

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

related to micafungin, although micafungin could have contributed to worsening hepatic failure.

Serious Hepatic Adverse Events in Micafungin-treated Patients who died

A number of serious hepatic adverse events, not reviewed previously, were noted in patients who died of another cause in these studies. These are listed in the table below. In several of these cases the serious adverse event was considered possibly related to micafungin.

Table 105. Serious Hepatic Adverse Events in other Micafungin-Treated Patients who died. (Adapted from Applicant's Item 10, 6 January, 2005 response)

Patient Number	Study Protocol	Final Dose Micafungin	Day of Death	Primary Cause of Death	Serious Adverse Events
059533	98-0-043	4	8	Shock	Enlarged abdomen, arrhythmia, heart failure, hemorrhage, hepatomegaly, hyperventilation, hypervolemia, lung disorder, pain, sepsis, cardiomegaly
241773	98-0-046	9	27	Shock	Bilirubinemia*
262779	98-0-046	33	37	Infection	Bilirubinemia*, convulsion, infection
404773	98-0-046	129	132	Intracranial hemorrhage	Arrhythmia, encephalopathy, convulsion, intracranial hemorrhage, hypotension, infection, abnormal kidney function, abnormal liver function tests
98-0-046	475172	107	121	Relapse of primary malignancy	Bilirubinemia, respiratory failure
006874	98-0-047	3	11	Shock	Abnormal liver function tests*, shock, respiratory failure
031880	98-0-047	27	64	Lymphoma	Hyperventilation, abnormal thinking, bile duct disorder, lymphoma
063872	98-0-047	64	73	Respiratory failure	Acidosis, respiratory acidosis, cholecystitis, dyspnea

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2492001	98-0-050	13	36	Heart arrest	Bilirubinemia, shock, respiratory failure
5904	FJ0003	17	19	Coagulation disorder	Ascites, bilirubinemia, increased BUN, increased creatinine, coagulation disorder, pleural effusion

* Serious adverse event considered possibly related to micafungin

Medical Officer Comments: The patients were all exceedingly complex, with multiple medical conditions and concomitant medications. Those with hepatic adverse events considered related to micafungin are summarized further below.

Patient 262779 was a 2 year-old Caucasian female with a rhabdomyosarcoma, who had received chemotherapy, received micafungin doses from 17.1 mg/day to 33 mg/day over 33 days for aspergillosis involving the sinuses and orbit in protocol 98-0-046. A narrative summary was not available, and information here was obtained from the patient profile. Baseline conditions included thrombocytopenia, hyperventilation, hypocalcemia, fever, mucositis, lung disorder, bilirubinemia, anorexia, leucopenia, skin disorder, tachycardia, hypophosphatemia, hypoproteinemia, anemia, and nausea. Bilirubinemia was reported as a serious adverse event on study day 29, and infection on day 32. Bilirubin was 5.7 mg/dL at baseline and increased throughout the study to 17.6 mg/dL on day 29. There was no evidence of significant hemolysis based on review of hematologic laboratory values; although the patient did receive transfusions of packed red blood cells (study day 4). AST and ALT were normal at baseline, and were moderately elevated at that time (184 U/L, and 92 U/L, respectively). Alkaline phosphatase was somewhat elevated at baseline and day 29 (229 U/L and 240 U/L, respectively). Concomitant medications included nystatin (topical), benadryl, zofran, TPN, lipids, G-CSF, Tylenol, ativan, ketoconazole cream, promethazine, peridex, Abelcet®, itraconazole, spironolactone, morphine, Demerol, ceftazidime, rifampin, vancomycin, potassium chloride, calcium chloride, afrin, dilaudid, primaxin, inhaled pentamidine, amphotericin B, lasix, DDAVP, fentanyl, dilantin, ampicillin, bactrim, amikacin, versed, zantac, and dobutrex. The patient died on study day 37 due to an infection, not further described. An autopsy report described the cause of death as adenovirus hepatitis, with diffuse pulmonary alveolar damage. The liver described as enlarged, with hemorrhagic nodules and necrosis, and microscopic examination showed severe adenovirus hepatitis and marked intrahepatic cholangitis.

Medical Officer Comment: With proven adenoviral hepatitis, it seems unlikely that the hyperbilirubinemia and death were related to micafungin.

Patient 241773 was a 52 year-old Caucasian male who had received a kidney transplant. A narrative summary was not available, and information for this summary was obtained from the patient profile. In study 98-0-046, the patient received micafungin 75 mg/day for 9 days for proven pulmonary aspergillosis. Baseline conditions included congestive heart failure, acute kidney failure, respiratory failure, asthenia, diabetes mellitus, anemia,

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agitation, coagulation disorder, cachexia, hypotension, hyponatremia, hypoproteinemia, pneumonia, skin disorder, tachycardia, sinusitis, hypothyroidism, thrombocytopenia, and abnormal liver function tests. Bilirubinemia was reported as a serious adverse event on study day 3, and was considered possibly related to micafungin. Baseline bilirubin was 1.5 mg/dL. Bilirubin increased to 7.9 mg/dL by study day 9 and to 10.1 mg/dL by day 27. AST and ALT were normal at baseline and throughout the treatment period, with minimal elevation (61 U/L and 60 U/L, respectively) on day 27. Alkaline phosphatase was elevated at baseline (358 U/L), decreased during micafungin treatment (167 U/L on day 9), and then increased to 614 U/L on study day 27. Sepsis was reported as an adverse event (non-serious) on study day 8, esophageal and gastrointestinal hemorrhage on day 6. Hemolysis or anemia was not reported as an adverse event, and review of the laboratory data did not reveal any significant changes in hemoglobin or hematocrit. Shock was reported as a serious adverse event on study day 27, and the patient died on that day. Concomitant medications included Abelcet®, insulin, epogen, synthroid, Demerol, Tylenol, albuterol, benadryl, vancomycin, atrovent, Zemplar, azactam, cleocin, neupogen, solucortef, ativan, TPN, digoxin, nitroglycerin, dopamine, ciprofloxacin, versed, cardizem, solumedrol, diprivan, and flagyl.

Medical Officer Comments: I would suspect that the bilirubinemia in this case was related to sepsis, but there was insufficient information to determine any potential relationship to micafungin.

Patient 006874 was a 43 year old oriental female awaiting heart transplant, who received micafungin 50 mg/day for 3 days for candidemia in study 98-0-047. A narrative summary was not available, and information here was obtained from the patient profile. Baseline conditions included tachycardia, bronchitis, anemia, enlarged abdomen, fever, pneumonia, pulmonary hypertension and heart failure. Abnormal liver function tests and respiratory failure were reported as a serious adverse event on study day 3, and shock on day 11. AST increased from 48 U/L on day 1 to 6158 on day 3; ALT increased from 35 U/L on day 1 to 3074 on day 3; while bilirubin remained normal and alkaline phosphatase was only minimally elevated. The abnormal liver function tests were considered possibly related to micafungin by the investigator. Concomitant medications included ferrous sulfate, ceftazidime, tobramycin, Tylenol, atrovent, potassium chloride, furosemide, megace, fluconazole, ativan, compazine, colace, insulin, calcium, sodium bicarbonate, epinephrine, pavulon, ativan, versed, Ambisome®, vancomycin, vitamin K and sodium phosphate. The patient died on study day 11 due to shock.

Medical Officer Comments: This patient had hepatocellular injury on study day 3, with significant elevation of the hepatic transaminases. With multiple concomitant medications, and other conditions in this seriously ill patient, it would be difficult to attribute these abnormal hepatic laboratory values to micafungin alone.

Micafungin Discontinuations Due to Hepatic Adverse Events

Among 1980 subjects, a number of hepatic adverse events resulted in micafungin discontinuation. These included abnormal liver function tests (9 patients); bilirubinemia

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(7 patients), increased alkaline phosphatase (3 patients), increased AST (2 patients) hepatitis, nonspecific (2 patients), and cholestatic jaundice, hepatic failure, liver damage, and veno-occlusive liver disease, each in one patient. Hepatic adverse events considered drug-related included abnormal liver function tests in 7 (0.4%), bilirubinemia in 6 (0.3%), increased alkaline phosphatase in 3 (0.2%) patients, hepatitis in 1 (0.1%), liver damage in 1 (0.1%), and increased AST in 1 (0.1%) patient. Adverse events leading to study drug discontinuation, and those considered drug-related in the fluconazole-controlled studies are shown in the table below.

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Table 106. Adverse Events Resulting in Study Drug Discontinuation in Fluconazole-Controlled Studies* (adapted from Applicant's Appendices 9.1.3, and 9.2.3)

Adverse Event (AE)** COSTART Term	Micafungin N=932	AE Related to Micafungin N=932	Fluconazole N= 787	AE Related to Fluconazole N=757
Abnormal liver function tests	1 (0.1)	1 (0.1)	5 (0.6)	5 (0.6)
Hepatic failure	1 (0.1)	0	2 (0.3)	1 (0.1)
Liver damage	0	0	2 (0.3)	2 (0.3)
Hepatitis, non-specific	0	0	1 (0.1)	1 (0.1)
Bilirubinemia	3 (0.3)	3 (0.3)	4 (0.5)	2 (0.3)
ALT increased	0	0	1 (0.1)	0

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

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

Medical Officer Comments: For each drug-related adverse event listed above, fluconazole was discontinued more often than micafungin.

Dose Relationship of Hepatic Adverse Events in Clinical Studies

Studies 97-7-003, 97-0-041, 98-0-043, FG463-21-03, and FG-463-21-09 were all dose-ranging studies analyzed for dose response. The next table shows hepatic adverse events as a function of micafungin dose (≥ 150 mg/day vs. < 150 mg/day for at least 10 days). Events that occurred at a higher incidence in patients treated with higher dose or duration of micafungin included increased AST, alkaline phosphatase, ALT, abnormal liver function tests, increased GGT, and hepatic failure.

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Table 107. Hepatic Adverse Events in Patients who received ≥ 150 mg/day Micafungin for at least 10 days vs. < 150 mg/day Micafungin

Hepatic Adverse Event COSTART Term	Micafungin ≥ 150 mg/day N=606	Micafungin < 150 mg/day N=1796
	n (%)	n (%)
Any hepatic AE	129 (21.3)	352 (19.6)
AST increased	42 (6.9)	93 (5.2)
Alkaline phosphatase increased	29 (4.8)	74 (4.1)
ALT increased	45 (7.4)	91 (5.1)
Bilirubinemia	36 (5.9)	126 (7.0)
Liver function tests abnormal	30 (5.0)	75 (4.2)
Jaundice	14 (2.3)	48 (2.8)
GGT increased	13 (2.1)	3 (0.2)
Liver damage	1 (0.2)	3 (0.2)
Hepatic failure	3 (0.5)	7 (0.4)
Hepatitis	0 (0)	1 (0.1)
Hepatitis, nonspecific	1 (0.2)	2 (0.1)

n (%) = number and percentage of subjects (patients or volunteers) with adverse event.
 Note that one person could experience more than 1 adverse event within a body system.

The applicant concluded that the higher incidence of adverse events in patients with a higher dose/duration of micafungin was driven by 62 patients who received a mean daily dose of > 4.0 mg/kg micafungin (240 mg in a 60 kg person). Of these patients, 42 (67.7%) had an underlying malignancy, received chemotherapy, or underwent HSCT. The following table shows an increased incidence of certain hepatic adverse events in this group who received the highest mean doses of micafungin. The duration of micafungin therapy was not taken into account in this analysis.

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Table 108. Hepatic Adverse Events by Mean Daily Dose of Micafungin-Treated Patients
 (adapted from Applicant's Appendix 1.1.2, Safety Update, July, 2004)

Hepatic Adverse Event COSTART Term	Micafungin < 1 mg/kg/day N=822	Micafungin 1.0-1.9 mg/kg/day N=804	Micafungin 2.0-2.9 mg/kg/day N=487	Micafungin 3.0-3.9 mg/kg/day N=215	Micafungin ≥ 4.0 mg/kg/day N=62
Liver function tests abnormal	38 (4.6)	38 (4.7)	20 (4.1)	9 (4.2)	0 (0)
Jaundice	29 (3.5)	16 (2.0)	8 (1.6)	5 (2.3)	3 (4.8)
Hepatic failure	4 (0.5)	2 (0.2)	2 (0.4)	2 (0.9)	0 (0)
Liver damage	2 (0.2)	2 (0.2)	0 (0)	0 (0)	0 (0)
Hepatitis, nonspecific	1 (0.1)	1 (0.1)	1 (0.2)	0 (0)	0 (0)
Hepatitis	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)
Bilirubinemia	84 (10.2)	38 (4.7)	14 (2.9)	8 (3.7)	18 (29.0)
ALT increased	42 (5.1)	50 (6.2)	25 (5.1)	7 (3.3)	12 (19.4)
AST increased	35 (4.3)	57 (7.1)	24 (4.9)	8 (3.7)	11 (17.7)
Alkaline phosphatase increased	27 (3.3)	42 (5.2)	23 (4.7)	6 (2.8)	5 (8.1)
GGT increased	2 (0.2)	3 (0.4)	1 (0.2)	2 (0.9)	8 (12.9)

Medical Officer Comments: Because these are pooled data from studies with very different patient characteristics, particularly differences in underlying diseases, these data are difficult to interpret. For several of these adverse events, a bimodal distribution is suggested. For example, bilirubinemia and jaundice were seen most frequently in patients who received < 1.0 mg/kg/day and > 4.0 mg/kg/day. For the adverse events of abnormal liver function tests, hepatic failure, hepatitis, no obvious dose-reponse was noted; whereas for ALT, AST, Alkaline phosphatase, and GGT, a dose-response is suggested.

Hepatic laboratory abnormalities

The mean and median hepatic laboratory values for all micafungin-treated subjects at baseline and end-of-therapy are shown in the table below. For each of the laboratory parameters shown there was an increase in the mean value at the end-of-therapy. However, standard deviations were large, and except for alkaline phosphatase, the median values did not change significantly, indicating that the changes observed were most likely due to a number of outlier values.

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Table 109. Hepatic Laboratory Values at Baseline and End-of Therapy for Micafungin-treated Subjects in Pooled Safety Database (from applicant's summary Table 16 and Appendix 12.1.1)

Hepatic Laboratory Value	N	Baseline Mean ± SD	EOT Mean ± SD	Baseline Median (range)	EOT Median (range)
Total Bilirubin	2226	1.01 ± 2.23	1.38 ± 3.65	0.60 (0.60-36.50)	0.60 (0.10-51.5)
AST	2211	39.2 ± 50.6	58.7 ± 435.2	26.0 (3.0-975.0)	27.0 (1.0-18040)
ALT	2190	37.7 ± 51.5	45.7 ± 134.0	25.0 (2.0-1132)	26.0 (1-3737)
Alkaline phosphatase	2229	165.6 ± 192.4	192.6 ± 257.4	109.0 (8.0-2798)	120.0 (24.0-3188)

N= all subjects (patients and volunteers who received at least one dose of micafungin)
 AST= aspartate aminotransferase; ALT= alanine aminotransferase

Medical Officer Comments: A total of 48 patients with AST and/or ALT elevations to > 10 times ULN at any time after the baseline measurement, were identified by the applicant in the safety database. The extremely elevated AST value of 18,040 U/L was reported for patient number 3423101 in study 98-0-050. The clinical course for this patient is reviewed below.

Patient 3423101 was a 7-month old female with acute lymphocytic leukemia in remission, who received an allogeneic bone marrow transplant, and received a mean daily dose of micafungin 5.6 mg/day for 22 days for antifungal prophylaxis. Baseline conditions included urinary tract infection, decreased gamma globulin, alopecia, cachexia, and anemia. Abnormal liver function tests were reported as a non-serious adverse event on study day 18, and were considered unrelated to micafungin. The patient developed *Pseudomonas* pneumonia on study day 7, hypotension and respiratory syncytial virus (RSV) pneumonia on day 13, graft versus host disease (maximum grade II) on day 14, hyponatremia (day 15), acute renal failure and acidosis (day 16), a seizure (day 19), and an intracranial hemorrhage which resulted in death on day 23. The cause of death was intracranial hemorrhage. The death was considered not related to micafungin. The patient received multiple concomitant medications, including (but not limited to) methylprednisolone, acyclovir, furosemide, cyclosporine, nifedipine, piperacillin/tazobactam, tobramycin, ceftazidime, dopamine, digoxin, adenosine, esmolol, bactrim, vancomycin, milrinone, ribavirin, dilantin, and ciprofloxacin. Hepatic laboratory values for this patient are presented in the table below.

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Hepatic Laboratory Values for Patient 3423101*

Study Day	AST U/L	ALT U/L	Alkaline phosphatase U/L	Total Bilirubin Mg/dL
Baseline	--	25	--	--
Day 1	27	--	213	0.2
Day 7	16	--	165	0.2
Day 14	47	--	48	0.5
Day 17	1742	472	139	4.4
Day 20	14240	2151	629	21.4
Day 22	18040	2793	633	31.4

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

***Medical Officer Comments:** This case was not reviewed with serious adverse events, because the transaminase abnormalities were not reported as such. According to the database, an autopsy was performed, but was not available for review. The cause of the extreme elevation in hepatic transaminases is not clear, but I would suspect that this magnitude of abnormality was due to shock liver (secondary to hypotension and/or hypoperfusion). Hypotension was reported as an adverse event (non-serious) on day 13, and cardiovascular disorder on day 14). The patient received a number of medications to treat hypotension (dopamine) or cardiac failure (milrinone). Another potential cause of transaminase elevation of this magnitude would be viral hepatitis. The patient had RSV pneumonia; but hepatitis is not a common manifestation of RSV disease. I would concur that the extreme transaminase elevations in this patient were not likely related to micafungin.*

The following table shows the shift in hepatic laboratory values from baseline to end-of-therapy for all micafungin-treated subjects presented by baseline laboratory values.

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Table. 110. Shifts in Hepatic Laboratory Parameters from Baseline to End of Therapy for All Subjects (applicant's Table 17)

Hepatic Laboratory			
Parameters	Baseline Number of	Subjects who had Increased of	
Value at Baseline	Subjects	Levels† at End of Therapy	
Total Bilirubin			
Normal	2104	96/2104	(4.6%)
Elevated	122	27/122	(22.1%)
SGOT/AST			
Normal	2049	113/2049	(5.5%)
Elevated	162	15/162	(9.2%)
SGPT/ALT			
Normal	2038	147/2038	(7.2%)
Elevated	152	8/152	(5.3%)
Alkaline Phosphatase			
Normal	1994	130/1994	(6.5%)
Elevated	235	40/235	(17.0%)
Subject base: all subjects who received at least one dose of micafungin (FK463). ULN: upper limit of normal; SGOT/AST: serum glutamic oxaloacetic transaminase/aspartate aminotransferase; SGPT/ALT: serum glutamic pyruvic transaminase/alanine aminotransferase; Normal: <2.5 X ULN; Elevated: ≥2.5 X ULN. † Increased levels means increased to any level higher than the baseline level (Normal < High 1 < High 2 < High 3). Source: Integrated Table 12.1.3			

Medical Officer Comments: In patients who had an elevated bilirubin or alkaline phosphatase at baseline, further elevation at the end-of-therapy was observed more frequently than in patients who had normal values at baseline. Although these data reflect population shifts of laboratory values rather than shifts in individual patients, they suggest that micafungin could worsen existing hepatic laboratory abnormalities, and perhaps underlying liver disease.

The magnitude of shifts in hepatic laboratory values from baseline to end-of therapy for all micafungin-treated subjects is shown in the following series of tables. The table below shows the shift in total bilirubin during treatment with micafungin. A total of 96/2104 (4.6%) subjects experienced further bilirubin elevation above a “normal” ($\leq 2.5x$ ULN) baseline; while 20/76 (26.3%) of those with an elevated bilirubin ($2.5x-5X$ ULN) at baseline experienced further bilirubin elevation; 7/22 subjects (31.8%) with baseline bilirubin of $5x- <10x$ ULN experienced further elevation of bilirubin; and 17/24 subjects (71%) with a baseline bilirubin of $\geq 10x$ ULN had levels in the same range at the end-of therapy.

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Table 111. Shift in Total Bilirubin from Baseline to End-of Therapy for Micafungin-treated subjects (from applicant's Appendix 12.1.3)

Baseline Total Bilirubin	EOT $\leq 2.5x$ ULN*	EOT 2.5x-<5x ULN	EOT 5x-<10x ULN	EOT $\geq 10x$ ULN	No data	Total N
$\leq 2.5x$ ULN*	2008	54	27	15	0	2104
2.5x-<5x ULN	36	20	13	7	0	76
5x-<10x ULN	7	3	5	7	0	22
$\geq 10x$ ULN	2	3	2	17	0	24
No data	0	0	0	0	0	0
Total N	2053	80	47	46	0	2226

EOT= end of therapy

* $\leq 2.5x$ ULN was considered normal

ULN= upper limits of normal

N= number of subjects

Medical Officer Comments: Overall 173/2226 (7.8%) micafungin-treated subjects had a total bilirubin of at least 2.5 X ULN at the end of micafungin therapy. These data also suggest that subjects with baseline elevations in bilirubin were more likely to experience further bilirubin elevations during micafungin treatment.

The magnitude of shift in AST values during micafungin treatment is shown in the table below. A total of 140/2049 (6.8%) subjects with a "normal" ($< 2.5x$ ULN) baseline developed further AST elevations during treatment; 15/130 (11.5%) subjects with baseline AST 2.5x to $< 5x$ ULN developed further AST elevations, while none of the 19 subjects with baseline AST of 5x to $< 10x$ ULN developed further increases in AST.

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Table 112. Shift in AST from Baseline to End-of-Therapy for Micafungin-treated Subjects (adapted from applicant's Appendix 12.1.3)

Baseline AST	EOT AST ≤ 2.5x ULN*	EOT AST 2.5x-<5x ULN	EOT AST 5x-<10x ULN	EOT AST ≥ 10x ULN	No data	Total N
≤ 2.5x ULN*	1936	69	27	17	0	2049
2.5x-<5x ULN	81	34	12	3	0	130
5x-<10x ULN	15	1	3	0	0	19
≥ 10x ULN	7	1	3	2	0	13
No data	0	0	0	0	0	0
Total N	2039	105	45	22	0	2211

EOT= end of therapy

* ≤ 2.5x ULN was considered normal

ULN= upper limits of normal

N= number of subjects

Medical Officer Comments: The overall number of subjects who had an AST above "normal" (< 2.5x ULN) at the end of micafungin treatment was 172/2211 (7.8%) subjects; while 162/2211(7.3%) subjects had AST elevations at baseline. The trend for subjects with elevated AST at baseline to experience further AST elevations at the end of therapy is not as evident as it was with total bilirubin.

The table below shows the magnitude of shifts in ALT levels from baseline to the end of therapy for micafungin-treated subjects. A total of 147/2038 (7.2%) subjects with a "normal" (< 2.5x ULN) baseline ALT developed further ALT elevations during treatment with micafungin; while 8/115 (6.9%) subjects with a baseline ALT of 2.5X to < 5X ULN developed further ALT elevations. None of the subjects with baseline ALT of 5X to < 10X ULN developed further ALT elevations.

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Table 113. Table. Shift in ALT from Baseline to End-of-Therapy for Micafungin-treated Subjects (adapted from applicant's Appendix 12.1.3)

Baseline ALT	EOT ALT ≤ 2.5x ULN*	EOT ALT 2.5x-<5x ULN	EOT ALT 5x-< 10x ULN	EOT ALT ≥ 10x ULN	No data	Total N
≤ 2.5x ULN*	1891	103	34	10	0	2038
2.5x-<5x ULN	86	21	5	3	0	115
5x-< 10x ULN	24	5	0	0	0	29
≥ 10x ULN	2	2	2	2	0	8
No data	0	0	0	0	0	0
Total N	2003	131	41	15	0	2190

EOT= end of therapy

* ≤ 2.5x ULN was considered normal

ULN= upper limits of normal

N= number of subjects

Medical Officer Comments: Overall 187/2190 (8.5%) subjects had an ALT level at least 2.5 x ULN at the end of micafungin treatment; while 152/2190 (6.9%) subjects had an elevated ALT at baseline. There was no obvious trend in subjects with baseline ALT elevations to experience greater elevations at the end of micafungin treatment.

The magnitude of shift in alkaline phosphatase values during micafungin treatment is shown in the following table. For those with a "normal" (< 2.5 x ULN) alkaline phosphatase at baseline, 130/1994 (6.5%) subjects experienced further alkaline phosphatase elevation during micafungin treatment. For those with a baseline alkaline phosphatase of 2.5 x to < 5 x ULN, 31/169 (18.3%) developed further alkaline phosphatase elevation, and for those with baseline alkaline phosphatase between 5 x to < 10 x ULN, 9/55 (16.4%) subjects experienced further alkaline phosphatase elevation.

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Table 114. Shift in Alkaline Phosphatase (AP) from Baseline to End-of-Therapy for Micafungin-treated Subjects (adapted from applicant's Appendix 12.1.3)

Baseline AP	EOT AP ≤ 2.5x ULN*	EOT AP 2.5x-<5x ULN	EOT AP 5x-< 10x ULN	EOT AP ≥ 10x ULN	No data	Total N
≤ 2.5x ULN*	1864	105	23	2	0	1994
2.5x-<5x ULN	56	82	23	8	0	169
5x-< 10x ULN	5	20	21	9	0	55
≥ 10x ULN	0	0	4	7	0	11
No data	0	0	0	0	0	0
Total N	1925	207	71	26	0	2229

EOT= end of therapy

* ≤ 2.5x ULN was considered normal

ULN= upper limits of normal

N= number of subjects

Medical Officer Comments: Overall, 304/2229 (13.6%) subjects had alkaline phosphatase values above "normal" (< 2.5 x ULN) at the end of treatment with micafungin; while 235/2229 (10.5%) subjects had elevated alkaline phosphatase at baseline. As in the case of total bilirubin, subjects with baseline elevations of alkaline phosphatase developed further enzyme increases during treatment than those with "normal" alkaline phosphatase at baseline.

The applicant analyzed the magnitude of AST and/or ALT elevation by mean daily dose of micafungin in subjects with normal transaminase values at baseline, as shown in the following table.

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Table 115. Elevations in Transaminase Values by Mean Daily Dose at End of Therapy for Subjects with Normal Transaminase Values at Baseline

Mean Daily Dose† of Micafungin	n	Transaminase Value at End of Therapy		
		SGOT/AST and/or SGPT/ALT >3 x ULN	SGOT/AST and/or SGPT/ALT >5 x ULN	SGOT/AST and/or SGPT/ALT >10 x ULN
50 mg	589	27 (4.6%)	15 (2.5%)	6 (1.0%)
75 mg	137	7 (5.1%)	5 (3.6%)	2 (1.5%)
100 mg	166	2 (1.2%)	1 (0.6%)	0
150 mg	289	15 (5.2%)	7 (2.4%)	2 (0.7%)
200 mg	137	5 (3.6%)	0	0
Total	1318	56 (4.2%)	28 (2.1%)	10 (0.8%)

SGOT/AST: Serum glutamic oxaloacetic transaminase/aspartate aminotransferase;

SGPT/ALT: Serum glutamic pyruvic transaminase/alanine aminotransferase;

ULN: Upper limit of normal

† 50mg=[≤62.5]; 75mg=[>62.5 to ≤87.5]; 100mg=[>87.5 to ≤125]; 150mg=[>125 to ≤175]; 200mg=[>175]

Medical Officer Comments: These data reflect transaminase values in all subjects in the safety database with normal transaminase values at baseline, and thus included subjects from 32 different studies, who differ significantly in baseline demographics, most notably underlying disease. No convincing dose-response is demonstrated for micafungin relative to transaminase elevations in this analysis.

Dose-Response Relationships of Hepatic Laboratory Abnormalities with Micafungin

The applicant explored the micafungin dose-hepatic toxicity relationship, modeling elevations in liver enzymes as the endpoints in the 3 studies on esophageal candidiasis (see Biopharmaceutics consult by Dr. Dakshina Chilukuri). The applicant concluded that neither micafungin dose nor duration of exposure was related to liver function elevations post-baseline.

However, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) reviewers further conducted a logistic regression dose toxicity analysis in patients with significant transaminase elevations defined as (3×ULN), > 5×ULN, >10×ULN. Although a statistically significant dose effect on the elevations in enzyme values could not be demonstrated, the proportion of patients with elevated enzyme values as a function of dose indicates that a higher number of patients receiving 150 mg dose had elevated alkaline phosphatase, SGOT and SGPT, as shown in the figure below. None of the patients had a bilirubin elevation > 5 x ULN in these studies, and a dose-response was not obvious for micafungin and bilirubin elevation.

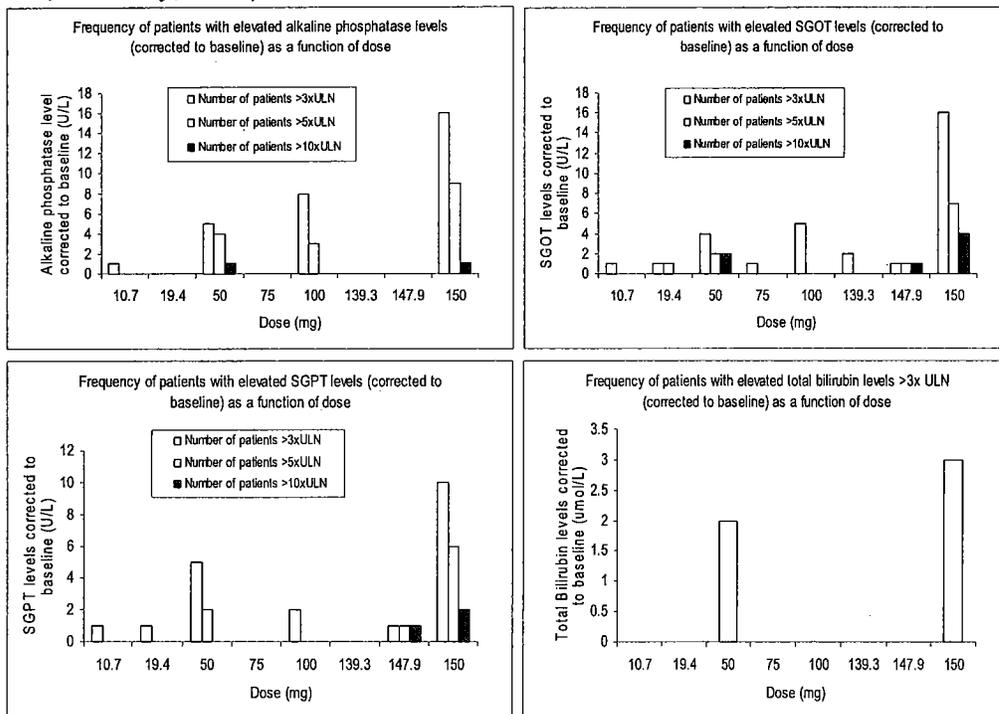
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Figure 4. A frequency plot of patients with elevated enzyme levels as a function of dose. (from Clinical Pharmacology and Biopharmaceutics Review for NDA 21-506 and 21-754, February, 2005)



Medical Officer Comments: In the three studies analyzed by Dr. Chilukuri, 03-7-005, FG463-21-09, and 97-7-003, (all patients with esophageal candidiasis), there appeared to be a relationship between increasing micafungin dose and elevated AST, ALT, and alkaline phosphatase, although this was not statistically significant.

Hepatic Laboratory Data in Fluconazole-Controlled Studies

Fluconazole-controlled studies included 97-0-041, 98-0-050, FG463-21-09 and 03-7-005. The mean increase in hepatic laboratory values from baseline to end-of-therapy was similar in both micafungin- and fluconazole-treated patients as shown in the following table.

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Table 116. Mean±SD Values for Hepatic Laboratory Parameters at Baseline and End of Therapy in Fluconazole-Controlled Trials* (Applicant's Table 19, Safety Update)

Hepatic Laboratory Parameter	Micafungin			Fluconazole		
	n	Baseline	End of Therapy (Median Change from Baseline)	n	Baseline	End of Therapy (Median Change from Baseline)
Total Bilirubin (mg/dL)	881	0.59±0.37	0.95±1.77 (0.10)	757	0.58±0.28	0.92±1.26 (0.10)
SGOT/AST (U/L)	884	39.1±38.0	62.4±611.1	753	36.7±37.3	55.0±269.3 (0)
SGPT/ALT (U/L)	857	35.4±35.5	42.5±107.7	737	36.0±45.0	44.8±89.4 (0)
Alkaline Phosphatase (U/L)	884	120.1±106.0	142.7±166.2 (5)	753	115.3±120.4	124.2±144.4 (3)

Subject base: all patients who received at least one dose of study drug.

SD: standard deviation;

SGOT/AST: serum glutamic oxaloacetic transaminase/aspartate aminotransferase; SGPT/ALT: serum pyruvic Transaminase/alanine aminotransferase.

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

Medical Officer Comments: The magnitude of the mean alkaline phosphatase increase from baseline to end-of-therapy was somewhat higher for micafungin-treated patients than in those who received fluconazole; while mean increases in AST, ALT and bilirubin were similar for the two treatment groups. It is notable that the standard deviation around the mean was high, particularly for AST.

The applicant also analyzed the magnitude of hepatic transaminase elevation at the end-of-therapy by mean daily dose of micafungin in comparison to fluconazole-treated patients. As shown in the table below, there was no apparent relationship between AST or ALT elevation and micfungin dose. Additionally, the magnitude of transaminase elevation was similar in the micafungin and fluconazole treatment groups.

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Table 117. Transaminase Elevations in Fluconazole-Controlled Studies (Applicant's Table 20)

Table 20: Elevations in Transaminase Values by Mean Daily Dose at End of Therapy in Fluconazole-Controlled Studies

Mean Daily Dose of Micafungin†	n	Transaminase Value at End of Therapy		
		SGOT/AST and/or SGPT/ALT ≥3 X ULN	SGOT/AST and/or SGPT/ALT ≥5 X ULN	SGOT/AST and/or SGPT/ALT >10 X ULN
50 mg	317	15 (4.7%)	8 (2.5%)	3 (0.9%)
75 mg	4	0	0	0
100 mg	23	0	0	0
150 mg	142	1 (0.7%)	1 (0.7%)	1 (0.7%)
200 mg	3	0	0	0
Total Micafungin	489	16 (3.3%)	9 (1.8%)	4 (0.8%)
Fluconazole	439	22 (5.0%)	9 (2.1%)	4 (0.9%)

Note: Data are provided for patients with normal transaminase values at baseline. SGOT/AST: serum glutamic oxaloacetic transaminase/aspartate aminotransferase; SGPT/ALT: serum glutamic pyruvic transaminase/alanine aminotransferase, ULN: Upper limit of normal.

† 50mg=[>62.5]; 75mg=[>62.5 to ≤87.5]; 100mg=[>87.5 to ≤125]; 150mg=[>125 to ≤175]; 200mg=[>175]

Fluconazole-Controlled Trials: Studies 97-0-041, 98-0-050, 03-7-005, and FG-463-21-09.

Source: Integrated Table 12.10.3

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Medical Officer Comments: In this analysis, no evidence for a micafungin dose-response relative to transaminase elevation was noted.

Shifts in Hepatic Laboratory Values in Fluconazole-Controlled Studies

The following table shows shifts in hepatic laboratory values from baseline to the end-of-therapy in micafungin- and fluconazole-treated patients, as described below. For patients with normal (<2.5x ULN) AST and/or ALT at baseline, under 1% of micafungin-treated patients experienced elevations to > 10 x ULN, while approximately 1% of fluconazole-treated patients with a normal (<2.5x ULN) baseline developed AST and/or ALT elevations to that magnitude. No patients in either treatment group who had a normal (<2.5 x ULN) alkaline phosphatase at baseline had an alkaline phosphatase of > 10 x ULN at the end-of-therapy; and only a few patients in each treatment group had a total bilirubin of > 10 x ULN at the end-of-therapy if they had a normal (<2.5 x ULN) baseline value. The proportion of patients with moderate elevations of AST or ALT, alkaline phosphatase or bilirubin (≥ 2.5 x to < 10 x ULN) in those who had normal (<2.5 x ULN) baseline values was similar in those treated with either fluconazole or micafungin.

In patients who had an elevated AST (≥ 2.5 x ULN) at baseline, 32 % of micafungin-treated, and 24% of fluconazole-treated patients had an elevated value at the end-of-therapy. A similar proportion (approximately 17%) of those with an elevated ALT at baseline in each treatment group had an elevated ALT at the end-of-therapy; while 1 patient (16.7%) with an elevated bilirubin at baseline in the micafungin-treatment group developed a bilirubin of 2.5 x to < 10 x ULN at the end-of-therapy in comparison to no fluconazole-treated patients. Moderate elevations of alkaline phosphatase (2.5x to < 10 x ULN) occurred in more micafungin- than fluconazole-treated patients who had elevated

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values at baseline (31/47 (70%) vs. 15/38 (53.6%), for micafungin and fluconazole groups, respectively).

Elevation of hepatic laboratory values to > 10x ULN in patients with elevated values ($\geq 2.5x$ ULN) at baseline was similar in micafungin- and fluconazole-treated patients, except for alkaline phosphatase, in which case 5/46 (10.6%) micafungin-treated, and 1/28 (3.6%) patients developed alkaline phosphatase elevations to this magnitude at the end-of-therapy.

Table 118. Shift in Hepatic Laboratory Values from Baseline to End-of Therapy in Fluconazole-Controlled Studies (from applicant's Appendix 12.3.1.5)

Hepatic Laboratory Parameter	Normal* baseline				Elevated Baseline ($\geq 2.5x$ ULN)		
	N	2.5x to < 10x ULN at EOT	$\geq 10x$ ULN at EOT		N	2.5x to < 10x ULN at EOT	$\geq 10x$ ULN at EOT
Micafungin-treated patients:							
AST	828	24 (2.9)	5 (0.6)		56	18 (32.1)	2 (3.6)
ALT	806	44 (5.5)	5 (0.6)		51	9 (17.6)	2 (3.9)
Total Bilirubin	875	28 (3.2)	6 (0.7)		6	1 (16.7)	0 (0)
Alkaline phosphatase	837	34 (4.1)	0 (0)		47	31 (70.0)	5 (10.6)
Fluconazole-treated patients							
AST	720	26 (3.6)	8 (1.1)		33	8 (24.2)	2 (6.1)
ALT	696	39 (5.6)	7 (1.1)		41	7 (17.1)	1 (2.4)
Total Bilirubin	757	36 (4.8)	2 (0.3)		0	0 (0)	0 (0)
Alkaline phosphatase	725	18 (2.5)	0 (0)		28	15 (53.6)	1 (3.6)

*normal = < 2.5x ULN

Medical Officer Comment: Overall the changes in hepatic laboratory parameters from baseline to end-of-therapy were similar in micafungin- and fluconazole-treated patients. The proportion of micafungin-treated patients with elevated AST, ALT, and alkaline phosphatase at baseline who developed further increases in these laboratory values at the end-of therapy was higher than in patients who had normal values at baseline. This phenomenon was also noted in fluconazole-treated patients. These data suggest that micafungin (and fluconazole) could

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cause a worsening of hepatic laboratory abnormalities, and potentially of liver dysfunction.

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Conjoint Elevation of Hepatic Transaminases and Bilirubin in Micafungin Safety Database

The applicant analyzed these data in all subjects in the safety database with normal transaminases at baseline. The data from “worst value for transaminase and bilirubin at any time during treatment” are presented in the table below, although the same pattern of conjoint transaminase and bilirubin elevation was seen at the end-of therapy, but with a somewhat lower incidence at the end-of-therapy.

Table 119. Conjoint Elevation of Bilirubin and Transaminases in Subjects during Treatment

TREATMENT	WORST TOTAL BILIRUBIN	-----Worst of SGOT/AST or SGPT/ALT (*)-----			TOTAL
		<=ULN	>ULN AND <=3 X ULN	>3 X ULN	
FR463	<=ULN	626	192	41	859
	>ULN AND <=3 X ULN	127	107	42	276
	>3 X ULN	27	34	21	82
	TOTAL	780	433	104	1317
FLUCONAZOLE	<=ULN	181	108	23	312
	>ULN AND <=3 X ULN	28	56	18	102
	>3 X ULN	5	13	7	25
	TOTAL	214	177	48	439

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Medical Officer Comments: Overall, 21/1317 (1.6%) subjects treated with micafungin, who had normal transaminase and bilirubin values at baseline, had conjoint elevation of bilirubin and transaminases to > 3 x ULN at some time during the study. Conjoint elevation to this magnitude occurred in 7/439 (1.6%) fluconazole-treated subjects. When only patients with underlying hematologic malignancy or bone marrow transplant were evaluated in this manner, 18/526 (3.4%) of those treated with micafungin, and 7/298 (2.3%) of those who received fluconazole. In comparison, when the subset of patients who did not have a hematologic malignancy or did not receive a HSCT were analyzed for conjoint transaminase and bilirubin elevation, 3/446 (0.7%) micafungin-treated, and 0 of 141 (0%) fluconazole-treated patients developed conjoint elevations of > 3 x ULN. These analyses are limited because of the pooling of patients with different underlying diseases and different micafungin doses and durations received; however, these data suggest that micafungin has a potential for hepatotoxicity similar to that seen with fluconazole.

Dose-Relationship of Conjoint Bilirubin and Transaminase Elevation

The applicant analyzed the incidence of conjoint bilirubin and transaminase elevation by micafungin dose, as shown in the table below.

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Table 120. Conjoint Elevation of Bilirubin and Transaminases by Dose of Micafungin in all Subjects with normal transaminases at baseline (adapted from applicant's Appendices 13.1.4.1, 13.1.4.2, 13.1.5.1, 13.1.5.2, 13.2.4.1, 13.2.4.2, 13.2.5.1, 13.2.5.2)

Dose and Duration of Micafungin	Bilirubin and AST or ALT > 3X ULN (at any time during treatment)	Bilirubin and AST or ALT > 3X ULN (at end-of-therapy)
≥ 100 mg/day for at least 10 days	10/427 (2.3%)	3/427 (0.7%)
< 100 mg/day for at least 10 days	11/827 (1.3%)	6/886 (0.7%)
≥ 150 mg/day for at least 10 days	6/337 (1.8%)	1/337 (0.3%)
< 150 mg/day for at least 10 days	15/980 (1.5%)	8/976 (0.8%)

Medical Officer Comments: These data suggest that conjoint elevation of bilirubin and transaminases is not related to dose or duration of micafungin therapy. Additionally, these data suggest that concurrent elevation of bilirubin and transaminases is transient during the treatment period, with more conjoint elevation of these laboratory values at some time during treatment than at the end-of-therapy. However, because these data are pooled across many studies, and subjects were treated for variable lengths of time, these data reflect population, rather than data in individual patients.

Potential Drug Interactions and Hepatic Safety

Several drug-interaction studies in healthy volunteers revealed significant elevation of hepatic transaminases in subjects who received concomitant mycophenolate mofetil, fluconazole and ritonavir, as summarized in the table below. These studies were summarized in more detail in the section on hepatic safety in healthy volunteers above. No serious hepatic adverse events occurred in these studies. Two subjects with transaminase elevation in the micafungin-mycophenolate mofetil study had ALT elevation to approximately 8 x ULN; while one subject in the micafungin-ritonavir study had an ALT which was 5 x ULN; and one subject in the micafungin-fluconazole study had an ALT elevation between 5-10 x ULN.

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Table.121. Transaminase Elevations in Healthy Volunteer Drug Interaction Studies

Study Protocol	Study Drugs	N	Subjects with AST or ALT \geq 2 x ULN n (%)	Subjects with AST or ALT \geq 5 x ULN n (%)
03-0-175	Micafungin 150 mg/day (days 8-22)+ Sirolimus 6 mg/day (days 1 and 22)	30	0	0
03-0-176	Micafungin 150 mg /day (days 8-22) + Mycophenolate mofetil 1500 mg (days 1 and 11)	30	9(30.0)	2 (6.7)
03-0-177	Micafungin 150 mg/day (days 8-22) + Fluconazole 200 mg (days 1 and 22)	30	8 (26.7)	1 (3.3%)
03-0-178	Micafungin 150 mg/day (days 8-22)+ Nifedipine 10 mg (days 1 and 22)	30	8 (26.6)	0
FG-21-04	Micafungin 200 mg/day (days 1,7,16) + tacrolimus 2mg twice daily (days 7-15)	24	5 (20.8)	0
FG-21-05	Micafungin 200 mg/day (days 1, 7,16) + cyclosporine 50 mg twice daily (days 7-15)	24	2 (8.3)	0
FG-21-06	Micafungin 200 mg (days 1 and 12) + prednisolone 20 mg/day (days 5-14)	24	0	0
FG-21-15	Micafungin 200 mg (days 1 and 10) +Ritonavir 300 mg twice daily (days 6-17)	25	6 (28.0)	1 (4.0%)
FG-21-16	Micafungin 200 mg (days 1 and 12) + rifampin 600 mg/day (days 5-15)	24	0	0
FJ005	Micafungin alone 25, 50, 75, 150 mg (single dose)	24	1 (4.2)	0

Medical Officer Comments: Although the applicant attributed the transaminase elevations in the micafungin-mycophenolate study to diets high in carbohydrates in some subjects, the magnitude of the ALT elevation ($> 5 \times$ ULN) in 2 subjects would suggest otherwise. Fluconazole and ritonavir have known potential for hepatotoxicity, and the ALT elevation in these subjects could be due to either drug alone, or to the combination with micafungin.

Because of the unexplained transaminase elevations in healthy volunteers in these studies, additional information regarding hepatic adverse events and hepatic laboratory

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abnormalities was requested from the applicant regarding the concomitant use of ritonavir, mycophenolate, fluconazole, nifedipine, tacrolimus and cyclosporine in patients in clinical studies.

Concurrent use of Micafungin or Fluconazole with Cyclosporine, Tacrolimus, Mycophenolate mofetil, and Nifedipine in Study 98-0-050

In an attempt to determine whether the concurrent use of micafungin with these medications resulted in an excess of hepatic adverse events or laboratory abnormalities, we evaluated patients enrolled in the *Candida* prophylaxis study 98-0-050, who received micafungin or fluconazole alone, in comparison to those who received study drug plus one of these concomitant medications. These patients were HSCT recipients and 475/882 (53.9%) patients received immunosuppressive agents for prophylaxis or treatment of graft versus host disease. A total of 169/425 (39.8%) of patients who received micafungin, and 194/457 (42.5%) of those who received fluconazole, also received cyclosporine during the treatment period for prevention or treatment of GVHD. Similarly, tacrolimus was administered to 46/425 (10.8%) micafungin and 53/457 (11.6%) fluconazole patients. Active graft-versus-host disease was present in 96/425 (22.6%) of patients in this study who received micafungin, and in 22.3% (102/457) patients who received fluconazole for prophylaxis.

The following table shows the incidence of serious hepatic adverse events and transaminase elevation to ≥ 5 times the upper limit of normal (ULN) in patients who received micafungin alone, fluconazole alone, in comparison to patients who received the study drug in addition to the concomitant medication in question. Only 4 patients were identified in this study who received sirolimus in addition to micafungin, and no serious hepatic adverse events or significant transaminase elevations were reported in those patients.

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Table 122. Serious Hepatic Adverse Events and Transaminase elevations (which occurred any time during or after treatment) in Patients who received Micafungin plus Selected Concomitant Medications in Study 98-0-050 (requested data received from applicant 2/18/05)

Study Drug ± Concomitant Medication	N	Hepatic SAEs	AST/ALT ≥ 5 x ULN
Micafungin + MMF*	35	0	6 (17.1)
Micafungin*	390	7 (1.8)	47 (12.1)
Fluc +MMF*	32	0	9 (28.1)
Fluconazole*	425	10 (2.4)	65 (15.3)
Micafungin + cyclosporine**	169	6 (3.6)	35 (20.7)
Micafungin**	256	1 (0.4)	17 (6.6)
Fluconazole + cyclosporine**	194	6 (3.1)	39 (20.1)
Fluconazole**	263	3 (1.1)	30 (11.4)
Micafungin + tacrolimus†	46	1 (2.2)	7 (15.2)
Micafungin †	379	6 (1.6)	46 (12.1)
Fluconazole + tacrolimus†	53	2 (3.8)	13 (24.5)
Fluconazole†	404	8 (2.0)	60 (14.9)
Micafungin + nifedipine#	48	1 (2.1)	6 (12.5)
Micafungin#	377	6 (1.6)	42 (11.1)
Fluconazole + nifedipine#	58	1 (1.7)	9 (15.5)
Fluconazole#	399	9 (2.3)	60 (15.0)
Micafungin (all patients)#	425	7 (1.6)	48 (11.3)
Fluconazole (all patients)#	457	10 (2.2)	69 (15.1)

MMF= mycophenolate mofetil

*Patient may have also received cyclosporine, or tacrolimus

**Patient may have also received tacrolimus or MMF

†Patient may have also received cyclosporine or MMF

Patients may have also received cyclosporine, MMF, or tacrolimus

Medical Officer Comments: These data are confounded by the fact that many patients who received micafungin or fluconazole “alone” in this study, actually received one of the other immunosuppressive agents. Similarly, many patients who received nifedipine also received immunosuppressive agents. Additionally, many patients received more than one immunosuppressant medication. Despite the limitations of this analysis, the incidence of serious hepatic adverse events was no higher in patients who received micafungin plus mycophenolate, tacrolimus, and nifedipine than micafungin “alone” (or in all patients who received micafungin in the study); while somewhat more serious adverse events

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occurred in patients who received micafungin or fluconazole plus cyclosporine than in the subset of those who received the study drug "alone".

The incidence of significant transaminase elevation ($\geq 5 \times \text{ULN}$) was similar in the subset of patients who received micafungin plus mycophenolate, or micafungin "alone", in patients who received micafungin plus tacrolimus or micafungin "alone", or micafungin plus nifedipine or micafungin "alone". However, the incidence of transaminase elevation was higher in the subset of patients who received micafungin (or fluconazole) plus cyclosporine in comparison to study drug "alone". The higher incidence of transaminase elevation in the subset of patients who received cyclosporine may be attributable to a higher incidence of active graft-versus host disease in patients who received cyclosporine than those who did not. Additionally, cyclosporine itself has been associated with elevations in transaminases and bilirubin.

An additional analysis was performed to evaluate the incidence of serious hepatic adverse events and significant transaminase elevations in patients who received concomitant micafungin plus mycophenolate mofetil. At the Agency's request, the applicant compiled a listing of all patients who received micafungin plus mycophenolate mofetil in the pooled micafungin safety database. A total of 109 patients were identified from several clinical studies, of these patients, 2/109 (1.8%) experienced a serious hepatic adverse event (neither was related to micafungin), and 13/109 (11.9%) patients had an AST or ALT elevation $\geq 5 \times \text{ULN}$.

To put these data in some perspective, in the overall micafungin safety database, 28/1318 (2.1%) patients who had transaminases measured at the end-of-therapy had an AST/ALT elevation of $\geq 5 \times \text{ULN}$, and 10/1318 (0.8%) patients had transaminase elevations greater than $10 \times \text{ULN}$. The overall incidence of serious hepatic adverse events in the pooled micafungin safety database was 1.4% (28/190). In the fluconazole controlled studies, the incidence of serious hepatic adverse events was 1.1%, the incidence of transaminase elevations $\geq 5 \times \text{ULN}$ was 1.8%, and the incidence of transaminase elevations greater than $10 \times \text{ULN}$ was 0.8% for patients who received micafungin, as shown in the table below. These results are similar to those observed in patients who received fluconazole.

Table. 123. Serious Hepatic Adverse Events (during studies) and Transaminase Elevations (at end-of therapy) in Pooled Fluconazole-Controlled Studies (03-7-005, FG-21-09, 98-0-050, 97-0-041)

	Micafungin N=932	Fluconazole N=787
AST/ALT $\geq 5 \times \text{ULN}$	9 (1.8%)	9 (2.1%)
AST/ALT $\geq 10 \times \text{ULN}$	4 (0.8%)	4 (0.9%)
Serious hepatic AE during studies	10 (1.1%)	11 (1.4%)

ULN= upper limit of normal

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Medical Officer Comments: *These data are not directly comparable to those reported in Table 122 above, as the former reflect serious hepatic adverse events and transaminase elevations which occurred at any time during treatment; while this table shows transaminase data only for end-of-therapy values. In comparison to the incidence of serious hepatic adverse events in the patients who received concomitant micafungin or fluconazole plus mycophenolate, tacrolimus, or nifedipine in study 98-0-050, the incidence of serious hepatic adverse events observed in the pooled fluconazole-controlled studies was similar; while the incidence of serious hepatic adverse events was only slightly higher in patients who received cyclosporine plus micafungin or fluconazole than in the pooled fluconazole studies overall.*

The following table shows serious hepatic adverse events and transaminase elevations (any time during treatment) in each of the individual fluconazole-controlled studies. Note that the incidence of significant transaminase elevation is higher in each of the individual studies than in the pooled studies, because the latter were analyzed only at end-of therapy, as shown above.

Table 124. Transaminase Elevations and Serious Hepatic Adverse Events in Individual Fluconazole-Controlled Studies

Study	Micafungin AST/ALT \geq 5 x ULN	Fluconazole AST/ALT \geq 5 x ULN	Micafungin Serious hepatic AE	Fluconazole Serious hepatic AE
98-0-050	48/425 (11.3%)	69/457 (15.1%)	7/425 (1.6%)	10/457 (2.2%)
FG463-21-09	14/185 (7.6%)	ND	2/185 (1.1%)	0/185 (0)
03-7-005	12/260 (4.6%)	ND	1/260 (0.4)	1/258 (0.4%)
97-0-041	3/62 (4.8%)	ND	0/62 (0)	0/12 (0)

ND= not determined

In patients who received micafungin, the incidence of significant transaminase elevation was higher in patients in the 98-0-050 study than in the other fluconazole-controlled studies. This may be due in part, to the differences in demographics. In study 98-0-050, most patients were HSCT recipients; while in 03-7-005 and FG 463-21-09 most patients had underlying HIV disease. Additionally, more than 50 % of patients in study 98-0-050 received immunosuppressive agents for treatment or prophylaxis of GVHD, and approximately 20% patients in the study developed GVHD, which can be associated with transaminase elevation.

In study 98-0-050, the applicant summarized mean AST, ALT and bilirubin values during treatment in patients who received micafungin or fluconazole plus cyclosporine, as shown in the following tables. Overall, there was minimal change in the mean laboratory values for AST and ALT from baseline in patients who received micafungin or

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fluconazole plus cyclosporine; however, the mean bilirubin values increased throughout the sampling period for both treatment groups.

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Table 125. Mean AST values in Patients who received Concomitant Cyclosporine in study 98-0-050 (applicant's Table 33, study report 98-0-050)

	FK463		Fluconazole	
	n	Mean † SD (U/L)	n	Mean † SD (U/L)
Baseline	162	30.5 ±24.6	183	33.8 ±41.3
Week 1	128	42.7 ±150.6	148	38.8 ±48.8
Week 2	148	27.7 ±24.4	171	40.2 ±93.9
Week 3	114	26.1 ±22.1	117	29.1 ±42.6
Week 4	50	37.1 ±43.0	47	35.1 ±20.3

Patient base: all randomized patients who received at least one dose of study drug.

SD: standard deviation

Table 126. Mean ALT values in Patients who received Concomitant Cyclosporine in Study 98-0-050 (Applicant's Table 34, study report 98-0-050)

	FK463		Fluconazole	
	n	Mean † SD (U/L)	n	Mean † SD (U/L)
Baseline	151	36.8 ±34.6	177	43.8±65.8
Week 1	124	55.6 ±111.1	137	60.2±115.2
Week 2	151	43.7 ±50.1	167	64.6±138.0
Week 3	117	38.4 ±35.2	112	43.2±44.9
Week 4	47	48.4 ±59.1	44	55.5 ±60.1

Patient base: all randomized patients who received at least one dose of study drug.

Table 127. Mean Bilirubin Values in Patients who received Concomitant Cyclosporine in Study 98-0-050 (Applicant's Table 34, study report 98-0-050)

	FK463		Fluconazole	
	n	Mean † SD (U/L)	n	Mean † SD (U/L)
Baseline	159	0.65 ±0.38	181	0.60 ±0.32
Week 1	131	0.82 ±0.85	146	0.73 ±0.59
Week 2	155	1.17 ±0.92	175	1.27 ±2.34
Week 3	119	1.60 ±1.66	118	1.77 ±2.29
Week 4	52	2.15 ±3.84	48	2.76 ±5.58

Patient base: all randomized patients who received at least one dose of study drug.

SD: standard deviation

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Additional information regarding all hepatic adverse events in subsets of patients who received concomitant cyclosporine or tacrolimus in addition to study drug in study 98-0-050 was provided by the applicant, and is summarized below.

Table 128. Incidence of Clinical Hepatobiliary Adverse Events in Patients who received Cyclosporine or Tacrolimus in Study 98-0-050 (Table 1.1, 3 February, 2005)

Hepatobiliary Adverse Events MedDRA Preferred Term	Micafungin + Cyclosporine N=169	Fluconazole + Cyclosporine N= 194	Micafungin + Tacrolimus N=46	Fluconazole + Tacrolimus N=53
Any AE	55 (32.5)	57 (29.4)	5 (10.9)	10 (18.9)
Hyperbilirubinemia	33 (19.5)	32 (16.5)	3 (6.5)	4 (7.5)
Jaundice	19 (11.2)	30 (15.5)	0	1 (1.9)
Hepatomegaly	7 (4.1)	4 (2.1)	0	0
Veno-occlusive liver disease	4 (2.4)	4 (2.1)	0	2 (3.8)
Cholelithiasis	2 (1.2)	0	0	1 (1.9)
Hyperbilirubinemia, aggravated	2 (1.2)	0	0	0
Hepatic failure	1 (0.6)	0	0	1 (1.9)
Hepatitis	1 (0.6)	0	1 (2.2)	0
Cholestasis	0	1 (0.5)	0	0
Hepatosplenomegaly	0	2 (1.0)	0	0
Hepatotoxicity	0	1 (0.5)	0	1 (1.9)

Medical Officer Comments: The incidence of clinical hepatobiliary adverse events was similar in patients who received micafungin or fluconazole plus cyclosporine. For patients who received tacrolimus with fluconazole the incidence of hepatobiliary adverse events was somewhat higher than in those who received micafungin.

Table 129. Incidence of Hepatic Laboratory Adverse Events in Patients who Received Cyclosporine or Tacrolimus in Study 98-0-050 (Applicant's Table 1.1, 3 February, 2005)

Hepatobiliary Adverse Events MedDRA Preferred Term	Micafungin + Cyclosporine N=169	Fluconazole + Cyclosporine N= 194	Micafungin + Tacrolimus N=46	Fluconazole + Tacrolimus N=53
ALT increased	19 (11.2)	23 (11.9)	2 (4.3)	4 (7.5)
AST increased	12 (7.1)	13 (6.7)	2 (4.3)	4 (7.5)
Bilirubin increased	10 (5.9)	16 (8.2)	1 (2.2)	3 (5.7)
Liver function tests abnormal	10 (5.9)	14 (7.2)	5 (10.9)	5 (9.4)
Alkaline phosphatase increased	5 (3.0)	9 (4.6)	1 (2.2)	2 (3.8)

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Medical Officer Comments: Although the overall incidence of hepatic laboratory adverse events could not be determined from these data, similar proportions of patients who received tacrolimus with either micafungin or fluconazole experienced these adverse events. Additionally, there was no difference in the incidence of hepatic laboratory adverse events in patients who received cyclosporine with either micafungin or fluconazole, although these differences were generally attributable to 1 or 2 patients.

Conclusions Regarding Concomitant Use of Micfungin and Immunosuppressants

The incidence of significant AST/ALT elevation was higher in study 98-0-050 than in the other fluconazole-controlled studies for patients who received micafungin. This rate however, was similar in patients who received either micafungin or fluconazole. Many of these patients received cyclosporine or other immunosuppressants, and most patients were hematopoietic stem cell transplant recipients. The incidence of serious hepatic adverse events was similar in patients who received micafungin plus tacrolimus, mycophenolate mofetil, or nifedipine, and slightly higher in those who received cyclosporine, than in patients who received micafungin without the specified concomitant drug. However, these data are confounded by the fact that many patients received an alternate immunosuppressive agent. The data showing similar rates of transaminase elevation and serious hepatic adverse events in patients who received either micafungin or fluconazole with cyclosporine, mycophenolate, tacrolimus and nifedipine is reassuring. Likewise, the data showing a similar incidence of any hepatobiliary adverse event in patients who received tacrolimus or cyclosporine with micafungin or fluconazole does not suggest a hepatic safety signal beyond the hepatic PRECAUTION recommended for the final micafungin label.

Concomitant Use of Micafungin plus Ritonavir in Patients in Study FG463-21-09

Ritonavir is a common component of highly active antiretroviral therapy (HAART) for treatment of HIV infection. Most patients in the clinical studies which enrolled patients with HIV and esophageal candidiasis did not receive HAART. Only 8/185 (4.3%) patients in study FG463-21-09 received both ritonavir and micafungin, and 1/60 (1.7%) patients received fluconazole plus ritonavir; while none of the patients in study 03-7-005 received ritonavir plus micafungin or fluconazole. The following table shows the incidence of serious hepatic adverse events and of significant transaminase elevation in patients who received ritonavir with micafungin or fluconazole in comparison to those who received study drug alone.

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Table 130. Serious Hepatic Adverse Events and Transaminase Elevation in Patients who received Micafungin or Fluconazole and Ritonavir in study FG463-21-09 (requested data received from Applicant 18 February, 2005)

Study Drug ± Concomitant Medication	N	Patients with Serious Hepatic Adverse Events n (%)	Patients with AST or ALT ≥ 5 x ULN n (%)
Micafungin	177	2 (1.1)	11 (6.2)
Micafungin + Ritonavir	8	0	0
Fluconazole	59	0	3 (5.1)
Fluconazole + Ritonavir	1	0	0

N= number of patients for each analysis

Medical Officer Comments: The incidence of serious hepatic adverse events or significant transaminase elevation did not increase with concomitant micafungin and ritonavir use, although the sample size is too small to draw firm conclusions. Additionally, because only 1 patient received fluconazole plus ritonavir, we don't have a valid comparator.

Concomitant Fluconazole and Micafungin in Studies 97-0-041, 98-0-043, 98-0-046, and 98-0-047

Concomitant use of micafungin and fluconazole was excluded in the esophageal candidiasis studies 03-7-005, FG463-21-09, and 97-7-003. Study 98-0-050 (*Candida* prophylaxis) was not used for this analysis because fluconazole may have been used in some patients for treatment of proven, probable, or suspected fungal infections in the post-micafungin treatment period, potentially confounding the analysis. The following table shows the incidence of serious hepatic adverse events and of significant transaminase elevation in patients who received fluconazole with micafungin in comparison to those who received micafungin alone.

Table 131. Serious Hepatic Adverse Events and Transaminase Elevation in Patients who received Concomitant Micafungin and Fluconazole in studies 97-0-041, 98-0-043, 98-0-046, and 98-0-047 (requested data received from Applicant 18 February, 2005)

Study Drug ± Concomitant Medication	N	Patients with Serious Hepatic Adverse Events n (%)	Patients with AST or ALT ≥ 5 x ULN n (%)
Micafungin	712	16 (2.2)	97 (13.6)
Micafungin + Fluconazole	106	0	15 (14.2)

N= number of patients for each analysis

Medical Officer Comments: In this analysis, the incidence of serious hepatic adverse events did not increase in patients who received micafungin plus fluconazole in comparison to those who received micafungin alone. Likewise, the

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incidence of clinically significant AST or ALT elevation was similar in patients who received this combination to those who received micafungin alone.

Conclusions Regarding Hepatic Safety of Micafungin with Concomitant Medications

Significant transaminase elevation $\geq 5 \times$ ULN was observed in healthy volunteers who received micafungin plus mycophenolate mofetil, or micafungin plus fluconazole or ritonavir, but not with cyclosporine, tacrolimus or sirolimus. Fluconazole and ritonavir have known potential for hepatotoxicity, which may explain the transaminase elevation with those drugs, but mycophenolate mofetil has not been associated with hepatic effects. The transaminase elevation in healthy individuals who received both micafungin and mycophenolate mofetil suggested some type of drug interaction resulting in a higher incidence and magnitude of ALT elevation than what was expected with micafungin alone.

In clinical practice, hematopoietic stem cell transplant recipients commonly receive immunosuppressive medications to prevent or treat GVHD, and might also be expected to receive micafungin for prophylaxis (NDA 21-506, pending approval), so potential interaction of micafungin with mycophenolate or the other immunosuppressant drugs is of some importance. Pharmacokinetic studies established that there were no pharmacokinetic interactions which would increase micafungin exposure; however both nifedipine and sirolimus AUC were increased with micafungin.

Further analysis of patients who received concomitant micafungin and immunosuppressive therapy (mycophenolate, cyclosporine, and tacrolimus) in the clinical trial database was performed to determine if patients who received these medications concurrently with micafungin had a higher incidence of serious hepatic adverse events or significant transaminase elevations in comparison to those who did not received immunosuppressant medications. Although the data was highly confounded, there was no apparent increase in the incidence of serious hepatic adverse events or transaminase elevation in patients who received micafungin in combination with mycophenolate mofetil, or tacrolimus, in comparison to patients who did not receive those combinations. For patients treated with micafungin plus cyclosporine the incidence of serious hepatic adverse events and transaminase elevations was somewhat higher than in those who received micafungin without cyclosporine. Thus, the data from the drug interaction studies in healthy volunteers did not predict the occurrence of transaminase elevations in patients receiving immunosuppressive therapy. If those studies were predictive, patients who received mycophenolate plus micafungin would have had the highest incidence of significant transaminase elevation, and cyclosporine the least; while in fact, the opposite occurred. This subset analysis does not take into account differences in patient demographics (eg. allogeneic versus autologous transplant), or development of GVHD, and the advantages of a randomized, blinded study are lost with this type of analysis. Thus, firm conclusions can not be drawn regarding hepatic safety of the combination of micafungin with these immunosuppressant medications; however, because the incidence of serious hepatic adverse events did not differ significantly in patients who received

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micafungin plus an immunosuppressant in comparison to micafungin alone, these drug combinations do not appear to represent a major safety issue at this time. A PRECAUTION regarding the potential hepatic effects of micafungin was proposed for the final micafungin label, stating that patients who develop abnormal liver function tests during Mycamine therapy should be monitored for evidence of worsening hepatic function and evaluated for the risk/benefit of continuing Mycamine therapy.

Postmarketing Hepatic Adverse Events in Japan

The ODS, in consultation with the DSPIDP evaluated serious hepatic adverse events in patients who received micafungin in the Japanese postmarketing database from 8 April, 2003 to 8 April, 2004. During this time period, there were 63 serious hepatobiliary adverse events reported. A total of 27 serious hepatic adverse events were identified for further review. These adverse events are summarized in the table below, along with conclusions regarding assessment of relationship to micafungin.

Table 132. Serious Hepatic Adverse Events in Japanese Postmarketing Experience (April, 2003 to April, 2004) (from ODS consultation by Dr. Adrienne Rothstein, January, 2005)

Serious Adverse Event	N	Relationship to Micafungin as assessed by ODS (n)
Hepatic failure	6	Possible (1); unlikely (4); not determined (1)
Hepatitis	1	Not related (1)
Hepatocellular damage	3	Possible (1); unlikely (2)
Liver disorder	2	Possible (2)
Hyperbilirubinemia	5	Possible (2); unlikely (3)
Abnormal hepatic function	10	Possible (4); unlikely (5); not determined (1)

Medical Officer Comments: A number of serious hepatic adverse events were considered at least possibly related to micafungin in the Japanese postmarketing database. Post-approval of micafungin, vigilance for serious hepatic postmarketing adverse events will be of considerable importance.

Conclusions Regarding Hepatic Safety of Micafungin

1. Animal studies showed that the liver is a target organ for micafungin toxicity.
2. A number of healthy volunteers developed transient increases in hepatic laboratory values in drug-drug interaction studies with micafungin. None of the significant transaminase elevations could be definitively attributed to micafungin or to the combination of micafungin with the concomitant medication. In the clinical studies, patients who received micafungin (or fluconazole) in combination with mycophenolate mofetil, tacrolimus, fluconazole, nifedipine, and ritonavir did not have an increased incidence of serious hepatic adverse events or significant transaminase elevation in comparison to those who received study drug without these medications. Patients who received concomitant micafungin (or fluconazole) and cyclosporine in clinical studies had a somewhat higher incidence

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of serious hepatic adverse events and clinically significant transaminase elevation in comparison to those who received study drug without cyclosporine.

3. Increases in AST, ALT, alkaline phosphatase and bilirubin were common in micafungin-treated patients; and the proportion of patients with significant ($> 3 \times$ ULN) conjoint elevation of transaminases and bilirubin was similar in patients who received micafungin or fluconazole.
4. Although there was no statistically significant dose-relationship between micafungin and clinically significant elevations of AST, ALT, and alkaline phosphatase in patients with esophageal candidiasis, a trend suggestive of a dose response was noted, with more hepatic enzyme elevation in patients who received 150 mg/day micafungin.
5. A number of serious clinical hepatic adverse events were reported in the micafungin safety database. Some of the cases of hepatic failure or liver damage were possibly related to micafungin, as determined by an expert panel of hepatologists, with concurrence by Dr. John Senior of the ODS. Micafungin may exacerbate pre-existing liver disease in some patients. Because of these findings, a PRECAUTION is proposed regarding the potential hepatic effects of micafungin for the final product labeling.
6. Serious hepatic adverse events possibly related to micafungin have been identified in the Japanese postmarketing database. Continued surveillance for such adverse events will be important post-micafungin approval in the U.S.

7.1.12.5 Injection Site Reactions

The overall incidence of injection site reactions in the clinical studies was 8.3% (199/2402) subjects. In fluconazole-controlled studies, injection site reactions occurred in 9.9% (92/932) patients who received micafungin and in 4.4% (35/787) of those treated with fluconazole. The most common adverse events in this category included phlebitis, thrombophlebitis, and injection site inflammation. There was only 1 serious drug-related adverse event reported, a case of thrombophlebitis. Most adverse events in this category were mild, and most did not require micafungin discontinuation. Some evidence is provided below that phlebitis and thrombophlebitis may be associated with higher doses of micafungin.

Preclinical Studies

In rats, hemorrhage and cellular infiltration in perivascular tissue was noted in a 4-week, repeat-dose study, at doses of 10 mg/kg (5 mg/mL) and 32 mg/kg (16 mg/mL) micafungin. This effect was concentration-dependent. When rats received an infusion of 1.6 mg/ml (3.2 mg/kg), the incidence of vascular lesions was similar to that in rats which received normal saline.

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No evidence of vascular irritation was observed in dogs in repeated bolus studies at 4, 13, and 39 weeks with a micafungin dose of 32 mg/kg (16 mg/mL). The applicant interpreted these finding to show that rats were more sensitive than dogs to vascular irritation; and that differences between animal could be due to differences in blood vessel anatomy. According to the applicant, the inner and cross-sectional diameters of blood vessels of dogs are 5 and 25 times larger, respectively, than in rats. In rabbits, intra-arterial, and perivenous injections of micafungin at concentrations of 0.5 mg/mL, 1 mg/mL, 2 mg/mL, and 4 mg/mL did not result in any treatment-related local reactions.

Studies in Healthy Volunteers

Adverse reactions categorized as injection site reactions in single- and repeat-dose micafungin studies in healthy volunteers are shown in the table below.

Table 133. Injection Site Reactions in Healthy Volunteers in Micafungin Studies (adapted from applicant's appendix 2.3)

Adverse Reaction (COSTART Body System and Term)*	Micafungin-treated Volunteers (Repeat-dose studies)** N=184	Micafungin-treated Volunteers (Single-dose studies) † N=198
Injection Site Reaction:		
Injection site edema	6 (3.3)	2 (1.0)
Injection site pain	4 (2.2)	8 (4.0)
Injection site inflammation	2 (1.1)	11 (5.6)
Injection site reaction	0 (0)	3 (1.5)
Cardiovascular System:		
Phlebitis	17 (9.2)	0 (0)
Thrombophlebitis	3 (1.6)	0 (0)
Thrombosis	0 (0)	1 (0.1)

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

** included studies 01-0-104, 01-0-105, 03-0-175, 03-0-176, 03-0-177, 03-0-178, FJ0002, and FJ0005 (6 subjects in latter study received repeat-dose micafungin).

† included studies 97-0-040, FJ0001, FJ0004, FJ0005 (24 single-dose patients), FG-21-04, FG-21-05, FG-21-06, FG-21-15, FG-21-16

Injection site reactions by micafungin dose are shown in the table below. The micafungin doses shown in this table are actually dose ranges, as follows: 50 mg = ≤ 62.5 mg; 75 mg = $> 62.5 \leq 87.5$ mg; 100 mg = $> 87.5 \leq 125$ mg; 150 mg = $> 125 \leq 175$ mg micafungin.

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Table 134. Injection Site Reactions in Healthy Volunteers by Micafungin Dose in Repeat-Dose Studies** (adapted from Applicant's Appendix 1.5, ISS, 15 April, 2004)

Adverse Reaction (COSTART Body System and Term)*	Micafungin 50 mg/day N=6	Micafungin 75 mg/day N=6	Micafungin 100 mg/day N=53	Micafungin 150 mg/day N=119	Micafungin Total N=184
Injection Site Reaction:					
Injection site edema	0	0	6 (13.2)	0	6 (3.3)
Injection site pain	0	0	4 (7.5)	0	4 (2.2)
Injection site inflammation	0	0	2 (3.8)	0	2 (1.1)
Cardiovascular System:					
Phlebitis	0	0	0	17 (14.3)	17 (9.2)
Thrombophlebitis	0	0	0	3 (2.5)	3 (1.6)

** included studies 01-0-104, 01-0-105, 03-0-175, 03-0-176, 03-0-177, 03-0-178, FJ0002, FJ0005 (6 repeat-dose subjects)

Medical Officer Comments: Phlebitis or thrombophlebitis occurred only in volunteers who received 150 mg/day of micafungin, and not lower doses. It is notable that all cases of phlebitis and thrombophlebitis occurred in subjects in studies 03-0-175, 03-0-176, 03-0-177, and 03-0-178, all drug interaction studies with micafungin. There is no plausible explanation as to why injection site reactions (edema, pain, inflammation) occurred in subjects who received micafungin 100 mg/day, but not at 150 mg/day. The injection site reactions which occurred with the 100 mg dose of micafungin occurred in studies 01-0-104 (cyclosporine-micafungin-interaction study), and in 01-0-105 (tacrolimus-micafungin interaction study). This may be due to differential reporting of adverse events by different investigators.

In the repeat-dose studies, all of the adverse events in this category occurred in subjects who received at least 10 days of micafungin, with the exception of phlebitis, which also occurred in 2 subjects who received less than 10 days of micafungin, as shown below.

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Table 135. Injection Site Reactions by Duration of Micafungin in Repeat-Dose Micafungin Studies** in Healthy Volunteers (adapted from Applicant's Appendix 2.3, ISS, 15 April, 2004)

Adverse Reaction (COSTART Body System and Term)*	Micafungin duration 1-9 days N=45	Micafungin duration ≥ 10 days N=139	Total Micafungin N=184
Cardiovascular System:			
Phlebitis	2 (4.4)	15 (10.8)	17 (9.2)
Thrombophlebitis	0	3 (2.2)	3 (1.6)
Injection Site Reaction:			
Injection Site Edema	0	6 (4.3)	6 (3.3)
Injection Site Pain	0	4 (2.9)	4 (2.2)
Injection site Inflammation	0	2 (1.4)	2 (1.1)

** included studies 01-0-104, 01-0-105, 03-0-175, 03-0-176, 03-0-177, 03-0-178, FJ0002, FJ0005 (6 repeat-dose subjects)

Medical Officer Comments: It appears that injection site reactions, including phlebitis or thrombophlebitis were associated with longer durations of micafungin administration.

Clinical Studies

Injection site reactions, as defined by the applicant, include the COSTART terms, phlebitis, thrombophlebitis, deep thrombophlebitis, injection site inflammation, injection site pain, injection site edema, injection site hemorrhage, and injection site reaction. The overall incidence of injection site reactions was 8.3% (199/2402) in subjects, and 7.6% (150/1980) in patients, as shown below. Those adverse events considered drug-related were phlebitis, which occurred in 37 (1.5%), thrombophlebitis in 7 (0.3%), injection site inflammation in 30 (1.2%), injection site pain in 5 (0.2%), injection site reaction in 3 (0.1%) subjects, and injection site edema in 1 (0.1%) subject.

Table 136. Injection Site Reactions in all Micafungin-treated patients and subjects (adapted from applicant's Appendix 11.3.1.1, safety update)

Adverse Reaction (COSTART Term)	Micafungin-treated subjects N=2402	Micafungin-treated Patients N=1980
Any adverse event	199 (8.3)	150 (7.6)
Phlebitis	97 (4.0)	80 (4.0)
Injection site inflammation	30 (1.2)	17 (0.9)
Thrombophlebitis	28 (1.2)	25 (1.3)
Injection site pain	15 (0.6)	2 (0.1)
Injection site reaction	8 (0.3)	5 (0.3)
Deep thrombophlebitis	24 (1.0)	24 (1.2)
Injection site edema	8 (0.3)	0 (0)

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Injection site hemorrhage	1 (0.0)	1 (0.1)
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Medical Officer Comments: The term "subjects" includes patients and volunteers. A significant number of these reactions occurred in volunteers, as shown in the table above, particularly phlebitis and injection site pain, edema, and inflammation.

Serious Injection Site Reactions

Serious adverse events in this category occurred only in patients, and not in volunteers. Additionally, no deaths occurred due to injection site reactions. Serious injections site adverse events are shown in the table below.

Table 137. Serious Injection Site Reactions in Patients who received Micafungin (adapted from Applicant's Appendix 8.1.2, ISS, 15 July, 2004)

Serious Adverse Event* COSTART Body System and Term	All Serious Adverse Events N=1980	Drug-related Serious Adverse Events N=1980
Cardiovascular System:		
Deep thrombophlebitis	7 (0.4)	0
Thrombophlebitis	1 (0.1)	1 (0.1)
Thrombosis	1 (0.1)	0
Skin and appendages:		
Skin necrosis	1 (0.1)	0

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

Medical Officer Comments: Most of the patients in the micafungin safety database were seriously ill and hospitalized for prolonged time period, so events like deep venous thrombosis more likely reflect underlying disease and prolonged hospitalization rather than any relationship to micafunign.

Injection Site Reactions in Patients in Fluconazole-Controlled Studies

The overall incidence of injection site reactions was higher in patients treated with micafungin, 9.9% (92/932) than in those who received fluconazole, 4.4% (35/787), as depicted in the following table.

Table 138. Injection Site Reactions in Patients in Fluconazole-controlled Studies*

Adverse Event COSTART Term	Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787
Any adverse event	92 (9.9)	35 (4.4)
Injection site inflammation	17 (1.8)	10 (1.3)
Phlebitis	50 (5.4)	14 (1.8)
Deep thrombophlebitis	8 (0.9)	3 (0.4)
Injection site hemorrhage	1 (0.1)	0 (0)
Injection site reaction	3 (0.3)	2 (0.3)

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Thrombophlebitis	16 (1.7)	6 (0.8)
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*includes studies 97-0-041, 98-0-050, FG463-21-09, and 03-7-005

Medical Officer Comments: Phlebitis and thrombophlebitis were reported in a higher proportion of patients who received micafungin than fluconazole. These data, and that from animal studies and healthy volunteer studies, provide evidence that injection site reactions, particularly phlebitis and thrombophlebitis are probably caused by micafungin. If micafungin causes vascular irritation or inflammation resulting in phlebitis or thrombophlebitis, there is some concern regarding other more serious vascular events such as deep venous thrombosis, pulmonary embolism, myocardial ischemia or infarct, vasculitis, or stroke, as discussed below.

Serious adverse events in the fluconazole-controlled studies were reviewed to determine if there were excess serious vascular events such as myocardial infarction or stroke, pulmonary embolism in micafungin-treated patients. In these studies, no cases of myocardial ischemia or infarction were reported; and only 1 case was reported among 2402 subjects in the overall safety database. Only a few serious vascular events occurred in the fluconazole-controlled studies, as shown in the table below; while in the safety database of 2402 subjects, 8 cases of pulmonary emboli, 7 cases of intracranial hemorrhage, 5 cases of cerebral hemorrhage, and 3 cases of cerebrovascular accident were reported in micafungin-treated subjects.

Table.139. Serious Vascular Adverse in Fluconazole-controlled studies (data derived from Table R9 1.1, November 1, 2004 request)

Serious Adverse Event (COSTART Body System and Term)	Micafungin-treated Subjects N=932	Fluconazole-treated Patients N=757
Respiratory System:		
Pulmonary embolus	1 (0.1)	0
Cardiovascular System:		
Heart arrest	1 (0.1)	3(0.4)
Deep thrombophlebitis	1 (0.1)	0
Nervous System:		
Cerebral hemorrhage	0	1 (0.1)
Cerebrovascular accident	1 (0.1)	1 (0.1)
Intracranial hemorrhage	1 (0.1)	0

Medical Officer Comments: There did not appear to be an excess of serious vascular adverse events of this nature in patients who received micafungin in comparison to those who received fluconazole in these studies. However, it would be prudent to monitor closely for this type of adverse in the postmarketing period.

Discontinuation of Micafungin due to Injection Site Reactions

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In the safety database of 2402 subjects, micafungin was discontinued due to an injection site reaction in 2 subjects; one was a patient with deep thrombophlebitis; while the other was a healthy volunteer with phlebitis. Additionally, 1 patient with phlebitis required either dose interruption or reduction of micafungin dose.

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Dose Relationship of Injection Site Reactions

The applicant compared the incidence of injection site reaction in subjects who received at least 150 mg/day micafungin for at least 10 days with those who received lower doses or a shorter duration of micafungin. The overall incidence of injection site reactions was higher in subjects who received micafungin for a minimum of 150 mg/day for at least 10 days, as shown in the table below.

Table 140. Injection Site Reactions and Micafungin Dose (adapted from applicant's appendix 11.3.4.1)

Adverse Event COSTART Term*	Micafungin-treated subjects who received ≥ 150 mg (or ≥ 3 mg/kg) for at least 10 days N= 606	Micafungin-treated subjects who received ≤ 150 mg (or ≤ 3 mg/kg) for less than 10 days N= 1796
Any adverse event	91 (15.0)	108 (6.0)
Injection site inflammation	6 (1.0)	24 (1.3)
Phlebitis	62 (10.2)	35 (1.9)
Injection site pain	0 (0)	15 (0.8)
Thrombophlebitis	15 (2.5)	13 (0.7)
Injection site reaction	3 (0.5)	5 (0.3)
Deep thrombophlebitis	6 (1.0)	18 (1.0)
Injection site hemorrhage	1 (0.2)	0 (0)

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

Medical Officer Comments: Phlebitis and thrombophlebitis were associated with higher doses or longer duration of micafungin. In most of the clinical studies, micafungin was infused over a period of 1 hour, regardless of total dose, so these reactions do not appear to be associated with rate of infusion, but rather to micafugin concentration or the duration of treatment. In rats, vascular irritation was shown to be concentration dependent, with no vascular irritation observed at the lower concentration of micafungin tested.

In study 03-7-005, the incidence of injection site reactions (most commonly phlebitis), was 19.2% (50/260) in patients who received 150 mg/day micafungin, and 5.0% (13/258) for fluconazole-treated patients. On the other hand, in study 98-0-050, 2.1% of patients who received micafungin 50 mg/day experienced injection site reactions compared to 2.1% of those who received fluconazole. In study FG463-21-09, the incidence of injection site reactions in all patients who received micafungin (50 to 150 mg/day), was 11.4%, with no obvious dose effect, compared to 20.0% in those who received fluconazole. The numbers of patients in each treatment group were relatively small in that study, however. The applicant noted that in study 03-7-005, most patients had peripheral intravenous catheters, and concluded that micafungin, given at a dose of 150 mg/day by peripheral venous irritation, has a venous irritation effect. The applicant also noted that

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most of these events were mild, and did not prevent completion of therapy.

Micafungin discontinuation due to injection site reactions is discussed above.

Injection Site Reactions- Postmarketing Adverse Events In Japan

In review of the postmarketing adverse event data submitted by the applicant with the 120-day safety update, and in the original NDA 21-754 submission, phlebitis was listed as a serious drug-related adverse event in the period from October, 2003 to April, 2004. In the cumulative postmarketing adverse event database, from January, 1998 to April, 2004 1 case of phlebitis was reported as a serious drug-related adverse event.

Conclusions Regarding Injection Site Reactions and Micafungin

In preclinical studies, vascular irritation was reported in rats who received high doses of micafungin. These reactions were concentration-dependent. Similar reactions were not observed in dogs, or in rabbits.

In healthy volunteers, injection site reactions occurred most commonly in repeat-dose micafungin studies. The most common adverse events in volunteers were phlebitis and thrombophlebitis, which occurred more frequently in those who received 150 mg/day micafungin for at least 10 days duration.

Injection site reactions including phlebitis, thrombophlebitis, and injection site inflammation, pain, edema, reaction, or hemorrhage, occurred overall in 8.3% (199/2402) subjects in the micafungin safety database. The most common adverse events in this category were phlebitis, which occurred in 4.0% (97/2402) subjects, injection site inflammation in 1.2% (30/2402), and thrombophlebitis in 1.2% (28/2402). Phlebitis and thrombophlebitis occurred more frequently in subjects who received \geq 150 mg/day micafungin for at least 10 days, than in those who received lower doses or durations of treatment.

In fluconazole-controlled studies, injection site reactions occurred more frequently in patients treated with micafungin (9.9%) than with fluconazole (4.4%). Phlebitis, thrombophlebitis, and injection site inflammation were again the most common events in these patients. Most of the phlebitis and thrombophlebitis occurred in study 03-7-005, patients with HIV and esophageal candidiasis. The majority of these patients had a peripheral intravenous catheter, and all received 150 mg/day micafungin. Thus, it follows that receipt of 150 mg/day dose of micafungin by a peripheral intravenous catheter may predispose to phlebitis or thrombophlebitis.

Only 1 serious adverse event, thrombophlebitis, which was considered drug-related, was reported in these studies. Most adverse events in this category did not require micafungin discontinuation.

We have proposed a statement in the ADVERSE EVENTS section of the micafungin label regarding the risk of phlebitis or thrombophlebitis with micafungin 50-150 mg/day, particularly in patients with a peripheral intravenous catheter.

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7.1.12.6 Renal Safety

A total of 232/2402 (9.7%) subjects experienced an adverse event associated with renal function. Twenty six (1.1%) of these subjects had events considered at least possibly related to micafungin. Increases in serum creatinine were reported as an adverse event in 4.5% (90/1980) patients; and in 13 (0.7%) of these patients, the event was considered at least possibly related to micafungin. Seventy two (3.6%) patients experienced renal failure (coded as acute kidney failure or kidney failure) as an adverse event; and in 6 (0.3%) of these patients, the event was considered related to micafungin. Similar events were reported in the Japanese postmarketing experience. A PRECAUTION statement is proposed for renal effects of micafungin, similar to that already present in the Japanese micafungin package insert.

Preclinical Data

In rats exposed to a micafungin dose of 32 mg/kg for 26 weeks, effects on the kidney included pigmentation in proximal tubular epithelium, dilatation of collecting ducts, swelling of collecting duct epithelium, and increased urine volume. Additionally, serum chemistry changes included increased creatinine in these animals.

Renal Adverse Events in Micafungin Safety Database

Studies in Healthy Volunteers

None of the 382 healthy volunteers who received micafungin in the single-dose or repeat-dose micafungin studies experienced a renal adverse event.

Studies in Patients

In the micafungin safety database, a total of 232/1980 (11.7%) patients experienced at least one renal adverse event. Twenty six (1.3%) patients had an adverse event considered by the investigator to be related to micafungin. The following table shows all renal adverse events reported in patients.

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Table 141. Renal Adverse Events in Micafungin-Treated Patients (adapted from applicant's Appendix 11.4.1.1, safety update)

Renal Adverse Event COSTART Term*	All Renal Adverse Events in Micafungin-treated Patients N=1980	Drug-Related** Renal Adverse Events in Micafungin- treated Patients N=1980
Any renal adverse event	232 (11.7)	26 (1.3)
Creatinine increased	89 (4.5)	13 (0.7)
BUN increased	76 (3.8)	12 (0.6)
Acute kidney failure	22 (1.1)	4 (0.2)
Kidney failure	50 (2.5)	2 (0.1)
Kidney function abnormal	42 (2.1)	2 (0.1)

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

** Relationship to study drug was determined by the investigator as possible, probably, or definitely related.

Medical Officer Comments: *If the terms, "acute kidney failure" and "kidney failure" are combined, a total of 72/1980 (3.6%) patients experienced renal failure, and 6/1980 (0.3%) patients had renal failure considered related to micafungin. In the safety database of 2402 subjects, additional adverse events listed under the COSTART body system, "Urogenital system", several other terms could be considered "renal" adverse events, including kidney tubular disorder in 2/2402 (0.1%) subjects, kidney tubular necrosis in 2 (0.1%) subjects, oliguria in 78/2402 (3.2%) subjects, and anuria in 6/2402 (0.2%) subjects.*

In the fluconazole-controlled studies, 74/932 (7.9%) micafungin-treated patients, and 85/787 (10.8%) fluconazole-treated patients experienced at least one renal adverse event. These adverse events are shown in the table below. Four (0.4%) micafungin-treated patients and 4 (0.5%) fluconazole-treated patients had renal adverse events considered by the investigator to be related to the respective study drugs. The overall incidence and pattern of renal adverse events was similar in patients who received either micafungin or fluconazole.

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Table 142. All Renal Adverse Events in Fluconazole-Controlled Studies† (adapted from applicant's Appendix 11.4.2.1, safety update)

Renal Adverse Events COSTART Term*	Micafungin-treated Patients N=932	Drug-Related** AEs in Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787	Drug-Related** AEs in Fluconazole-treated Patients
Any renal adverse event	74 (7.9)	4 (0.4%)	85 (10.8)	4 (0.5%)
Creatinine increased	36 (3.9)	2 (0.2%)	36 (4.6)	4 (0.5%)
Acute kidney failure	6 (0.6)	1 (0.1%)	9 (1.1)	0
BUN increased	20 (2.1)	1 (0.1%)	18 (2.3)	0
Kidney failure	13 (1.4)	1 (0.1%)	16 (2.0)	0
Kidney function abnormal	10 (1.1)	0	20 (2.5)	0

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

†Fluconazole-controlled studies included 97-0-041, 98-0-050, FG-21-09, and 03-7-005.

** Relationship to study drug was determined by the investigator as possible, probably, or definitely related.

Medical Officer Comments: If the terms, "acute kidney failure" and "kidney failure" are combined, a total of 19/932 (2.0%) of patients who received micafungin, and 25/ 787 (3.2%) patients experienced renal failure in these studies. Note that two micafungin-treated patients had renal failure which was considered drug-related; whereas none of the fluconazole-treated patients had renal failure related to study drug.

Serious renal adverse events were reported in 47/1980 (2.4%) patients, and were considered micafungin-related in 5 (0.3%) patients. Serious renal adverse events are shown in the following table.

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Table 143. Serious Renal Adverse Events in Micafungin-Treated Patients (adapted from applicant's Appendix 11.4.1.2, safety update)

Serious Renal Adverse Event COSTART Term*	All Serious Renal Adverse Events in Micafungin- treated Patients N=1980	Drug-Related** Serious Renal Adverse Events in Micafungin- treated Patients N=1980
Any serious renal adverse event	47 (2.4)	5 (0.3)
Creatinine increased	8 (0.4)	3 (0.2)
Acute kidney failure	10 (0.5)	2 (0.1)
BUN increased	6 (0.3)	1 (0.1)
Kidney failure	27 (1.4)	1 (0.1)
Kidney function abnormal	3 (0.2)	0 (0)

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

** Relationship to study drug was determined by the investigator as possible, probably, or definitely related.

Medical Officer Comments: Additional serious renal adverse events, not included in this table, included oliguria, which occurred in 3 patients, anuria, in 1 patient, and kidney tubular necrosis in 2 patients.

In fluconazole-controlled studies, 12/932 (1.3%) micafungin-treated patients, and 19/787 (2.4%) fluconazole-treated patients experienced a serious renal adverse event. These events are shown in the table below. None of the serious renal adverse events were considered study drug-related for either micafungin or fluconazole.

Table 144. Serious Renal Adverse Events in Fluconazole-Controlled Studies (adapted from applicant's Appendix 11.4.2.2, safety update)

Serious Renal Adverse Event COSTART Term*	Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787
Any serious renal adverse event	12 (1.3)	19 (2.4)
Acute kidney failure	4 (0.4)	5 (0.6)
Creatinine increased	1 (0.1)	1 (0.1)
Kidney failure	6 (0.6)	9 (1.1)
Kidney function abnormal	1 (0.1)	4 (0.5)

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

Medical Officer Comments: The overall incidence of renal failure reported as a serious adverse event was 1.1% (10/932) for micafungin- and 1.8% (14/787) for fluconazole-treated patients.

The following table summarizes patient information in those who experienced renal failure as a serious adverse event in the fluconazole-controlled studies.

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Table 145. Summary of Patients with Serious Renal Failure in Fluconazole-Controlled Studies† (COSTART Terms Kidney Failure, Acute Kidney Failure)

Patient Number	Study Protocol And Indication for Micafungin	Micafungin Dose and Duration (cumulative dose)	Serious Renal AE (COSTART Term) and onset of SAE (study day)	Prior or concomitant potentially nephrotoxic medications (study days)	Outcome
201007	97-7-003 EC	25 mg/day for 5 days (125 mg)	Kidney failure (day 5)	Ciprofloxacin (-1 to 4)	Death day 5 due to acute renal failure
10745031	03-7-005 EC	150 mg/day for 9 days (1350 mg)	Acute kidney failure (day 7)	Ciprofloxacin (-4 to -1); Bactrim (4 to 10)	Death day 17 due to acute kidney failure
10705001	03-7-005 EC	150 mg/day for 14 days (2100 mg)	Acute kidney failure (day 9)	Indocin (4-9) Septran DS (12-36); Voltaren (12) Toradol (13)	SAE Resolved day 15
10665037	03-7-005 EC	150 mg/day for 16 days	Kidney failure (day 14)	Voltaren (7-15); Bactrim (14-17);	Death day 17 due to pneumonia
10575046	03-7-005 EC	150 mg/day for 14 days (2100 mg)	Kidney failure (day 17)	Bactrim (6-14)	Death day 17 due to heart failure
02545016	03-7-005 EC	150 mg/day for 19 days (2850 mg)	Kidney failure (day 19)	Ibuprofen (-1 to 8); Diclofenac (1 and 16)	Death day 19 due to kidney failure
203605	98-0-050 prophyl-axis	36.7 mg/day for 8 days interrupted (294 mg)	Acute kidney failure day (day 13)	Ciprofloxacin (8-9); Tobramycin (8-20); Vancomycin (9-12); Amphotericin (12-16)	Death day 20 due to meningitis
1141003	98-0-050 prophyl-axis	50 mg/day for 21 days (1050 mg)	Kidney failure (day 3)	Vancomycin (9 and 11)	SAE resolved day 30

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Table 145. (continued) Summary of Patients with Serious Renal Failure in Fluconazole-Controlled Studies† (COSTART Terms Kidney Failure, Acute Kidney Failure)

1143501	98-0-050 prophylaxis	50 mg/day for 18 days (900 mg)	Acute kidney failure (day 18)	Tacrolimus (7-22); Mycophenolate (8-21); Vancomycin (16-34)	Death day 36 due to GVHD
4222102	98-0-050 prophylaxis	50 mg/day for 29 days (1450 mg)	Kidney failure (day 25)	Vancomycin (12-38); Cyclosporine (13-42); Gentamicin (20-28); Ganciclovir (25-41)	Death day 42 due to CMV pneumonitis
1008	FG463-21-09 EC	150 mg/day for 14 days (2100 mg)	Kidney failure (day 13)	Cotrimoxazole (2-15);	Death day 15 due to tuberculosis

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

EC= esophageal candidiasis; GVHD = graft versus host disease; CMV= cytomegalovirus; SAE= serious adverse event

Medical Officer Comments: Narrative summaries for patients who were enrolled in the fluconazole-controlled studies and select patients from the uncontrolled studies are provided below.

In studies 98-0-047 and 98-0-046, most of the patients had received amphotericin B or a lipid formulation of amphotericin prior to micafungin treatment. Because amphotericin has known renal toxicity, potentially confounding the analysis of renal failure in these patients, narrative summaries are provided for those patients who did not receive extensive prior amphotericin B or lipid formulations of amphotericin. All patients in these studies with kidney failure, acute kidney failure, kidney tubular necrosis, oliguria, or anuria listed as a serious adverse event are shown in the following table.

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Table 146. Summary of Patients with Serious Renal Failure in Studies 98-0-046 and 98-0-047 (COSTART Terms Kidney Failure, Acute Kidney Failure, Kidney Tubular Necrosis, Oliguira, or Anuria)

Patient Number	Study Protocol And Indication for Micafungin	Micafungin Dose and Duration (cumulative dose)	Serious Renal AE (COSTART Term) and onset of SAE (study day)	Prior or concomitant potentially nephrotoxic medications (study days)	Outcome
107871*	98-0-047 candidemia	50 mg/day for 4 days (200 mg)	Kidney failure (day 2)	Amphotericin B (single dose, day 1); vancomycin (day 3)	Death day 16 due to multi-organ failure
055885*	98-0-047 invasive candidiasis	50 mg/day for 5 days (250 mg)	Acute kidney failure (day 3)	Bactrim (-15 to 5); ganciclovir (-15 to 3; and 4-5); tobramycin (-4 to 1); vancomycin (-4 to 1); cipro (-1 to 1); Abelcet® (5)	Death day 6 due to pulmonary laceration and hemorrhage
055882*	98-0-047 invasive candidiasis	50 mg/day for 52 days (interrupted) (2600 mg)	Kidney failure (day 9)	Ciprofloxacin (-2 to 51); vancomycin (9-12); Bactrim (59- indefinite); ganciclovir (60- indefinite)	SAE continued until last evaluation (day 99)
020874	98-0-047 candidemia	50-150 mg/day fo 20 days (2250 mg)	Kidney failure (day 14)	Amphotericin B (-1-13); Abelcet® (14-20); bactrim; ganciclovir; foscarnet	Death day 21 due to multi-organ failure
287674	98-0-047 candidemia	50-125 mg/day for 27 days (3350 mg)	Kidney failure (day 14)	Amphotericin B (-2 to -1); vancomycin, amikacin, bactrim, levofloxacin; indocin; voltaren;	Death day 28 due to cardiac failure

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				ganciclovir	
253871	98-0-047 candidemia	50 mg/day for 5 days (250 mg)	Kidney failure (day 4)	Amphotericin B (-1 to 1); vancomycin	Death due to respiratory failure

Table 146. (continued) Summary of Patients with Serious Renal Failure in Studies 98-0-046 and 98-0-047 (COSTART Terms Kidney Failure, Acute Kidney Failure, Kidney Tubular Necrosis, Oliguria, or Anuria)

057871	98-0-047 candidemia	100-150 mg/day for 21 days (2800 mg)	Kidney failure (day 4)	Ambisome®; amphotericin; sulfadiazine; bactrim; ciprofloxacin	Death day 22 due to intracranial hemorrhage
031872*	98-0-047 candidemia	50 mg/day for 4 days (200 mg)	Acute kidney failure (day 4)	Ciprofloxacin (-4 to 4)	SAE improved by day 17
551873	98-0-047 invasive candidiasis	2 mg/kg/day for 21 days (128 mg)	Oliguria (day 7)	Liposomal amphotericin B; gentamicin; vancomycin	Death day 58 due to multi-organ failure
358475	98-0-047	50 mg/day for 22 days (1100 mg)	Oliguria	Captopril	Death day 47 due to shock
318373*	98-0-046 invasive aspergillosis	75 mg/day for 17 days	Kidney failure (day 17)	Sulfamethoxazole (-6 to 2; 5-11; 12-14); ciprofloxacin (-3 to 8); vancomycin (5 and 9)	Death day 18 due to "uremia"
063788*	98-0-046 invasive pulmonary aspergillosis	75 mg/day for 28 days (2100 mg)	Kidney failure (day 14)	Levofloxacin (1-indefinite); sirolimus (1-indefinite); amikacin (3-indefinite); cyclosporine (15-indefinite)	SAE ongoing day 28; then switched to AmBisome®
055775*	98-0-046 invasive pulmonary aspergillosis	75-300 mg/day for 36 days (8250 mg)	Kidney failure (day 36)	Ganciclovir; mycophenolate mofetil, and Bactrim (for months prior and concomitant); amphotericin B (22-26); Abelcet® (26-37)	Micafungin discontinued day 36; death 37 due to pulmonary aspergillosis

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Table 146. (continued) Summary of Patients with Serious Renal Failure in Studies 98-0-046 and 98-0-047 (COSTART Terms Kidney Failure, Acute Kidney Failure, Kidney Tubular Necrosis, Oliguria, or Anuria)

055774*	98-0-046 invasive pulmonary aspergillosis	75-300 mg/day for 43 days (10,800 mg)	Kidney failure (day 17)	Bactrim, cyclosporine, mycophenolate mofetil,(months prior and concomitant) ganciclovir (-6 to 1); foscarnet (1- indefinite); ketorolac (21); cyclosporine(30- indefinite); ibuprofen (43)	SAE ongoing day 84
474171	98-0-046 invasive aspergillosis	75 mg/day for 20 days (1500 mg)	Kidney failure (day1)	Amphotericin; gentamicin,	SAE persistent day 64
464774	98-0-046 invasive aspergillosis	75 mg/day for 47 ddays (3525 mg)	Kidney failure (day 25)	Amphotericin B; amphotericin B lipid formulation; pentamidine; amikacin;	Death day 48 due to respiratory distress
422771	98-0-046 invasive aspergillosis	35 mg/day for 2 days (70 mg)	Kidney failure (day 2)	Amphotec®; AmBisome®; amphotericin B inhalation	Death day 3 due to respiratory failure
287573	98-0-046 fungal sinusitis	100-200 mg/day for 114 days (21,075 mg)	Kidney failure (day 97)	Amphotericin B; vancomycin; bactrim; amikacin; foscarnet	Death day 114 due to cardiopulmonary arrest
262788	98-0-046 invasive pulmonary aspergillosis	75 mg/day for 10 days (750 mg)	Acute kidney failure (day 4)	AmBisome®; vancomycin; septra; tobramycin	Death day 10 due to acute respiratory distress syndrome
262780	98-0-046 invasive pulmonary aspergillosis	28-43 mg/day for 29 days (1077 mg)	Kidney failure (day 30)	Abelcet®; ganciclovir; vancomycin; foscarnet; tobramycin; ciprofloxacin	Death day 31 due to interstitial pneumonitis
262773	98-0-046	33 to 35	Kidney	Abelcet®;	Death day 24

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	invasive pulmonary aspergillosis	mg/day (interrupted) for 23 days (373 mg)	failure (day 21)	amphotericin B; vacnomycin; tobramycin; foscarnet; bactrim;	due to respiratory failure
205776	98-0-046 invasive pulmonary aspergillosis	75 mg/day for 5 days (375 mg)	Kidney failure (day 5)	Liposomal amphotericin B; ganciclovir; vancomycin; bactrim	Death day 5 due to disseminated <i>Aspergillus</i>
084782	98-0-046 invasive aspergillosis	7 -27 mg/day for 134 days (1446 mg)	Acute kidney failure (day 133)	Amphotericin B; ibuprofen; captopril; AmBisome®; vancomycin; gentamicin	Death day 134 due to <i>Aspergillus</i> endocarditis
076783	98-0-046 invasive pulmonary aspergillosis	75 mg/day for 102 days (interrupted) (7125 mg)	Kidney tubular necrosis (day 102)	Amphotericin B; Abelcet®; vancomycin; levofloxacin; acyclovir	Death day 102 due to acute pulmonary hemorrhage
076781	98-0-046 <i>Aspergillus</i> sinusitis	75 mg/day (interrupted) for 19 days (1350 mg)	Acute kidney failure (day 14)	Amphotericin B; tobramycin; ciprofloxacin; levofloxacin; vancomycin	Death day 19 due to pneumonia
076777	98-0-046 invasive pulmonary aspergillosis	75 mg/day for 4 days (300 mg)	Kidney failure (day 4)	Amphotericin B; Abelcet®; foscarnet; levofloxacin	Death day 5 due to invasive pulmonary aspergillosis
063780	98-0-046 invasive pulmonary aspergillosis	75-300 mg/day for 25 days (4525 mg)	Kidney tubular necrosis (day 2)	AmBisome®; acyclovir; levofloxacin; vancomycin; pentamidine; bactrim; ciprofloxacin	Death day 31 due to pulmonary aspergillosis
059782	98-0-046 invasive pulmonary aspergillosis	75-225 mg/day for 144 days (interrupted) (25,875 mg)	Kidney failure (day 143)	AmBisome®; ganciclovir; bactrim; vancomycin; caspofungin	Death day 152 due to intracranial hemorrhage
059773	98-0-046 invasive pulmonary	48 mg/day for 7 days (288 mg)	Kidney failure (day 7)	Amphotericin B; AmBisome®; gnetamicin;	Death day 7 due to renal failure

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	aspergillosis			ganciclovir; bactrim; vancomycin;	
002772	98-0-046 invasive pulmonary aspergillosis	60 mg/day for 5 days (540 mg)	Acute kidney failure (day 6)	Amphotericin B; bactrim; valganciclovir; Abelcet®; AmBisome®	Death day 6 due to cerebral edema
084774	98-0-046 invasive pulmonary aspergillosis	75 mg/day for 7 days (525 mg)	Oliguria (day 4)	Abelcet®; bactrim; levofloxacin; vancomycin;	Death day 13 due to pulmonary aspergillosis
318375	98-0-046	75 mg/day for 5 days (525 mg)	Anuria	Ciprofloxacin; vancomycin	Death day 7 due to gastrointestinal bleeding

*Narrative summaries provided below
 SAE = serious adverse event

Medical Officer Comments: Narrative summaries for the patients in these studies with the fewest confounding factors are provided below.

Narrative Summaries for Micafungin-treated Patients with Renal Failure reported as a Serious Adverse Event

Patient 201007 was a 39 year-old black male with HIV and AIDS, with a CD₄ count of 22 cells/mm³. He received micafungin 25 mg/day for 5 days in study 97-7-003 for esophageal candidiasis. Baseline conditions included lymphadenopathy and anemia. Micafungin was discontinued on day 5 due to acute renal failure. Concomitant medications included vitamin B12, ferrous fumarate and folic acid, ciprofloxacin (days -1 to 2), metaclopramide, and Ringer's lactate. The patient died on day 9 due to acute renal failure and progression of AIDS. Neither renal failure nor death in this patient was considered related to micafungin. The table below shows BUN and creatinine values during micafungin treatment.

Renal Function Laboratories for Patient 201007*

Study Day	BUN (mg/dL)	Creatinine (mg/dL)
Baseline (-3)	54	3.3
Day 3	22	1.7
Day 8	29	1.7

*Normal laboratory values are provided in Appendix 10.1.5

Medical Officer Comment: This patient had baseline renal insufficiency, which had improved by day 1 of micafungin treatment, and subsequently worsened (BUN only) by day 8 of micafungin treatment. No laboratory data beyond study

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day 8 was provided to determine if renal failure continued to worsen. The increase of BUN from 22 to 29 mg/dL was probably not clinically significant. Nothing in the narrative summary or case report form actually indicated exactly how the patient died from renal failure, (eg. anuria, or hyperkalemia, although potassium on day 8 was somewhat elevated at 5.1 mmol/L and 5.0 mmol/L was upper limit of normal). Because serum creatinine did not increase with micafungin treatment, any relationship of renal failure to micafungin seems unlikely.

Patient 10745031 was a 34 year old black male with HIV and AIDS, and a CD₄ count of 148 cells/mm³. He received micafungin 150 mg/day for 9 days for esophageal candidiasis in study 03-7-005. Micafungin was stopped on day 9 because the patient withdrew consent for the study. The patient experienced acute renal failure on day 7, and died on day 17 due to acute renal failure. Neither the acute renal failure nor the death in this patient was considered related to micafungin. At baseline, the patient had chronic gastroenteritis, anemia of chronic disease, submandibular lymphadenopathy, chronic sinusitis, atypical lower respiratory tract infection, and hypoalbuminemia. Concomitant medications included ciprofloxacin, stilpane (paracetamol plus meprobromate plus codeine phosphate), cough syrup, bactrim, immunocare (herbal medication), and lasix. Prior medications included dicloverine, hyoscine sodium butyl bromide, metoclopramide, immodium and normal saline for chronic gastroenteritis. The BUN and creatinine values for this patient increased from 42 mg/dL and 3.5 mg/dL at baseline to 76 and 6.9 on day 7.

***Medical Officer Comments:** Notably, on the case report form the investigator listed progression of HIV disease and consumption of traditional Zulu medication (starting study day 4) as contributing conditions leading to death, but later asked the sponsor to delete this information because the ingredients were not known. The patient had renal insufficiency at baseline, may have been dehydrated from the chronic gastroenteritis (received normal saline, and also received bactrim for an "atypical lower respiratory tract infection" from study days 4-10. The dose of bactrim is not provided in the case report form. Because of these confounding factors, it would be difficult to attribute renal failure to micafungin in this case.*

Patient 10705001 was a 44 year old black male with HIV and AIDS with esophageal candidiasis for which he received micafungin 150 mg/day for 14 days in study 03-7-005. At baseline, the patient had neuropathy, lymphadenopathy, *Pneumocystis jiroveci* (formerly *carinii*) pneumonia, and anemia. At the time of enrollment he was receiving a multivitamin, painamol (paracetamol), a cough medication, and ranceph (cephalexin). Acute renal failure was reported on day 9, and resolved by day 15. Baseline BUN and creatinine were 16 mg/dL and 1.2 mg/dL, respectively. On study day 8, BUN was 45 and creatinine 1.9 mg/dL, and on day 15, BUN was 10 mg/dL and creatinine 1.1 mg/dL. Comcomitant medications included articulen (indomethacin) (days 4-9), saline, bactrim (days 15- 29), voltaren (day 15), dextrose, dulcolax, toradol (day 16).

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Medical Officer Comments: In this case, renal insufficiency could also have been caused by indomethacin. Indomethacin was stopped on day 9, and micafungin on day 14. Because the renal insufficiency resolved so rapidly after stopping micafungin, a relationship to micafungin seems unlikely.

Patient number 10665037 was a 29 year old black female with HIV and AIDS who received micafungin 150 mg/day for 16 days for esophageal candidiasis in study 03-7-005. CD₄ count was unknown. Baseline conditions included asthenia, seizure disorder (epilepsy), anemia, and fever. The patient was receiving no medications at the time of enrollment. Renal failure, heart failure, pneumonia, and HIV progression were reported as serious adverse events on study day 14. Micafungin was discontinued on day 16 because of pneumonia, and the patient died on day 17 due to pneumonia. HIV progression, heart failure and renal failure were considered contributing factors in the death. Renal failure and death were not considered to be related to micafungin. No autopsy was performed. At baseline, BUN and creatinine were 7 mg/dL and 0.7 mg/dL, respectively. On study day 7, BUN was 15 mg/dL and creatinine 0.9 mg/dL; while on day 14, BUN was 16 mg/dL and creatinine was 0.8 mg/dL. Concomitant medications included voltaren (day 7-15), co-trimoxazole (days 14-17), cifran (ciprofloxacin) (days 14-17), and ativan.

Medical Officer Comments: In this patient, creatinine remained normal but BUN became slightly elevated. This pattern of renal laboratory abnormalities would be unusual for a drug-related process, where the opposite might be expected with toxic effects on the kidney. Additionally, the patient received concomitant voltaren, which may cause renal toxicity, so attribution of "renal failure" to micafungin would be difficult.

Patient 10575046 was a 31 year-old black male with HIV and AIDS, who received micafungin 150 mg/day for 14 days for esophageal candidiasis. At baseline, he had asthenia, anorexia, cachexia, impaired renal function, dehydration, tachycardia and anemia. At the time of enrollment he was receiving vitamin B complex, saline and lasix. On day 7, abnormal kidney function and diarrhea were reported as adverse events. On day 17, heart, renal and respiratory failure were reported, and the patient died due to heart failure. Progressive HIV disease was considered a contributing factor. No autopsy was performed. Other concomitant medications included bactrim (days -1 to 14). Renal function laboratories for this patient are shown in the table below.

Renal Function Laboratories for Patient 10575046*

Study Visit	BUN (mg/dL)	Creatinine (mg/dL)
Baseline	92	3.5
Day 7	157	6.5
Day 14	205	6.0

*Normal laboratory values are provided in Appendix 10.1.5

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Medical Officer Comments: *This patient had significant baseline renal insufficiency which worsened during treatment with micafungin. Additionally, in this case, a number of other factors could have resulted in worsening renal function, namely diarrhea, dehydration, use of a diuretic (lasix), resulting in further pre-renal azotemia, and bactrim. As such, it would be difficult to attribute the renal failure in this case to micafungin alone.*

Patient 02545016 was a 35 year old black male with HIV and AIDS, and a CD₄ count of 13 cells/mm³. He received micafungin 150 mg/day for 19 days for esophageal candidiasis in study 03-7-005. Significant baseline conditions included cachexia, tuberculosis, nausea, anemia, and fever. At the time of enrollment the patient was receiving augmentin (for possible pneumonia), ibuprofen (days -1 to 8), paracetamol (acetaminophen), metoclopramide, and a cough expectorant. On study day 19, the patient developed dehydration and severe vomiting. BUN and creatinine at that time were 64 mg/dL and 2.8 mg/dL, respectively, and had been normal at baseline (BUN, 13 mg/dL, and creatinine, 0.8 mg/dL). On the same day, the patient was reported to have severe neutropenia, and elevated LDH (7280 U/L), and the patient died of kidney failure. Neither the death nor the serious adverse event of kidney failure was considered related to micafungin. Additional concomitant medications included diclofenac (day 1 and 16), prochlorperazine, albumin, chlorpromazine, ringers solution. Renal laboratory values for this patient are shown in the table below.

Renal laboratory values for Patient 02545016*

Study Visit	BUN (mg/dL)	Creatinine (mg/dL)
Baseline	13	0.8
Day 7	56	2.2
Day 14	24	1.2
Day 19	64	2.8

*Normal laboratory values are provided in Appendix 10.1.5

Medical Officer Comments: *In this patient, renal function was normal at baseline, and progressed during micafungin treatment. However, renal insufficiency could have developed due to dehydration, or to the non-steroidal anti-inflammatory agents, ibuprofen and diclofenac which had been administered during the course of micafungin treatment. Because of these confounding factors, it would be difficult to attribute renal failure in this patient to micafungin alone.*

Patient 203605 was a 12 year old female with Fanconi's anemia treated with micafungin 36.7 mg/day for 8 days in study 98-0-050 for antifungal prophylaxis. This patient developed renal failure on study day 13, and died on day 20 due to meningitis. See narrative summary for this patient in section 8.4 on pediatric safety.

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Patient 1141003 was a 59 year-old Caucasian male with non-Hodgkin's lymphoma who received an autologous peripheral stem cell transplant. This patient received micafungin 50 mg/day for 21 days as antifungal prophylaxis in study 98-0-050. Baseline conditions included thrombocytopenia, hypomagnesemia, edema, dyspnea, fever, and anemia. On day 3 of micafungin, renal failure was reported as a serious adverse event. The micafungin dose was reduced by 50% on day 8 due to decreased creatinine clearance. The patient experienced a number of other serious adverse events, including altered mental status and respiratory distress (day 4), encephalopathy (day 7), hypotension, bleeding at the catheter site, and bacterial sepsis (day 8), bacterial pneumonia and respiratory failure (day 9), ototoxicity and atrial flutter (day 11), atrial fibrillation and respiratory failure (day 12); and coma (day 15). Micafungin was discontinued on study day 21 due to neutrophil recovery. Renal failure resolved on day 30. At the end of the study, the patient remained hospitalized, with persistent hypotension, bleeding at catheter site, ototoxicity, respiratory failure, pneumonia, and bacterial sepsis. The patient received multiple concomitant medications, and those which preceded the onset of renal failure as a serious adverse event included senekot, sodium bicarbonate, Tylenol, robitussin, prevacid, zofran, compazine, magnesium sulfate, lasix decadron, allopurinol, ativan, mesna, ursodiol, and lovenox. Renal laboratory values during the course of micafungin treatment for this patient are shown in the following table.

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Renal Laboratory Values for Patient 1141003*

Study Day	BUN (mg/dL)	Creatinine (mg/dL)
baseline	15	2.1
Day 1	14	2.2
Day 3	36	2.7
Day 8	39	4.3
Day 11	37	3.8
Day 15	66	4.4
Day 19	77	3.7
Day 21	78	3.6

*Normal laboratory values are provided in Appendix 10.1.5

***Medical Officer Comments:** Although this patient had renal insufficiency at baseline, creatinine increased throughout day 15 of micafungin treatment, then improved; while BUN continued to rise. Other than lasix, which could contribute to pre-renal azotemia by causing dehydration, none of the concomitant medications received prior to day 3 (onset of renal failure as a serious adverse event) are associated with renal toxicity. Certainly hypotension can cause renal impairment, but this was not reported as a serious adverse event until day 8. Additionally, the hypotension did not require use of vasopressors until later in the study. Although the investigator considered all the serious adverse events in this patient to be unrelated to micafungin, in the medical officer's opinion, the worsening renal failure in this case was possibly related to micafungin.*

Patient 1143501 was a 53 year old Caucasian male with chronic myelogenous leukemia (CML), who underwent an allogeneic peripheral stem cell transplant, who received micafungin as antifungal prophylaxis in study 98-0-050. Significant baseline conditions included hypertension and hyperglycemia. Prior to enrollment, the patient received ciprofloxacin, acyclovir, immune globulin, and bactrim. He developed coagulase-negative staphylococcal bacteremia on study day 14, and acute respiratory distress syndrome on day 17. Micafungin was discontinued on day 18 due to neutrophil recovery. Acute renal failure was reported as a serious adverse event on day 18. On the same day, the patient developed severe GVHD. The patient died on day 36 due to GVHD of the gastrointestinal tract and liver, with renal failure, CML, and gastrointestinal bleeding considered contributory conditions. No autopsy was performed. Neither the death nor the renal failure was considered related to micafungin. The patient received multiple concomitant medications prior to the onset of renal failure, including ursodiol, demadex, isoptin, Tylenol, benadryl, prinivil, fludarabine, allopurinol, Zoloft, Maalox, vitamin K, covera, hydrocortisone, prevacid, ativan, compazine, solumedrol, melphalan, zofran, tacrolimus, mannitol, potassium chloride, mycophenolate, restoril, neupogen, lasix, cefepime, Demerol, immodium, vancomycin, flagyl, magnesium sulfate, and sodium phosphate. Renal laboratories for this patient are shown in the table below.

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Renal Laboratory Values for Patient 1143501*

Study Day	BUN (mg/dL)	Creatinine (mg/dL)
Baseline	17	1.1
Day 4	13	1.0
Day 7	14	0.8
Day 10	16	0.9
Day 13	17	0.8
Day 17	21	1.5
Day 34	101	5.1

*Normal laboratory values are provided in Appendix 10.1.5

Medical Officer Comments: The temporal course of renal insufficiency does not suggest a relationship to micafungin. Renal function remained normal until between days 13 and 17. Micafungin was stopped on day 18, and no laboratory results were provided between days 1 and 34 when the creatinine had increased significantly. The patient had also received a number of other medications prior to the onset of renal failure that may have contributed to the development of this adverse event, including tacrolimus and vancomycin. I would concur with the investigator that renal failure in this patient was probably not related to micafungin.

Patient 4222102 was a 12 year-old black female with acute myelogenous leukemia who received an allogeneic matched sibling bone marrow transplant considered low risk of transplant-related mortality. She received micafungin as antifungal prophylaxis in study 98-0-050, and developed renal failure on day 25. The detailed narrative summary for this patient is in section 8.4, pediatric safety.

Patient 1008 was a 48 year old black male with HIV, and a CD₄ count of 290 cells/mm³. He received 150 mg/day micafungin for 14 days for esophageal candidiasis in study FG463-21-09. Significant baseline conditions included diarrhea, asthenia, pneumonia, and cachexia. Adverse events reported during micafungin treatment were bronchitis, nausea, and vomiting. On day 13, the patient experienced severe confusion, hepatic failure, kidney failure, and respiratory failure, and the patient died on day 15 due to tuberculosis. No autopsy was performed. Concomitant medications included betaclopramide, loperamide, bactrim, midazolam, hyoscine-N-butylbromide, and flumazenil. Renal laboratory values during micafungin treatment in this patient are shown in the following table.

Renal Laboratory Values for Patient 1008*

Study Day	BUN (mg/dL)	Creatinine (mg/dL)
Baseline	18	0.9
Day 7	10	0.9
Day 12	28	1.8

*Normal laboratory values are provided in Appendix 10.1.5

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Medical Officer Comments: *Additional information regarding this patient was obtained by the applicant in discussion with the investigator, and was provided with the case report form. Prior to day 13, the patient became confused and disoriented. On day 13, endoscopy was performed, using midazolam sedation, and the patient developed respiratory failure. A chest X-ray taken on day 14 revealed bilateral pulmonary infiltrates and small pleural effusion, and the investigator concluded that the patient had progressive pulmonary tuberculosis. The applicant interpreted this sequence of events as follows: progressive deterioration in pulmonary function caused the initial confusion and disorientation. The midazolam given at the time of endoscopy "pushed the patient into respiratory failure." Liver and renal decompensation ensued, possibly with progressive sepsis, resulting in multi-organ failure and death.*

The sequence of events in this case is not entirely clear. From the case report form, the cause of death, tuberculosis, was an assumption on the part of the investigator. The patient had not received any other medications that are known to be nephrotoxic, except for bactrim. On day 13, the patient's vital signs were recorded as blood pressure, 95/66; heart rate 114, and temperature 35.6 degrees Celcius, so the patient may have had sepsis syndrome, which could have resulted in renal insufficiency. Certainly more profound hypotension would be expected to cause the liver function test abnormalities noted (AST 2068 U/L, ALT, 211 U/L, bilirubin 0.8 mg/dL). Unfortunately laboratory data on the day of these events was not provided. In summary, the role of micafungin in the development of renal and hepatocellular damage in this patient is not clear, but remains possible.

Patient 107871 was a 78 year old Caucasian male with underlying Crohn's disease and candidemia treated with micafungin 50 mg/day for 4 days in study 98-0-047. Significant baseline conditions included *Klebsiella* bacteremia, myocardial infarction; chronic renal insufficiency; intermittent atrial fibrillation; hypothyroidism, thrombocytopenia; and hypomagnesemia. At the time of enrollment, the patient was receiving cefepime and metronidazole. On day 2, the patient developed worsening renal failure and acidosis, requiring continuous venous-venous hemofiltration. On day 4, the patient developed vancomycin-resistant enterococcal bacteremia, and worsening thrombocytopenia, and micafungin was discontinued at that time. The patient died on day 16 due to multi-organ failure, with renal failure and patient age considered contributing conditions. Neither death nor renal failure was attributed to micafungin. No autopsy was performed. In addition to the antibiotics noted above, concomitant medications included amphotericin B (single dose day 1), aspirin, vitamin K, sodium bicarbonate, magnesium sulfate, potassium chloride, digoxin, lasix, benadryl, sodium citrate, potassium phosphate, calcium chloride, hydrocortisone, vancomycin (day 3), fentanyl, fluconazole (day 6-15). BUN and creatinine were 24 mg/dL and 2.6, respectively, on day 1 of micafungin therapy, decreasing to 13 and 1.2 mg/dL for BUN and creatinine, respectively, on day 4.

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***Medical Officer Comments:** This patient had renal insufficiency prior to receiving micafungin, and the renal laboratories on study day 4 do not reflect worsening renal function. Unfortunately, no additional laboratory data is available prior to day 4. The patient also received a single dose of amphotericin on the first day of micafungin treatment. No other known nephrotoxic medications were administered prior to micafungin. Although this case is less confounded than others in study 98-0-047, it would be difficult to attribute the renal failure to micafungin alone.*

Patient 055885 was a 37 year old Caucasian male who had received a heart transplant, with *Candida* empyema and pneumonia for which he received micafungin 50 mg/day for 5 days in study 98-0-047. Significant baseline conditions included renal insufficiency, cardiomyopathy, hemothorax, leukocytosis, sacral decubitus, upper gastrointestinal bleeding, heparin-induced thrombocytopenia, anemia, hyperglycemia, hypocalcemia, and sepsis. At the time of enrollment, the patient was receiving piperacillin, prednisone, tobramycin, vancomycin, bactrim, cellcept, ciprofloxacin, ganciclovir, and fat emulsion. Acute renal failure was reported as a serious adverse event on days 3 to 6. Micafungin was discontinued on day 5 due to lack of efficacy. Other serious adverse events in this patient included pericardial effusion, hypotension, and "shock liver". The patient died on day 6 due to exsanguination from a pulmonary laceration, with contributing conditions including overwhelming fungal infection, and acute respiratory distress syndrome. Neither the death nor renal failure was considered related to micafungin. Additional concomitant medications included lasix, colace, xanax, total parenteral nutrition, zantac, primaxin, Abelcet (single dose on day 5), vitamin K, sodium bicarbonate, epinephrine, levophed, and erythromycin. BUN and creatinine were 26 mg/dL and 1.3 mg/dL at baseline, and 35 mg/dL, and 2.0 mg/dL, respectively, on day 6.

***Medical Officer's Comments:** This patient had baseline renal insufficiency, experienced hypotension, and received a number of other potentially nephrotoxic medications (tobramycin, vancomycin, ganciclovir, etc.) any of which could have resulted in renal failure. I think it is unlikely that the renal failure was caused by micafungin alone.*

Patient 055882 was a 55 year old Caucasian male with underlying cirrhosis, and invasive candidiasis involving the biliary tract, treated with micafungin 50 mg/day for a total of 52 days in study 98-0-047. Significant baseline conditions included abdominal pain, ascites, biliary obstruction, cholangitis, cholestasis, coagulation disorder, retinal disorder, peripheral edema, depression, dehydration, diabetes mellitus, anorexia, cholestatic jaundice, kidney failure, adrenal disorder, sepsis, anemia, thrombocytopenia, splenomegaly, hypokalemia, abdominal pain, and hypotension. The patient was receiving demerol, fat emulsion, folic acid, potassium chloride, zinc sulfate, actigall, ciprofloxacin, nasonex, multivitamins, ampicillin, albumin, sodium bicarbonate, and magnesium upon enrollment in the study.

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Renal failure was reported as a serious adverse event on day 9, but was not considered related to micafungin. He received a liver transplant on study day 21. The patient completed the study, and renal failure was ongoing at the time of the last evaluation day 99). Additional concomitant medications included Tylenol, remeron, benadryl, thiamine, lasix, spironolactone, vancomycin (days 9-12), neutraphos, lasix, ultram, Ritalin, sorbitol, ranitidine, reglan, neomycin, methylprednisolone, zosyn, erythromycin, cellcept, alternagel, zantac, insulin, epinephrine, dopamine, alprostadil, trental, fluconazole, ganciclovir (days 22-31; and days 60-continuing), bactrim (days 59-continuing), and others. Renal laboratories for this patient are shown in the table below.

Renal laboratory Data for Patient 055882*

Study Day	BUN (mg/dL)	Creatinine (mg/dL)
Day 1	9	1.3
Day 8	5	0.9
Day 9	21	3.1
Day 17	62	5.7
Day 24	73	5.9
Day 31	68	5.2
Day 38	37	3.4
Day 45	18	2.7
Day 52	15	2.4
Day 99	25	2.4

*Normal laboratory values are provided in Appendix 10.1.5

***Medical Officer Comments:** This patient had mild renal insufficiency at baseline, with acute worsening on day 9, with a peak creatinine level on day 24. Other than vancomycin and ciprofloxacin, the patient had not received any potentially nephrotoxic medications prior to the onset of worsening renal failure. However, the worsening renal disease could potentially be attributed to hepatorenal syndrome in this patient with underlying cirrhosis, or to hypotension, which was reported on day 23. In this medical officer's opinion, micafungin was possibly related to worsening renal failure in this patient, although confounding factors make this conclusion tentative.*

Patient 031872 was a 55 year-old female with glioblastoma multiforme on hydrocortisone. She received micfungin 50 mg/day for 4 days for candidemia in study protocol 98-0-047, after receiving a single dose of fluconazole (800 mg). Significant baseline conditions included asthma, seizure disorder, left lower lobe atelectasis, thrombocytopenia, anemia, hypokalemia, and hyperglycemia. Renal failure was reported on day 4 as a serious adverse event, and micafungin was discontinued at that time. The investigator considered renal failure in this patient probably related to micafungin. The patient required dialysis from days 7-16, and renal function improved by day 17. However, BUN and creatinine remained elevated 6 weeks post-treatment (study day 44). Concomitant medications prior to the onset of renal failure included primaxin, unasyn, cardizem, pepcid, depakote, hydrocortisone, insulin, ciprofloxacin, omeprazole, vitamin

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C, folic acid, potassium chloride, Tylenol, dilantin, magnesium sulfate, and benadryl.

Renal laboratories for this patient are shown in the table below.

Renal laboratories for Patient 031872*

Study day	BUN (mg/dL)	Creatinine (mg/dL)
Day 1	17	0.9
Day 4	36	2.3
Day 13	48	1.8

*Normal laboratory values are provided in Appendix 10.1.5

Medical Officer Comments: This patient had normal renal function at baseline, and developed renal failure within 4 days of micafungin treatment. She was also receiving a number of antibiotics for an unspecified infection, but none of the concomitant medications is associated with significant nephrotoxicity. I agree with the investigator that renal failure in this patient was possibly or probably related to micafungin.

Patient 358475 was a 49 year old black female who had a nephrectomy and resection of an adrenal tumor. Post-operatively, she developed an abdominal abscess and fluid cultures were positive for *Candida*. She received micafungin 50 mg/day for 22 days in study 98-0-047, after failing fluconazole. Surgical drainage of the abscess was performed on study day 2, and oliguria was reported as a serious adverse event on that day. The patient had baseline chronic renal failure, requiring dialysis, in addition to nausea, vomiting, diarrhea, hypertension, melena, anemia, thrombocytosis, hyponatremia, hypokalemia, hypochloremia, hypomagnesemia, hypocalcemia, hypoalbuminemia, elevated alkaline phosphatase, and malnutrition. The patient was receiving imipenem at the time of enrollment. Other serious adverse events in this patient included shock (day 18), which resolved. The patient died on day 47 due to shock associated with acidosis and respiratory failure. An autopsy was not performed. Neither the death nor the adverse events were considered related to micafungin. Additional concomitant medications included propranolol, ranitidine, fluconazole, cisapride, metoclopramide, dipyrrone (phenylbutazone), acetaminophen, heparin, furosemide, methyldopa, captopril, vancomycin, and meropenem. Renal laboratories for this patient are shown in the following table.

Renal Laboratories for Patient 358475*

Study Day	BUN (mg/dL)	Creatinine (mg/dL)
Day 1	51	5.7
Day 8	78	5.0
Day 15	73	4.4
Day 22	56	4.1

*Normal laboratory values are provided in Appendix 10.1.5

Medical Officer Comments: This patient had baseline end-stage renal disease and developed oliguria which developed post-operatively and persisted until the

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time of death. The creatinine value in an end-stage renal disease patient on dialysis is not an accurate assessment of renal function. Except for captopril which was administered intermittently starting on day 5, and which can exacerbate renal function in patients with baseline renal insufficiency, hypovolemia, or reno-vascular hypertension, this patient had not received other potentially nephrotoxic medications. I would concur that oliguria in this patient was most likely not related to micafungin.

Patient 318373 was a 50 year old Mestizo male with HIV (CD₄ count not specified), with invasive pulmonary fungal infection. He received micafungin 75 mg/day for 17 days in study 98-0-046, after failing fluconazole. Significant conditions at baseline included tuberculosis, fever, vomiting, urinary tract infection, elevated creatinine, AST, and alkaline phosphatase levels, hypoalbuminemia, hypomagnesemia, hyponatremia, hypocalcemia, and staphylococcal sepsis. At the time of enrollment the patient was receiving zidovudine, didanosine, sulfamethoxazole, ciprofloxacin, rifampin and isoniazid. Kidney failure was reported as a serious adverse event on day 9, and micafungin was discontinued at that time. The patient was diagnosed with Hansen's disease on day 12, and patient died on day 17 due to kidney failure, with contributing conditions considered chronic renal failure, HIV and sepsis. Neither the death nor renal failure was considered related to micafungin. Additional concomitant medications included reglan, ranitidine, pyrazinamide, vancomycin (day 9), nelfinavir, prednisone, clarithromycin ethambutol, dapsone, clofazamine, benadryl, loperamide, and azithromycin. Renal laboratories for this patient are shown in the table below.

Renal Laboratories for Patient 318373*

Study day	BUN (mg/dL)	Creatinine (mg/dL)
Day 1	122	4.9
Day 7	136	4.1
Day 14	158	5.0

*Normal laboratory values are provided in Appendix 10.1.5

Medical Officer Comments: *This patient had baseline renal failure with worsening uremia (creatinine was relatively stable). He was receiving bactrim, presumably for Pneumocystis prophylaxis, but the dose was not provided. He also received nelfinavir, which can infrequently cause kidney stones and renal failure. Certainly sepsis can cause renal failure, and the patient reportedly had staphylococcal sepsis at baseline. In the medical officer's opinion, micafungin was unlikely related to worsening renal failure in this patient.*

Patient 063788 was a 28 year old Caucasian male with non-Hodgkins lymphoma who received an allogeneic bone marrow transplant. He received micafungin 75 mg/day for 28 days in study 98-0-046 for invasive pulmonary aspergillosis, after failing itraconazole. Significant baseline conditions included grade II GVHD, weakness, fatigue, blurry vision, anemia, oral leukoplakia, hypocalcemia, tachycardia, pulmonary crackles, cataracts, cardiomyopathy, thrombocytopenia, peripheral edema, depression, chronic

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renal failure, pneumonia, and dyspnea. Upon enrollment, the patient was receiving prevacid, imuran, hydralazine, prednisone, colace, albuterol, cefoxitin, calcium norvasc, atovaquone, levofloxacin, sirolimus, and desmopressin acetate. Kidney failure was reported as a serious adverse event on day 14. The investigator considered this adverse event possibly related to micafungin. Micafungin was stopped on day 28, and the patient was discharged from the hospital at that time. Renal failure was ongoing on the last study evaluation, day 28. Concomitant medications included amikacin (days 3-ongoing); calcium gluconate, lasix, amphojel, fentanyl, epogen, cyclosporine, zofran, Tylenol, vicodin, benadryl, ancef, clarithromycin, fentanyl, versed, acyclovir, and AmBisome (days 29-ongoing). Renal laboratory data for this patient are shown in the following table.

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Renal laboratory values for Patient 063788*

Study day	BUN (mg/dL)	Creatinine (mg/dL)
Day 1	78	5.0
Day 8	99	6.6
Day 15	53	5.0
Day 22	43	5.8
Day 29	19	4.2

*Normal laboratory values are provided in Appendix 10.1.5

Medical Officer Comments: This patient had baseline renal insufficiency, and in addition to micafungin, had also received several days amikacin prior to the laboratory data showing worsening renal failure. Because amikacin has known renal toxicity, in my opinion, the deterioration of renal function in this patient is more likely due to amikacin than to micafungin.

Patient 055775 was a 58 year-old male who had received immunosuppressive therapy due to a lung transplant. He initially received itraconazole for invasive pulmonary aspergillosis, but subsequently received micafungin, 75mg/day, at increasing doses to 300 mg/day for 36 days in study protocol 98-0-046 for efficacy failure. Other significant baseline conditions included chronic cough, neuralgia, elevated creatinine and alkaline phosphatase, and chronic pain. At the time of study enrollment, the patient was receiving trimethoprim-sulfamethoxazole, prednisone, tacrolimus, mycophenolate mofetil, and ganciclovir. Amphotericin B was added to micafungin on day 22 because of worsening pulmonary fungal infection. Abelcet replaced amphotericin B on day 26. Kidney failure was reported as a serious adverse event on study day 36. Micafungin was stopped on day 36 due to treatment failure. Hypotension was reported as an adverse event on day 37, and the patient died that day due to pulmonary aspergillosis, with adult respiratory distress syndrome and sepsis considered contributing conditions. No autopsy was performed. Neither the renal failure nor the death was considered related to micafungin. Additional concomitant medications included lasix, folic acid, colace, multivitamins, neurontin, magnesium, prochlorperazine, primaxin, tobramycin (day 22), Demerol, versed, benadryl, compazine, calcium carbonate, paxil, heparin, Tylenol, ceftazidime, clindamycin, morphine, zantac, glutamine, insulin, alternagel, kayexalate, neutrophos, potassium, thiamine, selenium, diamox, levophed, vaspressin, piperacillin, and atracurium. Renal laboratory values for this patient are shown in the table below.

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Renal Laboratory Values for Patient 055775*

Study day	BUN (mg/dL)	Creatinine (mg/dL)
Baseline	58	5.4
Day 8	19	1.0
Day 14	15	0.9
Day 21	19	0.9
Day 29	89	3.4
Day 35	83	1.5

*Normal laboratory values are provided in Appendix 10.1.5

***Medical Officer Comments:** This patient had baseline renal insufficiency, which actually improved during the first two weeks of micafungin treatment. BUN and creatinine, however, increased significantly after receipt of tobramycin, amphotericin B, and Abelcet®. I would agree that renal failure in this patient was not related to micafungin.*

Patient 055774 was a 56 year old Caucasian male who received immunosuppressive therapy for a heart transplant, and developed invasive pulmonary aspergillosis for which he received micafungin starting at 75 mg/day (and increased up to 300 mg/day) for 43 days in study 98-0-046. Baseline conditions included diabetes, renal insufficiency, cytomegalovirus colitis, anemia, hypocalcemia, hypoproteinemia, hypoalbuminemia, hypomagnesemia, hypertension, and hyperlipidemia. On enrollment, the patient was receiving prednisone, bactrim, cyclosporine, mycophenolate mofetil, ganciclovir, ferrous sulfate, calcium citrate, magnesium oxide, pravachol, prinivil, prevacid, robitussin and fosfamax. "Acute on chronic renal failure" was reported as an adverse event on day 17, and resolved on day 39. The investigator considered renal failure not related to micafungin. Additional concomitant medications included glucatrol, alteplase, ambient, diltiazem, foscarnet, (day 1- ongoing), prochlorperazine, zofran, hydrocortisone, cefazolin, albuterol, Tylenol, Tylenol #3, neutrphos, flexaryl, vicodin, benadryl, colyte, lasix, zantac, Demerol, vistaril, hydralazine, ketorolac (day 21), ativan, insulin, fat emulsion, neupogen, total parenteral nutrition, erythropoietin, morphine, cyclosporine, itraconazole, ibuprofen (day 43). Renal laboratory values for this patient are shown in the table below.

Renal laboratory Values for Patient 055774*

Study day	BUN (mg/dL)	Creatinine (mg/dL)
Day 1	45	2.8
Day 8	27	2.3
Day 15	33	2.9
Day 22	23	2.7
Day 29	36	3.0
Day 36	37	2.9
Day 41	14	1.9

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Day 84	57	2.1
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*Normal laboratory values are provided in Appendix 10.1.5

***Medical Officer's Comments:** This patient had baseline renal insufficiency which worsened during treatment with micafungin. However, several of the concomitant medications received are potentially nephrotoxic, including bactrim, ganciclovir, and foscarnet. Renal function improved after discontinuation of micafungin, but BUN and creatinine were again elevated by day 84. The improvement in renal function after stopping micafungin could be considered a positive de-challenge, and as such, renal failure was possibly related to micafungin.*

Patient 318375 was a 24 year old Mestizo male with upper gastrointestinal bleeding. He developed presumed fungal pneumonia for which he received micafungin 75 mg/day for 7 days in study protocol 98-0-046. The patient developed life-threatening gastrointestinal hemorrhage on study day 3, and anuria on day 5. Micafungin was stopped on day 7 for gastrointestinal bleeding, and the patient died on that day due to gastrointestinal hemorrhage, with thrombocytopenia and exacerbation of bleeding considered contributing conditions. Neither the death nor the serious adverse events were considered related to micafungin. Significant baseline conditions included anemia, hyperbilirubinemia, elevated BUN and creatinine, hypocalcemia, hypoproteinemia, elevated liver enzymes, sepsis, multiple organ failure, and mesenteric lymphadenitis. At the time of enrollment the patient was receiving only meropenem. Additional concomitant medications included saline solution, furosemide, dopamine, ranitidine, lactulose, calcium gluconate, ciprofloxacin (day 1-7), cimetidine, dipirone, omeprazole, vitamin K, sodium bicarbonate, vitamin C, dobutamine, vancomycin (day 4), vitamin B, Ringers lactate solution, potassium chloride, fentanyl, and midazolam. Renal laboratory data for this patient is shown in the table below.

Renal Laboratory Data for Patient 318375*

Study Day	BUN (mg/dL)	Creatinine (mg/dL)
Baseline	342	7.8
Day 7	331	5.5

*Normal laboratory values are provided in Appendix 10.1.5

***Medical Officer Comments:** This patient had significant renal insufficiency at baseline, mostly pre-renal azotemia, most likely due to gastrointestinal bleeding. He may also have had hypotension, related to hypovolemia, resulting in ischemic damage to the kidneys. In addition, he received concomitant vancomycin and ciprofloxacin, both of which can have renal toxicity. Because of all these confounding factors, it is unlikely that micafungin caused the anuria in this patient.*

Discontinuation of Micafungin due to Renal Adverse Events

Micafungin was discontinued due to increased creatinine in 3/1980 (0.1%) patients, due to kidney failure in 4 (0.2%) patients, and due to acute kidney failure in 1 patient. Renal

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adverse events considered drug-related which resulted in micafungin discontinuation occurred in 1 patient with acute renal failure, and in 2 patients with increased creatinine.

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Deaths Due to Renal Adverse Events

Seven of 1980 (0.4%) patients in these studies died due to renal failure. None of the deaths were attributed to micafungin. These patients are summarized in the table below. Most patients were described previously under serious renal adverse events, and two additional narrative summaries are provided below.

Table 147. Deaths due to Renal Failure (adapted from Applicant's Item 10, 06 January, 2005, requested data)

Patient Number	Study Protocol	Final dose of Micafungin (study day)	Day of Death	Primary Cause of Death	Serious Adverse Events
02545016	03-7-005	19	19	Kidney failure	Kidney failure; vomiting
10705024	03-7-005	14	39	Acute kidney failure	Anemia; acute kidney failure
10745031	03-7-005	9	10	Acute kidney failure	Acute kidney failure
201007	97-7-003	5	9	Kidney failure	Kidney failure
059773	98-0-046	7	7	Kidney failure	Anxiety, bradycardia, cyanosis, hypertension, hypoxia, kidney failure, sepsis, ventricular tachycardia, vasodilatation, respiratory failure
318373	98-0-046	17	18	Kidney failure	Kidney failure
107871	98-0-047	4	16	Acute kidney failure	Kidney failure; thrombocytopenia

Narratives for Patients who died due to Renal Failure

Narrative summaries were provided in the Serious Adverse Events section above, except for the following patients:

Patient 10705024 was a 34 year-old black South African female with suspected HIV. No CD₄ count was obtained, and the patient was not receiving antiretroviral therapy.

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Baseline conditions included *Pneumocystis jiroveci* (formerly *carinii*) pneumonia. The patient received micafungin 150 mg/day for 14 days. Concomitant medications included multivitamin, ferrous sulfate, xylocaine, depo-provera, coxsole (bactrim), ibuprofen, paracetamol, and midazolam. No adverse events were reported during the study. The patient died on day 39 due to acute renal failure, and worsening anemia. No autopsy was performed, and the death was not considered related to micafungin. Pertinent laboratory data for this patient is shown in the table below. Except for minimal elevation of AST (from 27 U/L at baseline to 47 U/L on day 13), other liver function tests, including ALT, bilirubin, and alkaline phosphatase remained normal throughout the study.

Laboratory Values for Patient 10705024*

Study day	WBC x 10 ⁹	Hemoglobin g/dL	Platelets x 10 ⁹	BUN mg/dL	Creatinine mg/dL	Sodium mmol/L	Potassium mmol/L
Baseline	6.5	8.1	229	18	1.4	130	4.6
Day 7	4.1	7.1	190	23	1.6	130	4.5
Day 13	8.2	7.3	151	27	1.3	132	3.6
Day 27	11.1	3.8	50	62	3.6	130	6.6
	Calcium mg/dL	Magnesium mg/dL	LDH U/L				
Baseline	10.6	1.9	764				
Day 7	10.4	1.1	993				
Day 13	10.7	1.6	1304				
Day 27	10.8	1.9	1457				

*normal laboratory values are shown in Appendix 10.1.5.

*Medical Officer Comments: This patient was anemic at baseline, but developed severe anemia by study day 27. Significant thrombocytopenia was also noted on day 27. Additionally, she had mild renal insufficiency at baseline, which progressed through the study period. Hyperkalemia was noted on study day 27. The progressive renal insufficiency and hyperkalemia could be attributed to bactrim, which the patient received for *Pneumocystis pneumonia*. Also at baseline, the patient had hyponatremia, and hypercalcemia, both of which persisted during and after treatment. LDH increased throughout the study period; while hypomagnesemia was noted during micafungin treatment. I would agree that the death was not related to micafungin given the time course of events.*

Patient 059773 was a 12 year old Caucasian male with acute lymphocytic leukemia who received an allogeneic bone marrow transplant. He received micafungin 48 mg/day in addition to AmBisome® 240 mg/day for suspected pulmonary aspergillosis in study 98-0-046. He had failed prior therapy with amphotericin B and AmBisome® alone. Baseline conditions included grade III graft versus host disease, cytomegalovirus, vancomycin-resistant *Enterococcus* infection, gastrointestinal bleeding, thrombocytopenia, acute respiratory distress requiring mechanical ventilation, hyperbilirubinemia, cardiac arrhythmias, metabolic acidosis, pulmonary edema, hepatosplenomegaly, bronchiectasis, and sinusitis.

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On the first day of micafungin infusion, the patient experienced flushing, hypertension, cyanosis, and anxiety, all reported as serious adverse events, and considered possibly related to micafungin. Micafungin dosing was interrupted on day 2 because of these events, and was restarted on day 3. Kidney failure was reported as a serious adverse event on day 4; and sepsis (*E. faecium* bacteremia), on day 5. Other serious adverse events during micafungin treatment (day 7) included bradycardia, hypoxia, ventricular tachycardia, and respiratory failure. None of these events was considered micafungin-related. The patient died due to renal failure on day 7, with respiratory failure, pulmonary aspergillosis, graft-versus-host disease and bacterial sepsis considered contributing factors. The final autopsy revealed diffuse pulmonary consolidation, with hemorrhage, bronchiolar obliteration, aspergillosis, and arterial intimal fibrosis, as well as chronic GVHD involving the lungs, gastrointestinal tract, and skin, hepatosplenomegaly, hepatic portal fibrosis and regenerative nodular hyperplasia, hemosiderosis, fibrinous pericarditis, and infarction and cystic encephalomalacia of the right parietal lobe. The full autopsy report was not available, and there was no mention of kidney disease in the final report. The patient received multiple concomitant medications including ganciclovir, bactrim, gentamicin, vancomycin, amphotericin B, AmBisome, cyclosporine, and others. Prior to study entry, the patient had also received itraconazole. Serum chemistry data for this patient is shown in the table below.

Laboratory Values for Patient 059773*

Study Day	AST U/L	ALT U/L	Total bilirubin U/L	Alkaline phosphatase U/L	BUN mg/dL	Creatinine mg/dL
Day 1	29	31	14.1	--	25	0.7
Day 2	24	30	15.2	526	39	0.8
Day 3	32	30	18.4	531	54	1.1
Day 5	45	48	27.0	738	88	1.3
Day 6	--	--	29.9	--	114	1.3
Day 7	--	--	27.8	--	122	1.7

*Normal laboratory values are shown in Appendix 10.1.5.

***Medical Officer Comments:** The etiology of renal failure in this patient is not clear. The highest creatinine reported was 1.7, and the BUN/creatinine ratio would suggest pre-renal azotemia, rather than drug-related renal toxicity. The patient also received multiple concomitant medications which have potential renal toxicity. The patient also had worsening bilirubinemia and increased alkaline phosphatase throughout micafungin treatment and neither hemolysis nor veno-occlusive liver disease was reported as adverse events. This is an extremely complex case with multiple confounding factors, and it seems unlikely that micafungin was related to renal failure in this patient.*

Micafungin Dose Relationship for Renal Adverse Events

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A total of 60/606 (9.9%) patients treated with at least 150 mg/day micafungin for 10 days or more, compared with 172/1796 patients (9.6%) who received micafungin at lower doses or for less than 10 days, experienced a renal adverse event. The following table shows renal adverse events for patients by dose and duration. The incidence of adverse events in patients who received the higher doses and/or duration of micafungin was generally similar to that in patients who received micafungin at lower doses or for shorter durations.

Table 148. Renal Adverse Events in Subjects by Micafungin Dose (adapted from Applicant's Appendices 11.4.4.1, and 11.4.3.1 120-day Safety Update)

Renal Adverse Event COSTART Term*	Patients who received micafungin \leq 100 mg/day for \leq 10 days N=1595	Patients who received micafungin \geq 100 mg/day for \geq 10 days N=807	Patients who received micafungin \geq 150 mg/day for at least 10 days N=606
Any renal adverse event	144 (9.0)	88 (10.9)	60 (9.9)
Creatinine increased	62 (3.9)	27 (3.3)	16 (2.6)
BUN increased	39 (2.4)	37 (4.6)	25 (4.1)
Acute kidney failure	16 (1.0)	6 (0.7)	4 (0.7)
Kidney failure	33 (2.1)	17 (2.1)	14 (2.3)
Kidney function abnormal	22 (1.4)	20 (2.5)	16 (2.6)

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

Medical Officer Comments: *This analysis is limited by the differences in patient characteristics compared in these dosing groups. Patients who received micafungin dosed at \geq 150 mg/day for at least 10 days were mostly HIV patients with esophageal candidiasis, healthy volunteers in pharmacokinetic studies, or patients with invasive aspergillosis who did not respond to lower doses, compared to patients with other indications for antifungal therapy.*

The following table shows serious renal adverse events by micafungin dose and duration.

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Table 149. Serious Renal Adverse Events in Subjects who received Micafungin by Dose (adapted from applicant's Appendices 11.4.3.2, and 11.4.3.2)

Serious Renal Adverse Event COSTART Term*	Subjects who received Micafungin \leq 100 mg/day for \leq 10 days N=1595	Subjects who received Micafungin \geq 100 mg/day for \geq 10 days N=807	Subjects who received Micafungin \geq 150 mg/day for \geq 10 days N=606
Any serious renal adverse event	31 (1.9)	16 (2.0)	14 (2.3)
Acute kidney failure	8 (0.5)	2 (0.2)	2 (0.2)
Creatinine increased	7 (0.4)	1 (0.1)	1 (0.2)
BUN increased	6 (0.4)	0 (0)	0 (0)
Kidney failure	15 (0.9)	12 (1.5)	10 (1.7)
Kidney function abnormal	2 (0.1)	1 (0.1)	1 (0.2)

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

Medical Officer Comments: For serious renal adverse events, there may be somewhat of a dose response, particularly for renal failure. If acute renal failure and kidney failure are combined as terms, 10/1595 (0.6%) subjects, compared to 14/807 (1.7%) subjects, and 12/606 (2.0%) subjects who received \leq 100 mg/day, \geq 100 mg/day, and \geq 150 mg/day micafungin, respectively experienced renal failure. This analysis, however, is limited by differing patient characteristics between the dosing groups shown above.

Laboratory Parameters of Renal Function

Mean and median values for BUN and creatinine treatment were calculated by the applicant, and are shown in the table below. No differences were observed in BUN or creatinine levels measured at baseline, at the end of micafungin treatment, or post-treatment. Additionally, in fluconazole-controlled studies, mean changes in BUN and creatinine over the course of treatment were similar for the two treatment groups.

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Table 150. Summary of Creatinine and Blood Urea Nitrogen (adapted from applicant's Table 9, and Appendices 12.1.1, 12.2.1, 12.3.1.1, and 12.3.1.3, safety update)

	All Studies		Fluconazole-Controlled Studies	
	All Subjects	All Patients	Micafungin	Fluconazole
Creatinine (mg/dL)				
Baseline	n=2308	n=1920	n=906	n=775
Mean±SD	1.03±0.83	1.03±0.88	0.86±0.36	0.88±0.41
Median	0.90	0.81	0.80	0.80
Range	0.1-10.3	0.1-10.3	0.1-5.0	0.2-6.8
End of Therapy				
Mean±SD	1.02±0.79	1.02±0.84	0.85±0.50	0.93±0.69
Median	0.85	0.80	0.74	0.80
Range	0.1-11.0	0.1-11.0	0.1-6.9	0.1-13.5
Mean Change	<0.01	<0.01	-0.01	0.05
BUN (mg/dL)				
Baseline	n=2286	n=1898	n=899	n=768
Mean±SD	19.1±18.79	20.0±20.21	13.4±8.87	13.5±8.85
Median	14.0	14.0	11.8	12.0
Range	1.4-342	1.4-342	1.4-103	0.4-97
End of Therapy				
Mean±SD	21.2±24.37	22.4±26.37	14.2±14.10	16.1±16.8
Median	14.0	14.0	11.0	11.5
Range	1.0-331	1.0-331	1.0-205	0-227
Mean Change	2.1	2.4	0.8	2.6

n: number of subjects/patients who received at least one dose of study drug (micafungin or fluconazole, as applicable)

BUN: Blood urea nitrogen; SD: Standard deviation

Fluconazole-Controlled Trials: Studies 03-7-005, FG-463-21-09, 98-0-050, and 97-0-041.

Medical Officer Comment: As seen in the wide range of BUN and creatinine values at each time point measured, the means and median laboratory values were likely affected by a number of outliers.

Japanese Postmarketing Adverse Events

The postmarketing data from Japan for the time period April 2003 to April 2004 was reviewed by Dr. Rothstein, the ODS consultant. A total of 25 serious renal adverse events, including 9 cases of renal failure, 13 cases of renal impairment, and 3 cases of hemolytic uremic syndrome were reviewed. For the cases with enough information to

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make a causal assessment, 1 case of renal failure, 5 of renal impairment, and 2 of hemolytic uremic syndrome were considered possibly related to micafungin. The ODS recommended a PRECAUTION statement regarding renal impairment in the U.S. label.

Medical Officer Comments: In the micafungin safety database, hemolytic uremic syndrome was not reported as an adverse event among 2402 subjects.

Renal Safety Summary

Micafungin appears to have the potential for renal toxicity. Some toxic effects on the kidneys were observed in rats who received micafungin at high doses. There were no renal adverse events (clinical or laboratory) in studies with healthy volunteers; and overall, the proportion of patients with renal adverse events event were similar in micafungin- and fluconazole-treated patients.

Among serious renal adverse events, renal failure was the most common event in these studies. Most micafungin-treated patients with serious renal failure were seriously ill, had multiple other medical conditions and received other potentially renal-toxic medications (prior or concomitant with micafungin). However, there were several cases in which renal failure was possibly related to micafungin.

Additionally, postmarketing surveillance in Japan identified a number of serious renal adverse events, some of which may have been related to micafungin. The Japanese label was revised in February 2004 to include acute renal failure as a clinically significant adverse reaction, based on the Japanese postmarketing experience. We have proposed to include a PRECAUTION regarding acute renal failure or renal impairment in the final micafungin label, and expect to perform postmarketing surveillance for serious renal adverse events.

7.1.12.7 Hematological Safety

A total of 927/2402 (38.6%) subjects experienced at least one hematological adverse event. Drug-related adverse events were reported in 117 (4.9%) subjects. The most common drug-related events included leukopenia (2.5%), anemia (1.2%), and thrombocytopenia (1.0%). Serious hematological adverse events were reported in 63/1980 (3.2%) patients, and in no healthy volunteers. Drug-related serious adverse events occurred in 13 (0.7%) patients; and micafungin was discontinued in 14 (0.7%) patients due to a hematological adverse event. One death, in a patient with pulmonary aspergillosis, was due to pancytopenia resulting in pulmonary hemorrhage. The pancytopenia and death were considered possibly related to micafungin,

Hemolysis was identified in preclinical studies as a potential toxicity of micafungin. Hemolysis and hemolytic anemia were also observed in the clinical safety database among patients and in at least one healthy volunteer. Hematological adverse events in the Japanese postmarketing experience were reviewed by the ODS in consultation with the

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DSPIDP. Recommendations from the office of drug safety included listing anemia, leukopenia, neutropenia, and thrombocytopenia as common adverse events under “Adverse Reactions”, and adding hemolytic anemia to the listing of adverse events from Japanese postmarketing sources in the U.S. label. ODS also recommended monitoring unlabeled hematologic adverse events such as idiopathic thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP) after micafungin approval in the U.S., because these events were reported post-marketing in Japan. We have proposed a PRECAUTION statement regarding hemolysis and hemolytic anemia for the final micafungin labeling.

Preclinical Data

Micafungin (500 micrograms/mL) hemolyzed rabbit blood in an *in vitro* study. This micafungin concentration is well above clinically relevant doses. The highest dose of micafungin administered in humans was 8 mg/kg which resulted in a C_{max} of 57 micrograms/mL. The applicant also noted that caspofungin also produced hemolysis in human washed red-blood cells at concentrations of 450 to 1800 micrograms/mL.

Micafungin exhibits surfactant action at concentrations of 100 micrograms/mL to 1000 micrograms/mL. At therapeutic doses in humans (150 mg/mL for esophageal candidiasis), the maximum plasma concentration (C_{max}) determined in pharmacokinetic studies was approximately 16 micrograms/mL, a concentration at which surfactant activity would not be expected for micafungin. At the highest human dose administered, 8 mg/kg micafungin, the measured C_{max} was approximately 61 micrograms/mL in hematopoietic stem cell transplant patients.

Medical Officer Comments: At the proposed dose for esophageal candidiasis, 150 mg/day micafungin, and that for antifungal prophylaxis, 50 mg/day, surfactant activity of micafungin, which could result in hemolysis or other cell lysis, would not be expected based on this pharmacokinetic information.

In rats which received 10 mg/kg or 32 mg/kg micafungin, findings which indicated hemolysis included increase in serum total bilirubin, increased potassium, congestion and brown pigmentation in the spleen, decreased RBC count, increased reticulocyte count, increased hematopoiesis in the spleen and hypercellularity in femoral bone marrow. In rats, splenic congestion was attributed to hemolysis at higher doses (32 mg/kg).

In dogs, hemolytic anemia was observed following a single dose of 200 mg/kg micafungin (approximately 100 times a human dose of 2-3 mg/kg or 150 mg micafungin). Signs of hemolytic anemia were not observed in repeat-dose studies in dogs. Splenic congestion was observed in dogs less frequently than in rats and was not associated with other evidence of hemolysis.

Hematologic Adverse Events in Healthy Volunteers

In nine single-dose micafungin studies in healthy volunteers, including 198 subjects, one subject experienced a hematologic adverse event, ecchymosis. However, the applicant

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noted that an additional subject had an adverse event reported as hemoglobinuria on the case report form, but was later diagnosed with acute intravascular hemolysis. The narrative summary for this subject is provided in the “Hemolysis and Hemolytic Anemia” section below.

Medical Officer Comments: Ecchymosis could be an indication of capillary fragility or decreased platelet count. Thrombocytopenia was not reported as an adverse event in this subject, however.

In 6 repeat dose studies of micafungin in healthy volunteers, 7/184 (3.8%) subjects who received either approximately 100 mg/day or 150 mg/day micafungin, had hematologic adverse events. No adverse events in this category were reported in subjects who received lower doses of micafungin; however, fewer subjects received lower doses. These data are shown in the table below.

Table 151. Hematologic Adverse Events in Healthy Volunteers in Repeat-Dose Micafungin Studies* (adapted from Applicant’s Appendix 1.5, integrated safety summary).

Hemic and Lymphatic System (COSTART Term)	Micafungin 50 mg N=6	Micafungin 75 mg N=6	Micafungin 100 mg N=53	Micafungin 150 mg N=119	Total Subjects N=184
Any adverse event	0	0	3 (5.7)	4 (3.4)	7 (3.8)
Ecchymosis	0	0	3 (5.7)	0	3 (1.6)
Anemia	0	0	0	2 (1.7)	2 (1.1)
Petechia	0	0	0	1 (0.8)	1 (0.5)
Thrombocytopenia	0	0	0	1 (0.8)	1 (0.5)

*includes studies 01-0-104, 01-0-105, 03-0-175, 03-0-176, 03-0-177, 03-0-178, FJ0002, FJ0005

Medical Officer Comments: The numbers of subjects treated with lower doses or shorter durations of micafungin were too low to draw any conclusions regarding a relationship between these adverse events and the micafungin dose or duration of administration.

A total of 4/119 (3.4%) healthy volunteers who received 150 mg micafungin in repeat-dose studies 03-0-175, 03-0-176, 03-0-177, and 03-0-177, experienced hematologic adverse events, including 2 with anemia, one with petechia, and one with thrombocytopenia. Interestingly, these adverse events were considered drug-related by the investigator in only 1 volunteer with anemia and 1 with thrombocytopenia. These adverse events in healthy subjects are reviewed below.

Subject 10970123 was a 37 year-old black male who received micafungin 150 mg/day for 15 days in study 03-0-175 (sirolimus-micafungin interaction study). Thrombocytopenia was reported as an adverse event on day 15. Baseline platelet count

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was $194 \times 10^9/L$; $169 \times 10^9/L$ on study day 1, $148 \times 10^9/L$ on day 15, $188 \times 10^9/L$ on day 18, and $248 \times 10^9/L$ on day 25.

Medical Officer Comments: This subject experience mild thrombocytopenia which resolved within a few days after micafungin discontinuation on day 15.

Subject 10110230 was a 48 year-old Caucasian male who received micafungin 150 mg/day for 3 days in study 03-0-178 (nifedipine-micafungin interaction study). Anemia, bilirubinemia and fever were reported as adverse events on study day 4. Bilirubinemia and fever were considered possibly related to micafungin. Anemia was considered a persistent condition at the end of the study. Pertinent laboratory values for this subject are shown in the following table. WBC, platelets, AST, ALT, and alkaline phosphatase values were normal in this subject throughout the study.

Laboratory Values for Subject 10110230*

Study Day	Hemoglobin (g/dL)	Hematocrit (%)	Total Bilirubin (mg/dL)
Baseline (-7 days)	14.7	43.7	0.9
Day 1	14.2	40.5	1.0
Day 4	12.6	33.7	2.3
Day 12	13.7	40.3	0.9

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

Medical Officer Comments: This subject developed anemia which was noted by decreased hemoglobin and hematocrit on study day 4. At the same time, the subject developed mild bilirubinemia. These laboratory abnormalities suggest mild, transient hemolysis, which had reversed by day 12.

Hematologic Adverse Events in Patients in the Micafungin Safety Database

Overall, 916/1980 (46.3%) patients treated with micafungin experienced an adverse event categorized in this category. The most common of these events were leukopenia in 501/1980 (25.3%) patients, thrombocytopenia in 464 (23.4%), and anemia in 311 (15.7%) patients. Notably, hemolytic anemia was reported in 3 patients, hemolysis in 2 patients, and abnormal erythrocytes in 2 patients in the safety database. These latter events are further discussed below in the section "Hemolysis and Hemolytic Anemia".

Hematological adverse events considered drug-related occurred in 115/1980 (5.8%) patients. The most common drug-related adverse events included leukopenia in 59/1980 (3.0%) patients, anemia in 28/1980 (1.4%), thrombocytopenia in 22/1980 (1.1%), and abnormal WBC in 10/1980 (0.5%) patients.

Drug-related hematological adverse events are shown in the table below. Additional drug-related adverse experiences which occurred in only one patient each included increased bleeding time, coagulation disorder, cyanosis, hemolysis, lymphocytosis,

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decreased prothrombin, reticuloendothelial hyperplasia, spleen disorder, and splenomegaly.

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Table 152. Drug-Related Hematological Adverse Events in Patients (adapted from Applicant's Appendix 6.12.)

Adverse Event COSTART Term	Micafungin N=1980
Any drug-related hematological adverse event	115 (5.8)
Leukopenia	59 (3.0)
Anemia	28 (1.4)
Thrombocytopenia	22 (1.1)
WBC abnormal	10 (0.5)
Eosinophilia	5 (0.3)
Thrombocythemia	4 (0.2)
Pancytopenia	3 (0.2)
Ecchymosis	1 (0.1)
Leukocytosis	2 (0.1)
Petechia	2 (0.1)

Hematological Adverse events in Fluconazole-controlled studies

A total of 521/932 (55.9%) micafungin-treated patients, and 489/787 (62.1%) fluconazole-treated patients in the fluconazole-controlled studies experienced a hematological adverse event. These events are listed in the following table. The most common adverse events in these studies were leukopenia, thrombocytopenia, and anemia. The incidence and profile of adverse events in this category was similar for the two treatments.

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Table 153. Hematological Adverse Events in Fluconazole-controlled studies* (adapted from Applicant's Appendix 2.7.4.3.3)

Hematological Adverse Events (COSTART Term)	Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787
Any hematological adverse event	521 (55.9)	489 (62.1)
Leukopenia	384 (41.2)	367 (46.6)
Thrombocytopenia	358 (38.4)	337 (42.8)
Anemia	206 (22.1)	215 (27.3)
Petechia	44 (4.7)	41 (5.2)
Ecchymosis	30 (3.2)	28 (3.6)
Coagulation disorder	12 (1.3)	22 (2.8)
Pancytopenia	11 (1.2)	12 (1.5)
Prothrombin decreased	12 (1.3)	11 (1.4)
Eosinophilia	7 (0.8)	9 (1.1)
WBC abnormal	11 (1.2)	8 (1.0)
Leukocytosis	5 (0.5)	7 (0.9)
Lymphadenopathy	7 (0.8)	7 (0.9)
Splenomegaly	4 (0.4)	5 (0.6)
Bleeding time increased	2 (0.2)	2 (0.3)
Normocytic anemia	1 (0.1)	2 (0.3)
Thrombocythemia	1 (0.1)	2 (0.3)
Thromboplastin time decreased	1 (0.1)	2 (0.3)
Cyanosis	0 (0)	1 (0.1)
Hypochromic anemia	0 (0)	1 (0.1)
Lymphoma	0 (0)	1 (0.1)
Purpura	3 (0.3)	1 (0.1)
Erythrocytes abnormal	1 (0.1)	0 (0)
Hemolysis	1 (0.1)	0 (0)
Hemolytic anemia	1 (0.1)	0 (0)
Marrow depression	1 (0.1)	0 (0)

* includes studies 97-0-41, 98-0-050, FG463-21-09, and 03-7-005

Medical Officer Comments: *Most of these events were more common in patients treated with fluconazole than with micafungin. A few adverse events occurred uncommonly in micafungin-treated patients, but were not reported in any fluconazole-treated patients, including hemolysis, hemolytic anemia, abnormal erythrocytes, and marrow depression. Similarly, purpura was observed in 3 patients who received micafungin and only one patient who received fluconazole.*

The applicant analyzed adverse events in relationship to mean daily dose in micafungin-treated subjects. These data are presented for hematologic adverse events of interest in the table below. No obvious dose relationship was noted for these adverse events.

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Table 154. Selected Hematologic Adverse Events by mean daily dose of Micafungin
 (adapted from Applicant's Appendix 1.1.2)

Hemic and Lymphatic System (COSTART Term)	Micafungin < 1.0 mg/kg/day N=822	Micafungin 1.0-1.9 mg/kg/day N=804	Micafungin 2.0-2.9 mg/kg/day N=487	Micafungin 3.0-3.9 mg/kg/day N=215	Micafungin ≥ 4 mg/kg/day N=62	Total* Micafungin-treated Subjects N=2390
Any adverse event	464 (56.4)	282 (35.1)	88 (18.1)	51 (23.7)	41 (66.1)	926 (38.7)
Leukopenia	329 (40.0)	119 (14.8)	29 (6.0)	20 (9.3)	4 (6.5)	501 (21.0)
Thrombocytopenia	319 (38.8)	88 (10.9)	18 (3.7)	14 (6.5)	26 (41.9)	465 (19.5)
Anemia	175 (21.3)	76 (9.5)	19 (3.9)	14 (6.5)	28 (45.2)	312 (13.1)
Pancytopenia	9 (1.1)	4 (0.5)	3 (0.6)	1 (0.5)	0 (0)	17 (0.7)
Coagulation disorder	16 (1.9)	13 (1.6)	5 (1.0)	0 (0)	2 (3.2)	37 (1.5)
Cyanosis	1 (0.1)	6 (0.7)	0 (0)	0 (0)	1 (1.6)	8 (0.3)
Hemolytic anemia	1 (0.1)	1 (0.1)	1 (0.2)	0 (0)	0 (0)	3 (0.1)
Erythrocytes abnormal	1 (0.1)	0 (0)	1 (0.2)	0 (0)	0 (0)	3 (0.1)
Hemolysis	2 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.1)

* Subjects with missing weight were excluded

Medical Officer Comments: *This analysis is limited by the fact that subjects from a number of different studies are combined by mean daily dose. Subject demographics differed significantly, particularly for age and underlying condition, between studies. No conclusions regarding dose-relationship for these adverse events can be drawn from this analysis.*

Serious Hematological Adverse Events (All Subjects)

As shown above, approximately one-half of all patients in the safety database experienced a hematological adverse event. Sixty three of 1980 (3.2%) patients experienced a serious hematological adverse event as shown in the next table. No healthy volunteer experienced a serious adverse event in this category. The most of these serious adverse events were leukopenia, thrombocytopenia. Anemia and coagulation disorder were considered serious in 6 (0.3%) patients each. Additional serious adverse events of concern in this category included cyanosis in 3 (0.2%) patients, pancytopenia in 3 (0.2%) patients, hemolysis in 2 (0.2%) patients, abnormal erythrocytes in 1 (0.1%) patient, and thrombotic thrombocytopenic pupura in 1 (0.1%) patient. Thirteen of 1980 (0.7%) patients who received micafungin had serious hematological adverse events considered drug-related by the investigator, as shown in the following table.

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Table 155. Serious Hematologic Adverse Events in Micafungin-Treated Patients

Hematological Adverse Event COSTART Term	Adverse Events in Micafungin-treated Patients N=1980	Drug-related* Adverse Events In Micafungin-treated Patients N=1980
Serious hematologic adverse event	63 (3.2)	13 (0.7)
Leukopenia	16 (0.8)	4 (0.2)
Thrombocytopenia	13 (0.7)	4 (0.2)
Acute myeloblastic leukemia	6 (0.3)	0
Anemia	6 (0.3)	1 (0.1)
Coagulation disorder	6 (0.3)	1 (0.1)
Cyanosis	3 (0.2)	1 (0.1)
Leukemia	3 (0.2)	0
Pancytopenia	3 (0.2)	2 (0.1)
Hemolysis	2 (0.2)	1 (0.1)
Lymphadenopathy	2 (0.1)	0
Lymphoma	1 (0.1)	0
Acute lymphoblastic leukemia	1 (0.1)	0
Chronic lymphocytic leukemia	1 (0.1)	0
Chronic myelocytic leukemia	1 (0.1)	0
Erythrocytes abnormal	1 (0.1)	0
Hypochromic anemia	1 (0.1)	0
Leukocytosis	1 (0.1)	0
Thrombocytopenic purpura	1 (0.1)	0

*Relationship determined by investigator as possibly, probably, or definitely related to study drug

Medical Officer Comments: Patients with leukemia or lymphoma listed as a serious adverse event had these conditions at baseline, and apparently worsened during the study. Serious adverse events of leukopenia, thrombocytopenia, anemia, pancytopenia, hemolysis, abnormal erythrocytes, and thrombocytopenic purpura are summarized below.

Serious Hematological Adverse Events in Fluconazole-Controlled Studies

The incidence of serious hematological adverse events was similar in micafungin and fluconazole treated patients as shown in the table below.

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Table 156. Serious Hematological Adverse Events in Fluconazole-controlled studies*
 (adapted from applicants's Table R9 1.2, Nov. 1, 2004)

Serious Hematological Adverse Events (COSTART Term)	Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787
Any AE	8 (0.9)	6 (0.8)
Anemia	3 (0.3)	3 (0.4)
Leukopenia	3 (0.3)	2 (0.3)
Coagulation disorder	0	1 (0.1)
Hemolysis	1 (0.1)	0 (0)
Thrombocytopenia	2 (0.2)	0 (0)

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

Medical Officer Comments: The incidence of serious hematological adverse events was similar in the micafungin and fluconazole treatment groups. See narrative summaries below for patients who experience serious hematological adverse events.

Narrative Summaries for Patients with Hematological Serious Adverse Events

Patients with serious hematological adverse events in the esophageal candidiasis studies are reviewed below. Only selected serious hematological adverse events from patients enrolled in studies 98-0-046, 98-0-047, and 98-0-050 were reviewed here, because most of these cases were highly confounded in patients with hematologic malignancies or who had received hematopoietic stem cell transplants.

Patient 02545002 was a 31 year old black male with HIV who developed anemia with micafungin treatment (150 mg/day) for esophageal candidiasis in study 03-7-005. **Anemia** was considered unrelated to micafungin by the investigator. See the narrative summary for this patient in study 03-7-005 review found in the Appendix, section 10.1.1.

Patient 03245019 was a 36 year old mestizo male with HIV who developed worsening **leukopenia** during treatment with micafungin (150 mg/day) for esophageal candidiasis in study 03-7-005. Leukopenia was considered unrelated to micafungin. See narrative summary for this patient in study 03-7-005 review found in the Appendix, section 10.1.1.

Patient 10755011 was a 42 year-old black female with HIV who received 14 days of micafungin (150 mg/day) for esophageal candidiasis in study 03-7-005. A narrative summary was not available for this patient, and information was obtained from a patient profile provided by the applicant. Baseline conditions included tremor, increased cough, infection, abdominal pain, hypoproteinemia, thrombocytopenia, anemia, and nail disorder. Anemia was reported as a serious adverse event on study day 7, but was not considered related to micafungin. The patient received a blood transfusion on study day 9, but anemia persisted through the end-of-the study. Other non-serious adverse events

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during micafungin treatment included phlebitis, chills headache, and hernia. Pertinent laboratory values for this patient are shown in the table below.

Laboratory Values for Patient 10755011*

Study Day	WBC x 10 ⁹ /L	Hemoglobin g/dL	Hematocrit %	Platelets X 10 ⁹ /L	Total Bilirubin mg/dL
Baseline	4.5	5.5	18.3	83	0.3
Day 7	5.7	4.5	15.7	74	0.3
Day 13	6.0	6.8	22.0	41	1.1
Day 27	5.2	6.3	21.9	26	3.1

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

Medical Officer Comments: *This patient had significant anemia and thrombocytopenia at baseline. She was not receiving antiretroviral therapy or other medications commonly associated with hematological toxicity, except for bacrim which she had been receiving for months prior to study entry. Bone marrow involvement by HIV or another infiltrative process (infection or malignancy) may cause leukopenia, thrombocytopenia, and anemia; however, the rapid decline in hematocrit and platelets, but not in leukocytes would suggest another process. The patient developed mild bilirubinemia without elevation of AST or ALT, although alkaline phosphatase increased during treatment. It is feasible that this patient developed an unrecognized hemolytic anemia. Insufficient information is provided to adequately assess causality in this case.*

Patient 401007 was a 30 year-old black male with HIV who received micafungin 75 mg/day for 13 days for esophageal candidiasis in study 97-7-003. 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 anemia, *Herpes simplex*, fever, lymphadenopathy, increased AST, pulmonary tuberculosis, and abdominal pain. Leukopenia was reported as a serious adverse event, unrelated to study drug on study day 3. Anemia was reported as a non-serious adverse event on study day 4, and abscess was noted as a serious adverse event on day 13. Baseline WBC was 4.7 x 10⁹/L, and decreased to 3.0 x 10⁹/L on day 3, and to 1.4 x 10⁹/L on day 6. Hemoglobin and hematocrit were 9.2 g/dL, and 28.7 % at baseline, 8.2 g/dL and 25 % on day 3, and 9.0 g/dL and 25.5% on day 6. Platelet count dropped slightly from baseline to 171 x 10⁹/L on day 3, and 112 x 10⁹/L on day 6. The patient died on study day 13, due to progressive AIDS. Concomitant medications included maxolon, iron sulfate, buscopan, panado, agarol, penicillin G, bacrim, (day 1 only), gentamicin, flagyl, serepax, cloxacillin (days 11 and 12), tagamet, streptomycin, rifampin, isoniazid, and ethambutol.

Medical Officer Comments: *This patient received a number of concomitant medications which have been associated with leukopenia. In addition, leukopenia and anemia may have been related to his underlying HIV disease, tuberculosis, or*

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other infection. I would concur that the progressive leukopenia in this patient was probably not related to micafungin.

Patient 071512 was a 48 year old Caucasian female with breast cancer who received an autologous stem cell transplant. A narrative summary was not available for this patient, and information was obtained from the patient profile provided by the applicant. The patient received micafungin 100mg/day for 7 days for antifungal prophylaxis in study 97-0-041. On study day 6, thrombocytopenia and epistaxis were reported as serious adverse events, and the patient received a platelet transfusion. Thrombocytopenia was considered unrelated to micafungin. Platelet count was $282 \times 10^9/L$ at baseline, $136 \times 10^9/L$ on study day 2, and $76 \times 10^9/L$ on day 3. Micafungin was discontinued on study day 7, at which time the platelet count was $17 \times 10^9/L$, and subsequently normalized by the end of the study. The patient was neutropenic at baseline and until at least study day 7. Concomitant medications included benadryl, heparin, ativan, prilosec, zofran, compazine, lithium, paxil, ceftriaxone (day 6-11), and vancomycin (days 8-11).

Medical Officer Comments: Although not listed as concomitant medications, this patient probably received recent chemotherapy, resulting in neutropenia, and possibly thrombocytopenia. Additionally, she received heparin, which is known to cause heparin-induced thrombocytopenia. Heparin was stopped simultaneously with micafungin, so it would be difficult to attribute the thrombocytopenia to micafungin alone.

Patient 059232 was a 7 year-old Caucasian male with a neuroblastoma, who underwent an autologous bone marrow transplant. A narrative summary was not available for this patient, and information was obtained from a patient profile provided by the applicant. The patient received micafungin 12.5 mg/day for 5 days in study 98-0-043 (febrile, neutropenic pediatric patients with hematologic malignancies or HSCT). The patient had no other baseline conditions reported. Micafungin was stopped after 5 days due to lack of efficacy, and the patient was treated subsequently with amphotericin B, followed by AmBisome®. Thrombocytopenia was reported as a serious adverse event on study day 7, and was considered unrelated to study drug. Epistaxis, gum/oral hemorrhage, and petechiae were reported concurrently. Platelet count was $53 \times 10^9/L$ on enrollment, and was 10, 48, 30, and $20 \times 10^9/L$ on study days 2, 4, 5, and 13, respectively. The patient was neutropenic on study entry, and remained so at least through day 13. Hemoglobin and hematocrit remained stable throughout the monitoring period, at 9.8 g/dL and 29%, respectively. Medications received concurrently with micafungin included mannitol, lasix, hydrocortisone, vancomycin, IL-2, dilaudid, G-CSF, and albumin.

Medical Officer Comments: Although not listed as concomitant medications, this patient obviously had received chemotherapy, resulting in neutropenia. Thrombocytopenia is also a frequent complication of antineoplastic chemotherapy. I would concur that the thrombocytopenia reported in this patient was probably not related to micafungin.

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Patient 249537 was a 3 year-old Caucasian female with acute lymphocytic leukemia, enrolled in study 98-0-043, and received micafungin 32.5 mg/day for 14 days. A narrative summary was not available for this patient, and information was obtained from a patient profile provided by the applicant. Fever and leukopenia were reported reported as a serious adverse events on study day 16, and were considered unrelated to study drug.

Medical Officer Comments: This patient was severely neutropenic at baseline (absolute neutrophil count, ANC of 108 cells/mm³), and throughout the study, declining to an ANC of 0 on study day 10. Neutrophil recovery started on study day 13 (ANC = 40 cells/mm³) and progressed through the end of study (ANC= 437 cells/mm³ on day 21). I would suspect that the neutropenia was related to the patient's underlying leukemia, and treatment with chemotherapy, although none was listed as a concomitant medication.

Pancytopenia

Three serious adverse events of pancytopenia are reviewed below:

Patient 084788 was a 45 year-old Caucasian female with lymphoma, who received an allogeneic bone marrow transplant. She received increasing doses of micafungin from 75 mg/day to 300 mg/day for invasive aspergillosis (pulmonary and brain) for 20 days. The patient received AmBisome® in addition to micafungin. A narrative summary was not available for this patient, and information was obtained from a patient profile provided by the applicant. Pancytopenia was reported as a serious adverse event on study day 5, and was considered unrelated to micafungin. The patient received a large number of concomitant medications, including cefipime for a *Pseudomonas* infection (site not clear from patient profile), ganciclovir for CMV antigenemia, as well as multiple other medications. The patient died on study day 21 due to "infection". A number of other adverse events were reported during treatment, including nausea, arrhythmia, ventricular extra-systoles, decreased prothrombin, esophagitis, graft versus host disease, amnesia, bilirubinemia, tremor, asthenia, confusion, increased alkaline phosphatase, procedural complication, dehydration, hemiplegia, urinary tract infection, pain, sepsis, convulsion, pruritis, respiratory disorder, stupor, and abnormal liver function tests. Hematology laboratory values for this patient are provided in the table below.

Hematology Laboratory Values for Patient 084788*

Study day	WBC x 10 ⁹ /L	Hemoglobin g/dL	Hematocrit %	Platelets x 10 ⁹ /L
Baseline	12.4	8.9	25.5	23
Day 7	1.2	10.9	30.2	5
Day 14	2.8	8.0	32.5	8
Day 20	6.6	7.8	22	26

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

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***Medical Officer Comments:** This case is exceedingly complex, and it would be difficult to attribute pancytopenia to micafungin, although there does appear to be a temporal relationship for leucopenia (worsened during micafungin treatment, and improved after micafungin discontinuation. However, it is not clear whether the patient received chemotherapeutic agents prior to receiving micafungin.*

Patient 466171 was a 44 year-old Caucasian male who was immunosuppressed due to chronic corticosteroid therapy. Significant baseline conditions included diabetes mellitus, emphysema, renal failure, pneumonia, coronary artery disease, and osteoporosis. He received micafungin from 75- 150 mg/day for 10 days for pulmonary aspergillosis in study 98-0-046. He also received concomitant amphotericin B and 5-flucytosine for treatment of the fungal infection. Flucytosine was stopped on study day 6, and amphotericin on day 10. Additional medications received during micafungin treatment included ceftazidime for *Pseudomonas* pneumonia, dopamine and dobutamine (for hypotension), among others. Sepsis was reported as an adverse event on day 10. Pancytopenia was reported as a serious adverse event considered possibly related to micafungin on study day 12; however micafungin had been discontinued on day 10 due to pancytopenia. On day 13, the patient developed a pulmonary hemorrhage, and died on day 14. The primary cause of death was pancytopenia resulting in pulmonary hemorrhage. The death was considered possibly related to micafungin. Laboratory hematology data for this patient is shown in the following table.

Hematology Laboratory Values for Patient 466171*

Study Day	WBC x 10 ⁹	Hemoglobin g/dL	Hematocrit %	Platelets x 10 ⁹
Baseline (-3)	40.3	7.5	22	364
Day 6	21.4	8.1	24	227
Day 10	9.5	7.9	24	27
Day 12	3.4	8.5	27	10
Day 13	2.0	7.4	23	1

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

***Medical Officer Comments:** Clearly this patient developed severe thrombocytopenia and leukopenia during the study, with worsening cell counts after micafungin was stopped. Anemia was present at baseline, and was relatively stable throughout the study. The patient had several potential reasons for pancytopenia, including sepsis, and 5-flucytosine, a drug well-known to cause marrow suppression. Thrombocytopenia to this degree is frequently associated with significant bleeding; however, this patient had pulmonary aspergillosis which is commonly associated with pulmonary hemorrhage. In the medical officer's opinion, too many confounding factors were present to attribute pancytopenia to micafungin.*