.9)
Procedural complication	6 (2.5)
Cardiovascular system:	
Hypotension	8 (3.3)
Hypertension	4 (1.6)
Tachycardia	4 (1.6)
Arrhythmia	3 (1.2)
Bradycardia	3 (1.2)
Shock	3 (1.2)
Nervous system:	
Convulsion	8 (3.3)
Intracranial hemorrhage	3 (1.2)
Meningitis	3 (1.2)
Hemic and lymphatic system	
Thrombocytopenia	5 (2.0)
Leukopenia	3 (1.2)
Digestive system:	
Mucositis	3 (1.2)
Metabolic and nutritional disorders:	
Bilirubinemia	3 (1.2)
Hypokalemia	3 (1.2)
Urogenital system:	
Kidney failure	6 (2.5)
Acute kidney failure	3 (1.2)

*Patients could have more than one event within a Body System

Medical Officer Comment: Other serious adverse events of interest in this age group which occurred infrequently and were not attributed to micafungin included heart failure in 2/244, (0.8%), ventricular tachycardia in 1/244 (0.4%), and hepatic failure in 1/244(0.4%).

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

Serious Drug-Related Adverse Events

Twelve of the 244 (4.9%) pediatric patients had a serious adverse event considered drug-related by the investigator. These are listed in the following table.

Table 191. Incidence of Serious Adverse Events Related to Study Drug

Serious Adverse Event	Micafungin (n=244)
All Systems	12 (4.9%)
Bilirubinemia	2 (0.8%)
Hypokalemia	2 (0.8%)
Dyspnea	2 (0.8%)
Hypoxia	2 (0.8%)
Hypertension	2 (0.8%)
Hypotension	1 (0.4%)
Vasodilatation	1 (0.4%)
Cyanosis	1 (0.4%)
Thrombocytopenia	1 (0.4%)
Anxiety	1 (0.4%)
Meningitis	1 (0.4%)
Nausea	1 (0.4%)
Acute Kidney Failure	1 (0.4%)

Patient base: all pediatric patients who received at least 1 dose of FK463.

Source: Appendix 4.3.2

Medical Officer Comments: Narrative summaries for some of these serious adverse events were included in the special safety studies section of this review, under the relevant system organ class.

Adverse Events Leading to Micafungin Discontinuation

Thirty (30) of 244 pediatric patients (12.3%) had adverse events that resulted in micafungin discontinuation. The most common events in this category included respiratory failure, intracranial hemorrhage, lung hemorrhage, meningitis, and abnormal liver function tests. In the pooled micafungin safety database, which included pediatric patients, 251/2402 (10.4%) subjects and 245/1980 (12.4%) patients, experienced adverse events leading to micafungin discontinuation. Adverse events resulting in micafungin discontinuation in pediatric patients are listed in the table below.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 192. Adverse Events Resulting in Micafungin Discontinuation in Pediatric Patients

(applicant's Appendix 4.4.1, section 5.3.5.3.2)

BODY SYSTEM (1)

FK463

COSTART TERM

(N=244)

ALL SYSTEMS 30 (12.3%)

RESPIRATORY SYSTEM

ANY AE 11 (4.5%)

RESPIRATORY FAILURE 5 (2.0%)

LUNG HEMORRHAGE 2 (0.8%)

DYSPNEA 1 (0.4%)

HYPOXIA 1 (0.4%)

LUNG EDEMA 1 (0.4%)

RESPIRATORY DISTRESS 1 (0.4%)

SYNDROME

NERVOUS SYSTEM

ANY AE 7 (2.9%)

INTRACRANIAL HEMORRHAGE 3 (1.2%)

MENINGITIS 2 (0.8%)

BRAIN EDEMA 1 (0.4%)

CONVULSION 1 (0.4%)

CARDIOVASCULAR SYSTEM

ANY AE 2 (0.8%)

HEART FAILURE 1 (0.4%)

SUBDURAL HEMATOMA 1 (0.4%)

DIGESTIVE SYSTEM

ANY AE 2 (0.8%)

LIVER FUNCTION TESTS 2 (0.8%)

ABNORMAL

HEMIC AND LYMPHATIC

SYSTEM

ANY AE 2 (0.8%)

LEUKEMIA 1 (0.4%)

LEUKOPENIA 1 (0.4%)

METABOLIC AND NUTRITIONAL

DISORDERS

ANY AE 2 (0.8%)

BILIRUBINEMIA 1 (0.4%)

SGOT INCREASED 1 (0.4%)

BODY AS A WHOLE

ANY AE 1 (0.4%)

CARCINOMA 1 (0.4%)

MUSCULOSKELETAL SYSTEM

ANY AE 1 (0.4%)

ARTHRALGIA 1 (0.4%)

SKIN AND APPENDAGES

ANY AE 1 (0.4%)

RASH 1 (0.4%)

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

UROGENITAL SYSTEM

ANY AE 1 (0.4%)

KIDNEY FAILURE 1 (0.4%)

*Patient could have more than one adverse event within a Body System

Seven of 244 (2.9%) pediatric patients discontinued micafungin because of an event considered drug-related by the investigator. These events included abnormal liver function tests in 2 patients, and leukopenia, bilirubinemia, arthralgia, convulsion and rash, each in 1 patient. The incidence of micafungin discontinuation due to drug-related adverse events was similar to that observed in the pooled micafungin safety database for all subjects, 3.0%, (73/2402) subjects, and all patients, 3.4%, (68/1980) patients.

Pediatric Deaths

A total of 49/244 pediatric patients (20.1%) who received micafungin died during these studies. None of the deaths was considered related to micafungin; while 29/44 deaths (65.9%) were due to fungal infection. Nine deaths occurred during treatment with micafungin; while 40 patients died during the post-treatment period. The incidence of mortality in pediatric patients in these studies was similar to that observed in patients between the ages of 16 and 65, 18.5%, (291/1573), but lower than that in patients ages 65 and older, 26.4%, (43/163). The following table lists the primary cause of death in all micafungin-treated pediatric patients.

**APPEARS THIS WAY
ON ORIGINAL**

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

Table 193. Primary Cause of Death in Micafungin-Treated Pediatric Patients (Applicant's Table 8, section 5.3.5.3.2)

COSTART Term	Total (n=244)
Any Death	49 (20.1%)
Respiratory Failure	6 (2.5%)
Sepsis	5 (2.0%)
Infection	4 (1.6%)
Shock	4 (1.6%)
Intracranial Hemorrhage	4 (1.6%)
Lung Hemorrhage	3 (1.2%)
Pulmonary Mycosis	2 (0.8%)
Dyspnea	2 (0.8%)
Respiratory Distress Syndrome	2 (0.8%)
Meningitis	2 (0.8%)
Acute Myeloblastic Leukemia	2 (0.8%)
Leukemia	2 (0.8%)
Pneumonia	1 (0.4%)
Interstitial Pneumonia	1 (0.4%)
Lung Edema	1 (0.4%)
Carcinoma	1 (0.4%)
Heart Arrest	1 (0.4%)
Heart Failure	1 (0.4%)
Endocarditis	1 (0.4%)
Brain Edema	1 (0.4%)
Cerebral Infarct	1 (0.4%)
Kidney Failure	1 (0.4%)

Medical Officer Comments: Most of the patients who died received micafungin in studies 98-0-046 and 98-0-047, and a few from 98-0-050.

Conclusions Regarding Safety of Micafungin in Pediatric Patients

A total of 244 pediatric patients under the age of 16 received at least one dose of micafungin in studies 98-0-050, 98-0-043, 98-0-046, 98-0-047, and 99-0-063, and were included in the safety database. Most of the patients in this age group had received a hematopoietic stem cell transplant, or had received chemotherapy for a hematologic malignancy.

The overall incidence of adverse events was higher in patients under 16 years of age than older patients, as was the incidence of serious adverse events; while the incidence of drug-related adverse events was somewhat lower in pediatric patients than in adults. The incidence of mortality in these studies was similar in pediatric and adult patients under the age of 65. These data are summarized in the following table.

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

Table 194. Summary of Micafungin Safety by Age Group for Subjects and Patients

Safety Parameter	Pediatric Subjects (< 16 years old) N=244	Adult Subjects (≥ 16 to < 65 years old) N=1972	Elderly Subjects (≥ 65 years old) N=186
Any Adverse Event	228 (93.4%)	1647 (83.5%)	153 (82.3%)
Drug-Related Adverse Event	60 (24.6%)	612 (31.0%)	45 (24.2%)
	Pediatric Patients (< 16 years old) N=244	Adult Patients (≥ 16 to < 65 years old) N=1573	Elderly Patients (≥ 65 years old) N=163
Serious Adverse Events	86 (35.2%)	418 (26.6%)	50 (30.7%)
Drug-Related Serious Adverse Events	12 (4.9%)	Not available	Not available
Adverse Events resulting in Micafungin Discontinuation	30 (12.3)	Not available	Not available
Deaths (all cause)	49 (20.1)	291 (18.5%)	43 (26.4%)

We have concluded from these data that insufficient numbers of pediatric patients were studied at the proposed doses for esophageal candidiasis and *Candida* prophylaxis to draw firm conclusions about the safety of micafungin in patients younger than 16 years old. In fact, because of the incidence of any adverse event and serious adverse events was higher in this age group than in adults, many questions remain regarding the safety of micafungin in pediatric patients. Thus, at this time, we cannot recommend approval of micafungin for pediatric use for either esophageal candidiasis or *Candida* prophylaxis. We have proposed wording in the final micafungin label stating that the efficacy and safety of micafungin in pediatric patients has not been established in clinical studies.

8.5 Advisory Committee Meeting

Not applicable

8.6 Literature Review

A literature review based on a PubMed Search was conducted by the Division on February 7, 2005 using the search term "micafungin AND adverse events". This search yielded the following results:

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

1: *Drugs*. 2004;64(18):1997-2020. Newer systemic antifungal agents : pharmacokinetics, safety and efficacy. Boucher HW, Groll AH, Chiou CC, Walsh TJ. Division of Geographic Medicine and Infectious Diseases, Tufts-New England Medical Center, Boston, Massachusetts, USA. PMID: 15341494 [PubMed - indexed for MEDLINE].

This publication does not present new safety information specific for micafungin and rather is an expert opinion regarding new antifungal agents.

2: *Ann Pharmacother*. 2004 Oct;38(10):1707-21. Epub 2004 Aug 31. Micafungin. Carver PL. College of Pharmacy, University of Michigan, 428 Church St., Ann Arbor, MI 48109-1065, USA. peg@umich.edu PMID: 15340133 [PubMed - indexed for MEDLINE]

This review of published information covering the periods 1978 to 2003 uncovered no new adverse events for micafungin that have not been described in this review.

3: *Scand J Infect Dis*. 2004;36(5):372-9. A multicenter, open-label clinical study of micafungin (FK463) in the treatment of deep-seated mycosis in Japan. Kohno S, Masaoka T, Yamaguchi H, Mori T, Urabe A, Ito A, Niki Y, Ikemoto H. Section of Molecular and Clinical Microbiology, Department of Microbiology and Immunology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan. s-kohno@net.nagasaki-u.ac.jp
PMID: 15287383 [PubMed - indexed for MEDLINE]

The study describes the safety and efficacy of micafungin in 70 patients who received micafungin 12.5-150 mg/day intravenously for up to 56 days for invasive pulmonary aspergillosis, candidemia, and esophageal candidiasis. The safety data from this publication forms part of the safety database in this NDA and has been reviewed by the Agency.

4: *Drugs*. 2004;64(9):969-82; discussion 983-4. Micafungin. Jarvis B, Figgitt DP, Scott LJ. Adis International Limited, 41 Centorial Drive, Mairangi Bay, Auckland 1311, New Zealand.
PMID: 15101786 [PubMed - indexed for MEDLINE]

This article summarizes the applicant's overall efficacy and safety conclusions, without providing new information other than that included in this NDA. They conclude "Micafungin is generally well tolerated. Adverse events were not dose- or infusion-related with micafungin 12.5-900 mg/day; no histamine-like reactions occurred. Micafungin was as well tolerated as fluconazole, with numerically fewer micafungin recipients discontinuing treatment (4.2% vs 7.2%)." This study uncovered no new safety concerns.

5: *Lancet*. 2003 Oct 4;362(9390):1142-51. Echinocandin antifungal drugs. Denning DW.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Education and Research Centre, Wythenshawe Hospital, Southmoor Road, M23 9LT,

Manchester, UK. ddenning@man.ac.uk

PMID: 14550704 [PubMed - indexed for MEDLINE]

This expert review of echinocandins in general concludes that “No drug target is present in mammalian cells” and that “Adverse events are generally mild, including (for caspofungin) local phlebitis, fever, abnormal liver function tests, and mild haemolysis; drug interactions are few. ... equivalent efficacy to amphotericin

B, with substantially fewer toxic effects.” No new information is provided that is not evaluated in the NDA.

6: Nippon Yakurigaku Zasshi. 2003 Oct;122(4):339-44.

[Antifungal activity and clinical efficacy of micafungin sodium (Funguard)]

[Article in Japanese] Ikeda F.

Department of Infectious Diseases, Medicinal Biology Research Laboratories,

Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan.

PMID: 14501170 [PubMed - indexed for MEDLINE]

A review of the abstract indicates that the safety data presented in this untranslated Japanese paper pertains to the 70 patients with systemic fungal infections described in the reference 3 above, and also reviewed in the NDA. No new information of concern is uncovered.

Micafungin has only been marketed in Japan. A review of the literature indicates reveals no independently reported safety events of concern.

8.7 Postmarketing Risk Management Plan

The postmarketing risk management for micafungin is directed by the limited range of proposed indications for the drug. We have recommended approval of Mycamine for a prophylactic indication (and not for _____ and for the treatment of a mucosal infection for which there exists multiple other alternative therapies whose efficacy and safety are well established. On February 4, 2005, in a Pre-Approval Safety Meeting, the Division requested ODS to monitor the following events following Micafungin's availability in the market. The proposed risk management plan is shown in the following table.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table.195. Postmarketing Risk Management Plan for Micafungin

Safety Issues

Risk Management Plan

Anaphylaxis/anaphylactoid reactions

Warning in label

Postmarketing surveillance by ODS

Hypersensitivity:

Rash, erythema multiforme, TEN

Postmarketing surveillance by ODS for serious rash, erythema multiforma, toxic epidermal necrolysis, Stevens Johnson syndrome

Hepatic safety:

Hepatic laboratory abnormalities, hepatic failure or dysfunction

Precaution in label

Postmarketing surveillance by ODS for serious hepatic failure or impairment, liver damage

Drug interactions:

Increased ALT in mycophenolate-micafungin interaction study

Hepatic Precaution in label

Renal safety:

Renal failure, renal impairment, renal laboratory abnormalities serious renal failure, hemolytic uremic syndrome

Precaution in label

Postmarketing surveillance by ODS for hemolytic uremic syndrome

Hematologic safety:

Hemolysis, hemolytic anemia

Precaution in label for hemolysis

Postmarketing surveillance by ODS for serious hemolysis, hemolytic anemia, TTP, ITP, pancytopenia,

Leukopenia, anemia, thrombocytopenia, pancytopenia, thrombotic thrombocytopenic purpura (TTP)

Vascular Reactions:

Phlebitis, thrombophlebitis

Postmarketing surveillance by ODS for serious deep venous thrombosis, arterial thrombosis, pulmonary embolism, myocardial infarct or ischemia, stroke

Cardiovascular Safety:

Shock, cardiac arrest, arrhythmia, serious events of shock, prolongation

Postmarketing surveillance by ODS for cardiac arrest, arrhythmia, QTc

Infusion-related Reactions:

Hypertension, hypotension,

Postmarketing surveillance by ODS for serious events of

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

vasodilatation, tachycardia, dyspnea

hypertension, hypotension, cyanosis.

cyanosis, chills/rigors

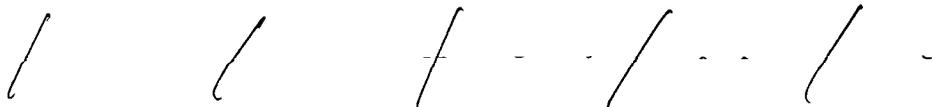
8.8 Other Relevant Materials

The following consultations were performed at the request of the DSPIDP:

ODS Consult for review of Japanese postmarketing data on micafungin was completed 18 February, 2005 and was discussed in the applicable sections of the Integrated Safety Summary.

ODS Consult by Dr. John Senior regarding hepatic safety was completed 31 January, 2005, and was discussed in the section on Hepatic Safety.

DDMAC Consult was completed 25 August, 2005, and recommended



These recommendations were all taken into consideration in the proposed labeling revisions.

These consultations are found in the Appendix, Section 10 of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy of Micafungin in Treatment of Esophageal Candidiasis

Two pivotal studies submitted with this NDA demonstrate the efficacy of micafungin in the treatment of esophageal candidiasis. Study 03-7-005 was a robust phase 3 study which showed that micafungin was non-inferior to fluconazole for the treatment of esophageal candidiasis by the primary endpoint, endoscopic cure, and the secondary endpoints, clinical cure, overall therapeutic cure, mycological eradication, and relapse at 2- and 4-weeks post-treatment. Micafungin was also effective in treating oropharyngeal candidiasis, however, relapse of OPC was higher at 2- and 4-weeks posttreatment with micafungin than with fluconazole. Study FG463-21-09 was a phase 2 study which showed a clear dose-response for 50 to 150 mg/day micafungin in the treatment of esophageal candidiasis. Two additional studies, 97-7-003 and 98-0-047 were submitted in support of the application, and also demonstrated the efficacy of micafungin in the treatment of esophageal candidiasis.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Safety of Micafungin

A total of 2402 subjects (patients and volunteers) received micafungin at doses of 12.5 to ≥ 150 mg/day for durations of 1 to 618 days in 32 clinical studies. A total of 606 subjects received the recommended dose of micafungin for esophageal candidiasis ≥ 150 mg/day micafungin for a minimum of 10 days. In the pooled safety database of 2402 subjects, the overall incidence of adverse events, regardless of causality, was 84.4% (2028/2402) subjects. In the fluconazole-controlled studies, the incidence of adverse events was similar in patients treated with micafungin, 91.6% (854/932) or fluconazole, 90.3%, (711/787). Those adverse events considered at least possibly drug-related were reported in 717/2402 (29.9%) subjects. In the fluconazole-controlled studies, drug-related adverse events occurred in 255/932 (27.4%) patients who received micafungin, and in 169/787 (21.5%) of those treated with fluconazole. Serious adverse events were reported in 554/1980 (28.0%) patients in the pooled safety database. No serious adverse events occurred in healthy volunteers. Micafungin was discontinued due to adverse events in 251/2402 (10.4%) subjects; while drug-related adverse events leading to micafungin discontinuation occurred in 73/2402 (3.0%) subjects. A total of 383/1980 (19.3%) patients died during the clinical studies. Two of these deaths were considered possibly related to micafungin by the investigator. The first death occurred in a patient with underlying pulmonary aspergillosis who developed pancytopenia and pulmonary hemorrhage; and the second was a patient with HIV, who died due to progression of AIDS. These cases were reviewed, and both deaths were considered unlikely related to micafungin by the medical officer.

A number of issues were identified in this review of micafungin safety. The liver was shown to be the primary target of micafungin toxicity in animals; and this was confirmed in the clinical studies. Transient, but significant hepatic transaminase elevations were observed in healthy volunteers in several drug interaction studies. Hepatic laboratory abnormalities were also fairly common among patients; and a number of serious hepatic adverse events were reported, some of which may have been related to micafungin as determined by an expert panel of hepatologists, and Dr. John Senior, in the Office of Drug Safety. Postmarketing surveillance in Japan has also identified a number of serious hepatic adverse events considered at least possibly related to micafungin, as reviewed by the ODS. We have proposed a PRECAUTION regarding hepatic effects in the final micafungin labeling.

Serious allergic and anaphylactoid reactions occurred in a number of patients in the clinical studies, and many of these reactions were at least possibly related to micafungin. Serious allergic reactions, including anaphylactic shock and anaphylactoid reactions were also identified in the Japanese postmarketing experience. Rash was also reported as a common drug-related adverse event in subjects in the clinical studies. One patient who received micafungin in the clinical studies experienced erythema multiforme. Additionally, at least one case of toxic epidermal necrolysis was considered possibly related to micafungin in the postmarketing period in Japan. We have proposed a

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

WARNING regarding the potential of micafungin for anaphylaxis or anaphylactoid reactions in the final micafungin labeling.

Hematologic adverse events, particularly hemolytic anemia and hemolysis were identified as safety concerns with micafungin. Hemolysis was described in the preclinical studies, and was observed in a healthy volunteer who experienced acute intravascular hemolysis with hemoglobinuria, but without significant anemia. Several serious cases of hemolysis or hemolytic anemia were also reported in patients in the clinical studies, as well as in the Japanese postmarketing experience. Leukopenia, neutropenia, anemia, and thrombocytopenia were common drug-related adverse events in the micafungin safety database. We have proposed a PRECAUTION regarding the potential of micafungin for hemolysis or hemolytic anemia in the final micafungin labeling.

Elevations in BUN and creatinine, as well as serious renal adverse events, particularly renal failure were reported in patients who received micafungin in the clinical studies, and in the postmarketing surveillance in Japan. Some of these adverse events may have been related to micafungin. Acute renal failure is described as a clinically significant adverse reaction in the Japanese label for micafungin. We have proposed a PRECAUTION regarding renal effects in the final micafungin labeling.

Additional safety issues identified in this review include injection site reactions with micafungin, particularly phlebitis and thrombophlebitis, which occurred commonly in patients treated with 150 mg/day micafungin in 03-7-005. At this time, there is no clear dose-relationship for these reactions, which may be associated with use of a peripheral intravenous catheter, rather than micafungin dose. Histamine-mediated reactions other than rash were also reported in the clinical studies, including pruritis, facial swelling, pruritis, vasodilatation, and other more non-specific reactions such as hypotension, hypertension, cyanosis, or tachycardia. Some of these reactions occurred during micafungin infusion. We have proposed wording which describes histamine-mediated reactions and injection site reactions in the ADVERSE REACTIONS section of the final micafungin labeling.

Pediatric safety was assessed in 244 patients under the age of 16. Most of these patients, 79.5% (194/244) were between the ages of 2 and 16 years old. In the pooled safety database, the incidence of adverse events was higher in patients under the age of 16, 93.4%, (228/244), than in those between the ages of 16 and 65 years, 83.5%, (1647/1972), and those 65 years and older, 82.3% (153/186). Although some of these differences may be due to differences in underlying disease, and because most of the pediatric patients received less than the proposed dose of micafungin for pediatric patients (3 mg/kg/day), questions regarding the safety of micafungin in pediatric patients remain unresolved. Additionally, only 4 pediatric patients received micafungin for treatment of esophageal candidiasis in these studies. These patients received between 1 and 2 mg/kg/day micafungin, _____ Because the pharmacokinetic data submitted for pediatric patients who received micafungin was inadequate to demonstrate bioequivalence with adult patients, we have concluded that

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

the safety and efficacy of micafungin in pediatric patients has not been established; and have proposed a statement in the final micafungin labeling to reflect this conclusion.

In elderly subjects (≥ 65 years old), the overall incidence of adverse events, 82.3% (153/186) was similar to that observed in subjects between the ages of 16 and 65 years, 83.5% (153/186). Drug-related adverse events were less common in elderly subjects, 24.2% (45/186) than in subjects between 16 and 65 years old, 31.0% (612/1972). Serious adverse events were reported in 50/163 (30.7%) elderly patients, and in 418/1573 (26.6%) of 16 to 65 year-olds; while the incidence of mortality was higher in the elderly, 26.4% (43/163) in comparison to younger adults (< 65), 18.5% (291/1573).

No significant differences were observed in the incidence of adverse events between male, 81.2% (1209/1489) and female, 89.7% (819/913) subjects in the pooled micafungin safety database.

The overall incidence of adverse events was highest in Caucasian subjects, 90.1% (1369/1519), in comparison to blacks, 79.5% (422/531), or in subjects of other races or ethnic background, 67.3% (237/352) in the pooled safety database. However, these differences can be attributed to differences in underlying disease between these groups. Most Caucasian subjects enrolled in the clinical studies had an underlying hematological malignancy, or had received a HSCT; while most black patients had underlying HIV disease. Drug-related adverse events were similar among the racial groups; and we concluded that there were no clinically significant differences in racial distribution for adverse events.

We have concluded that micafungin is effective in the treatment of esophageal candidiasis and is generally safe with the labeled WARNINGS and PRECAUTIONS for use in patients as an alternative to other approved products for this indication, including fluconazole, voriconazole, itraconazole, and caspofungin.

9.2 Recommendation on Regulatory Action

We recommend the approval of micafungin for the following indications in adults:

- Esophageal Candidiasis
- Prophylaxis of *Candida* infections in hematopoietic stem cell transplant (HSCT) recipients

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Following is a listing of the safety issues identified in this review, and the divisions's risk management plan for the identified risk, in consultation with the ODS.

<u>Safety Issues</u>	<u>Risk Management Plan</u>
Anaphylaxis/anaphylactoid reactions	Warning in label Postmarketing surveillance by ODS
Hypersensitivity: -Rash, erythema multiforme, TEN	Postmarketing surveillance by ODS for serious rash, erythema multiforme, toxic epidermal necrolysis, Steven's Johnson syndrome
Hepatic safety: Hepatic laboratory abnormalities Hepatic failure or dysfunction	Precaution in label Postmarketing surveillance by ODS for serious hepatic failure or impairment, liver damage
Drug interactions: Increased ALT in mycophenolate-micafungin interaction study	Hepatic precaution in label
Renal safety: Renal failure, renal impairment, renal laboratory abnormalities serious renal failure, hemolytic uremic syndrome	Precaution in label Postmarketing surveillance by ODS for hemolytic uremic syndrome
Hematologic safety: Hemolysis, hemolytic anemia Leukopenia, anemia, thrombocytopenia, pancytopenia, thrombotic thrombocytopenic purpura (TTP)	Precaution in label for hemolysis Postmarketing surveillance by ODS for serious hemolysis, hemolytic anemia, TTP, ITP, and pancytopenia
Vascular Reactions: Phlebitis, thrombophlebitis	Postmarketing surveillance by ODS for serious deep venous thrombosis, arterial thrombosis, pulmonary embolism, myocardial infarct or ischemia, stroke
Cardiovascular Safety:	

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Shock, cardiac arrest, arrhythmia

Postmarketing surveillance by ODS for serious events of shock, cardiac arrest, arrhythmia, QTc prolongation

Infusion-related Reactions:

Hypertension, hypotension,

Vasodilatation, tachycardia, dyspnea
cyanosis, chills/rigors

Postmarketing surveillance by ODS for serious events of hypertension, hypotension, cyanosis.

9.3.2 Required Phase 4 Commitments

Studies of micafungin for use in pediatric esophageal candidiasis and in *Candida* prophylaxis will be deferred at this time; _____

_____ No
phase 4 commitments will be required.

9.3.3 Other Phase 4 Requests

No other phase 4 studies are requested.

9.4 Labeling Review

The proposed proprietary name, Mycamine, was evaluated by the Division of Medication Errors and Technical Support (DMETS) in reviews dated 17 September, 2002, 7 July, 2004, and 16 November, 2004, and was found to be acceptable. In addition, DDMAC found the name, Mycamine, acceptable from a promotional perspective.

A consultation by DMETS was completed 4 November, 2004, regarding the micafungin container and carton labeling, as well as package insert labeling. Specific recommendations were made to the Applicant to _____

_____ Additionally, recommendations regarding storage of Mycamine in the package insert, to revise the statements to read _____

No medication guide or patient package insert will be required because Mycamine is for (intravenous) use only.

The following revisions were proposed to the applicant's draft label submitted with the 120-day safety update for NDA 21-754 and NDA 21-506:

- A WARNING section regarding potential serious anaphylactic or anaphylactoid reactions with micafungin
- A PRECAUTIONS section for hepatic, renal and hematological effects of micafungin

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

- An ADVERSE EVENTS section which describes the potential of micafungin for injection site and histamine-mediated reactions, as well as adequate characterization of of adverse events in the overall safety database and postmarketing experience
- Adequate characterization of the efficacy of micafungin in treatment of esophageal candidiasis, and in prophylaxis of *Candida* infections in HSCT recipients
- Elimination of _____
- A pregnancy category C label

See section 10.2 for the revised package insert for micafungin labeling as negotiated with the Applicant.

9.5 Comments to Applicant

We have no comments to the Applicant at this time.

**APPEARS THIS WAY
ON ORIGINAL**

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

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Clinical Trial # 1: Study 03-7-005:

A Phase 3, Randomized, Double-Blind, Comparative Trial of Micafungin (FK463) versus Fluconazole for the Treatment of Esophageal Candidiasis

Study Objectives: To determine safety and efficacy of micafungin 150 mg/day in comparison to fluconazole for the treatment of esophageal candidiasis.

Rationale: Esophageal candidiasis (EC) is an important opportunistic infection in patients with advanced HIV disease. Currently, several antifungal agents are approved for treatment of EC, including fluconazole, voriconazole, itraconazole (Sporanox®) oral solution, and intravenous caspofungin. Treatment of EC with fluconazole is currently the standard of care in the U.S. Three clinical trials have demonstrated efficacy of micafungin in the treatment of EC: study 97-7-003 (reviewed for this NDA) demonstrated a dose-response trend from 12.5 mg/day to 100 mg/day micafungin; study FG463-21-09 (reviewed for this NDA) showed a clear dose-response from 50 mg/day to 150 mg/day micafungin, with EC cure rates for the 150 mg/day micafungin dose comparable to that obtained with fluconazole 200 mg/day; and study 98-0-047 (reviewed previously for —), an open-label study for treatment of candidemia and invasive candidiasis, which enrolled 99 patients with EC, in which clinical success was achieved in approximately 92% of patients.

Study Design

This was a phase 3, multicenter, multinational, randomized (1:1), double-blind, parallel group, non-inferiority study to compare 150 mg/day intravenous micafungin to 200 mg/day intravenous fluconazole for treatment of EC in patients ≥ 16 years old.

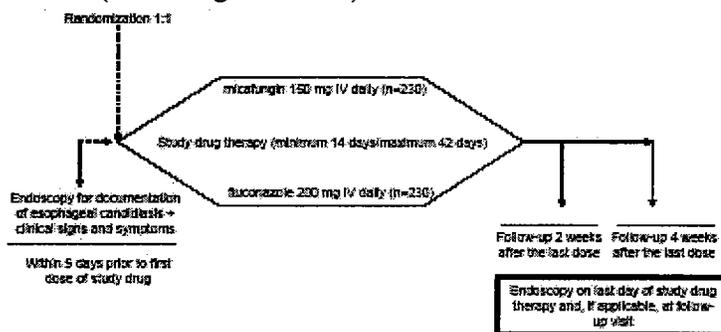
Protocol Overview

Patients with documented esophageal candidiasis were randomized to receive either micafungin 150 mg/day or fluconazole 200 mg/day for a minimum of 14 days and were evaluated at the end-of-therapy, and at 2 weeks and 4 weeks post-treatment. The following diagram outlines the general protocol design:

Figure 1. Experimental Design (applicant's Figure 1, study report)

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

Best Possible Copy



Randomization and Blinding

Patients were randomly assigned to receive micafungin or fluconazole using a 1:1 randomization schedule generated by the Research Data Operations Department at Fugisawa Healthcare, Inc. The study was double-blind, and except for the pharmacist or designee who was responsible for maintaining the security of randomization numbers, the sponsor and all investigative site staff were unaware of which study drug the patient received. The blind could be broken only in cases relating to patient safety or when critical therapeutic decisions were contingent upon knowing the study drug.

Primary Efficacy Endpoint: The primary endpoint was endoscopic cure, defined as mucosal grade 0 at the end of therapy (EOT).

Esophageal Candidiasis was endoscopically graded on a scale of 0 to 3 as described in the table below.

Table 1. Esophageal Mucosal Grades (Endoscopic)

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

Secondary Efficacy 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

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

- 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 the table below.

**APPEARS THIS WAY
ON ORIGINAL**

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

Table 2. Grading of Clinical Symptoms of Esophageal Candidiasis (from Appendix B)

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

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 1 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 ≤ 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.

Randomization and Blinding

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

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.

Changes in endoscopic assessment at EOT compared to baseline was determined by calculating the difference between the mucosal grade (Table 1 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 2 above) for each clinical symptom.

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 at baseline and EOT, as shown in the table below.

Table 3. 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

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 as shown in the following table:

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

Table 4. Definitions of 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

Best Possible Copy

Medical Officer Comment: This scheme seems reasonable, as it would not necessarily be in the patient's best interest to obtain an esophageal biopsy when endoscopic grade was 0, and no plaques were seen. In this schema, the outcome was scored as eradication only in patients with mucosal grade 0 and a negative culture, or in those with both negative histology and Candida culture. (Why isn't mycological response listed as secondary outcome measure?)

Treatment

Patients received either micafungin 150 mg/day or fluconazole 200 mg/day administered as an intravenous infusion once daily for a minimum of 14 days, or for 7 days after resolution of clinical symptoms of EC, whichever was longer. The maximum length of treatment was 42 days.

Dose adjustments for Adverse Events during Treatment

**APPEARS THIS WAY
ON ORIGINAL**

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

Intensity of the Event	Adjustments to Study Drug
Mild or moderate (Grade 1 or 2)	None
Severe (Grade 3)	For a grade 3 toxicity (adverse event) determined by the investigator to be related or at least possibly related to study drug, the study drug could be held until the toxicity (adverse event) resolved to a grade 2. Then the drug could be resumed at the original dose. If the same grade 3 toxicity (adverse event) recurred, the study drug could be held and the medical monitor contacted. For a grade 3 event not felt by the investigator to be due to the study drug, no interruption was necessary.
Life-threatening (Grade 4)	The study drug would be held until the toxicity (adverse event) resolved to a grade 2. Then the drug could be resumed at the original dose. If the same grade 4 toxicity (adverse event) recurred, the study drug could be held and the medical monitor contacted. For a grade 4 event not felt by the investigator to be due to study drug, no interruption was necessary.

Assessments and Procedures

Screening Procedures

After the patient or legal representative had signed and dated the IRB/IEC- approved consent form, a medical evaluation was performed, including physical examination and medical history, serologic testing to assess eligibility for enrollment in the study.

Baseline procedures and documentation:

- Documentation of demographic information, medical history, medications
- Pregnancy test within 14 days of first dose of study drug
- CD4 count if patient was HIV positive
- Documentation of esophageal candidiasis within 5 days prior to first dose of study drug, including endoscopic confirmation of EC and a least one clinical symptom of EC with a grade ≥ 0 . Assignment of endoscopic mucosal grade as shown in Table 2 above. Brushings of the esophageal mucosa were also obtained for fungal culture and cytology, and an esophageal biopsy was obtained for histologic evaluation. Fungal organisms were identified to the species level and sent to a centralized laboratory for susceptibility testing. The diagnosis of EC was confirmed if the esophageal mucosal grade was ≥ 0 , the histology was positive for a fungal infection; or if the cytology and a fungal culture were positive for Candida and the patient had at least one clinical symptom of EC with a grade ≥ 0 . Clinical signs and symptoms of OPC, if present, were graded as shown in Table 3 above.
- Within 72 hours prior to first dose of study drug, the following procedures were performed:
 - Physical examination, including weight, and vital signs- temperature, blood pressure, and heart rate
 - Documentation of baseline medical conditions

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

- Laboratory evaluations including hematocrit, hemoglobin, RBC, WBC with differential count, platelet count, and absolute neutrophil count, creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, chloride, calcium, magnesium, total protein, albumin, and lactic dehydrogenase

Study Procedures during Treatment:

- Documentation of study drug dosing information
- Assessment and documentation of adverse events through 72 hours after the last day of study drug
- Documentation of concomitant medications administered through the last day of therapy until the end of the study
- Documentation of vital signs weekly during treatment and on the last day of study drug
- Laboratory evaluation (serum chemistry and hematology as noted above) weekly during treatment, and on the last day of therapy
- Evaluation of clinical signs and symptoms of EC and OPC weekly during treatment and on the last day of therapy
- Esophageal endoscopic examination on the last day of study drug administration with biopsy if lesions are still present, and brushings of the esophageal mucosa for cytology and fungal culture.

Study Procedures Post-Treatment

At 2 weeks (and 4 weeks as added in the protocol amendment) post-treatment the following procedures or evaluation were performed:

- Laboratory evaluation of hematologic parameters and serum chemistry
- Documentation of deaths within 2 weeks of the last day of study drug
- Documentation of antifungal therapy administered during post-treatment period
- Evaluation of clinical signs and symptoms of EC and OPC (if present at baseline)
- Esophageal endoscopic evaluation if the patient has clinical symptoms of EC. If esophageal lesions are present, biopsy for histology, and obtain esophageal brushing for cytology and fungal culture

Protocol Amendments

The study protocol of March 13, 2003 was amended on August 20, 2003 as follows:

- The addition of a Modified Full Analysis Set (MFAS) in addition to the Full Analysis Set (FAS) and Per Protocol Set (PPS).
- The planned sample size was increased from 402 patients to 460 patients (230 in each treatment arm) to accommodate the addition of a MFAS.
- A post-treatment visit was included at 4 weeks in addition to the 2 week post-treatment visit.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

- Incidence of relapse at 4 weeks was included as a secondary endpoint.
- The diagnostic procedures for isolation, identification, and transportation of fungal isolates were clarified.
- The definition of mycological response was revised (see section on Secondary Endpoints below).
- The storage conditions for micafungin were modified.

Inclusion Criteria:

The following criteria were required for study participation:

- Informed consent of the patient or legally authorized representative
- Males or females 16 years of age or older
- Negative pregnancy test within 14 days prior to first dose of study drug for females of childbearing potential
- Confirmed diagnosis of EC (results of screening tests could be pending at the time the first dose of study drug was received)
- Sufficient venous access to permit study drug administration and laboratory monitoring

Exclusion Criteria:

The following criteria were grounds for study exclusion:

- Pregnancy or lactation
- Evidence of liver disease defined as AST or ALT > 10 x upper limit of normal or total bilirubin > 5x upper limit of normal
- Presence of another active opportunistic fungal infection, or receipt of systemic therapy for an opportunistic fungal infection
- Concomitant Herpes simplex or Cytomegalovirus esophagitis
- Receipt of an oral, non-absorbable (topical) antifungal agent within 48 hours, or a systemic antifungal agent within 72 hours prior to first dose of study drug
- Treatment with an oral topical or systemic antifungal agent for condition other than EC

Medical Officer Comments: oral (topical or systemic antifungal drugs, including amphotericin B, other systemic azole or triazole antifungal agents, other echinocandins, and investigational antifungal agents were not allowed during study drug dosing. If a patient required any of these agents, study drug was to be discontinued.

- Non-responsive to therapy in any prior systemic antifungal clinical trial
- History of more than 2 episodes of EC requiring systemic antifungal therapy
- History of anaphylaxis to azole compounds or the echinocandin class of antifungal agents

Clinical Review

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

Micafungin sodium for Esophgeal Candidiasis

Mycamine (Micafungin sodium)

- Presence of a concomitant medical condition in which study participation could create an unacceptable risk (in the opinion of the investigator or medical monitor)
- Previous enrollment in this study

Criteria for Study Withdrawal

The occurrence of any of the following required discontinuation of study drug:

- Requirement for another oral topical, or systemic antifungal agent
- Development of unacceptable toxicity
- Investigator decision that it was in patient's best interest to discontinue
- Patient declined further participation
- Study drug was held more than 3 days
- Patient had received a maximum of 42 days of study drug therapy

Medical Officer Comments: If study drug was stopped due to unacceptable toxicity, did the patient remain in the FAS for safety analysis? Was the patient considered an efficacy failure?

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis
Mycamine (Micafungin sodium)

Safety Evaluation

Adverse Events

An adverse event was defined as any reaction, side effect, or other untoward medical occurrence, regardless of relationship to study drug, which occurred during the conduct of the study. Intensity of an adverse event was assigned subjectively and graded on a 4 point scale as follows: grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening). Relationship of adverse event to the study drug was determined subjectively by the investigator. Adverse events were to be followed as long as necessary to adequately evaluate patient safety or until the event stabilized. Adverse events were monitored and documented throughout the treatment period. Adverse events that occurred more than 72 hours after the last dose of study medication were not captured on the case report form (CRF); however, adverse events that resulted in death at any time until 4 weeks after the last dose of study drug were captured on the CRF.

A serious adverse event was defined as an adverse event that met any of the following criteria:

- The event was fatal or life-threatening
- The event resulted in persistent or significant disability or incapacity
- The event required inpatient hospitalization or prolongation of hospitalization
- The event resulted in congenital anomaly or birth defect
- An important medical event that might jeopardize the patient or require intervention to prevent one of the other outcomes listed above

Serious adverse events required notification of the sponsor within 48 hours of occurrence.

Laboratory evaluations and vital signs were obtained at baseline, weekly during the course of treatment, and on the last day of study drug administration, as noted above.

Statistical Considerations

Full details regarding the statistical analyses can be obtained in the statistical review by Ms. LaRee Tracy.

The analysis of the primary efficacy endpoint (endoscopic response at EOT) was performed by calculating the difference in endoscopic success rates between the micafungin and fluconazole groups, and calculating the 95% confidence interval around the treatment difference. Non-inferiority of micafungin to fluconazole was defined as the lower bound of the 95% confidence interval ≥ -0.10 .

The sample size calculation was based on the results of study FG463-21-09 which showed an endoscopic cure rate of greater than 85% for patients who received micafungin 150 mg/day or fluconazole 200 mg/day. Based on an endoscopic cure rate of 85% and a one-sided large sample normal approximation non-inferiority test at 2.5%