

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 16. Common* Adverse Events (FAS) (Applicant's Table 9)

Body System Preferred Term	Micafungin Dose Level (mg/day)					
	n (%)					
	12.5 (n=26)	25.0 (n=22)	50.0 (n=26)	75.0 (n=22)	100.0 (n=24)	Total (n=120)
No. with Adverse Event	15 (57.7%)	16 (72.7%)	20 (76.9%)	18 (81.8%)	21 (87.5%)	90 (75.0%)
Body As A Whole						
Fever	0 (0.0%)	3 (13.6%)	3 (11.5%)	3 (13.6%)	9 (37.5%)	18 (15.0%)
Chills	0 (0.0%)	1 (4.5%)	2 (7.7%)	1 (4.5%)	3 (12.5%)	7 (5.8%)
Abdominal pain	1 (3.8%)	1 (4.5%)	0 (0.0%)	2 (9.1%)	1 (4.2%)	5 (4.2%)
Sepsis	0 (0.0%)	2 (9.1%)	2 (7.7%)	0 (0.0%)	1 (4.2%)	5 (4.2%)
Back pain	0 (0.0%)	0 (0.0%)	2 (7.7%)	2 (9.1%)	0 (0.0%)	4 (3.3%)
Cellulitis	2 (7.7%)	1 (4.5%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	4 (3.3%)
Cardiovascular System						
Phlebitis	1 (3.8%)	0 (0.0%)	1 (3.8%)	1 (4.5%)	2 (8.3%)	5 (4.2%)
Tachycardia	0 (0.0%)	1 (4.5%)	1 (3.8%)	0 (0.0%)	3 (12.5%)	5 (4.2%)
Chest pain	0 (0.0%)	0 (0.0%)	2 (7.7%)	1 (4.5%)	0 (0.0%)	3 (2.5%)
Digestive System						
Diarrhea	3 (11.5%)	1 (4.5%)	3 (11.5%)	7 (31.8%)	3 (12.5%)	17 (14.2%)
Vomiting	2 (7.7%)	2 (9.1%)	3 (11.5%)	2 (9.1%)	6 (25.0%)	15 (12.5%)
Nausea	1 (3.8%)	4 (18.2%)	3 (11.5%)	1 (4.5%)	4 (16.7%)	13 (10.8%)
LFT abnormal	3 (11.5%)	4 (18.2%)	2 (7.7%)	0 (0.0%)	0 (0.0%)	9 (7.5%)
Dyspepsia	0 (0.0%)	0 (0.0%)	2 (7.7%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
Rectal Disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	2 (1.7%)
Hemic & Lymphatic System						
Anemia	0 (0.0%)	2 (9.1%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	4 (3.3%)
Leukopenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	2 (1.7%)

Patient base: all patients who received at least 1 dose of micafungin (full analysis set).

*Common: experienced by at least 5% of patients in any dose group.

Alk phos increased: alkaline phosphatase increased

LFT increased: liver function test increased

Pul Tb reactivated: pulmonary tuberculosis reactivated

Within a body system, patients may report more than one event.

SGOT: serum glutamic oxaloacetic transaminase. (AST)

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 16. (continued) Common Adverse Events (FAS) (Applicant's Table 9)

Body System Preferred Term	FK463 Dose Levels (mg/day)					
	n (%)					
	12.5 (n=26)	25.0 (n=22)	50.0 (n=26)	75.0 (n=22)	100.0 (n=24)	Total (n=120)
Metabolic & Nutritional						
Alk phos increased	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	2 (8.3%)	3 (2.5%)
Hypokalemia	0 (0.0%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	3 (2.5%)
Hyperkalemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.3%)	2 (1.7%)
SGOT increased	0 (0.0%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
Nervous System						
Headache	2 (7.7%)	4(18.2%)	3 (11.5%)	3 (13.6%)	4(16.7%)	16(13.3%)
Nervousness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.3%)	2 (1.7%)
Thinking abnormal	0 (0.0%)	0 (0.0%)	2 (7.7%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
Respiratory System						
Pneumonia	2 (7.7%)	1 (4.5%)	2 (7.7%)	2 (9.1%)	2 (8.3%)	9 (7.5%)
Cough increased	0 (0.0%)	0 (0.0%)	1 (3.8%)	2 (9.1%)	2 (8.3%)	5 (4.2%)
Pul Tb reactivated	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	4(16.7%)	5 (4.2%)
Pharyngitis	0 (0.0%)	0 (0.0%)	2 (7.7%)	0 (0.0%)	1 (4.2%)	3 (2.5%)
Respiratory disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.3%)	2 (1.7%)
Skin & Appendages						
Rash	0 (0.0%)	1 (4.5%)	3 (11.5%)	2 (9.1%)	2 (8.3%)	8 (6.7%)
Special Senses						
Otitis media	2 (7.7%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	3 (2.5%)

Patient base: all patients who received at least 1 dose of micafungin (full analysis set).

*Common: experienced by at least 5% of patients in any dose group.

Alk phos increased: alkaline phosphatase increased

LFT increased: liver function test increased

Pul Tb reactivated: pulmonary tuberculosis reactivated

Within a body system, patients may report more than one event.

SGOT: serum glutamic oxaloacetic transaminase. (AST)

Drug-Related Adverse Events

A total of 35/120 (29.2%) patients had an adverse event considered possibly or probably related to micafungin. The most common drug-related adverse events were vomiting (6.7%), abnormal liver function tests (5.8%), nausea (5.0%), and rash (3.3%). Drug-related adverse events are listed in the table below.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 17. Incidence of Drug-Related Adverse Events (FAS) (Applicant's Table 13.5.2.1)

COSTART BODY SYSTEM (1)	COSTART TERM	FK463 DOSE LEVEL					TOTAL (N=120)
		12.5 mg/DAY (N=26)	25.0 mg/DAY (N=22)	50.0 mg/DAY (N=26)	75.0 mg/DAY (N=22)	100.0 mg/DAY (N=24)	
ANY AE		7(26.9%)	8(36.4%)	8(30.8%)	3(13.6%)	9(37.5%)	35(29.2%)
BODY AS A WHOLE	ANY AE	1(3.8%)	0	2(7.7%)	1(4.5%)	2(8.3%)	6(5.0%)
	CHILLS	0	0	2(7.7%)	0	0	2(1.7%)
	ABDOMINAL PAIN	1(3.8%)	0	0	0	0	1(0.8%)
	ALLERGIC REACTION	0	0	0	0	1(4.2%)	1(0.8%)
	FEVER	0	0	0	0	1(4.2%)	1(0.8%)
	FLU SYNDROME	0	0	0	1(4.5%)	0	1(0.8%)
CARDIOVASCULAR SYSTEM	ANY AE	1(3.8%)	2(9.1%)	2(7.7%)	0	2(8.3%)	7(5.8%)
	VASCULITATION	1(3.8%)	0	1(3.8%)	0	1(4.2%)	3(2.5%)
	HYPERTEMBION	0	1(4.5%)	1(3.8%)	0	0	2(1.7%)
	CHEST PAIN	0	0	1(3.8%)	0	0	1(0.8%)
	HYPOTENSION	0	0	0	0	1(4.2%)	1(0.8%)
	PALPITATION	0	0	1(3.8%)	0	0	1(0.8%)
	TACHYCARDIA	0	1(4.5%)	0	0	0	1(0.8%)
	VASCULAR HEADACHE	0	0	1(3.8%)	0	0	1(0.8%)
DIGESTIVE SYSTEM	ANY AE	5(19.2%)	4(18.2%)	5(19.2%)	1(4.5%)	4(16.7%)	19(15.8%)
	VOMITING	2(7.7%)	2(9.1%)	2(7.7%)	0	3(12.5%)	9(7.7%)
	LIVER FUNCTION TESTS ABNORMAL	3(11.5%)	2(9.1%)	2(7.7%)	0	0	7(5.8%)
	NAUSEA	1(3.8%)	1(4.5%)	1(3.8%)	0	1(4.2%)	6(5.0%)
	DIARRHEA	1(3.8%)	0	1(3.8%)	0	0	2(1.7%)
	CONSTIPATION	0	0	1(3.8%)	0	0	1(0.8%)
	DYSPEPSIA	0	0	1(3.8%)	0	0	1(0.8%)
	INJECTION SITE REACTION	1(3.8%)	0	0	0	0	1(0.8%)
METABOLIC AND NUTRITIONAL DISORDERS	ANY AE	0	2(9.1%)	1(3.8%)	0	1(4.2%)	4(3.3%)
	SODIUM INCREASED	0	2(9.1%)	0	0	0	2(1.7%)
	ALKALINE PHOSPHATASE INCREASED	0	0	0	0	1(4.2%)	1(0.8%)
	THIRST	0	0	1(3.8%)	0	0	1(0.8%)
	NEUROUS SYSTEM	0	1(4.5%)	3(11.5%)	0	2(8.3%)	6(5.0%)
	DIZZINESS	0	0	1(3.8%)	0	1(4.2%)	2(1.7%)
	HEADACHE	0	1(4.5%)	1(3.8%)	0	0	2(1.7%)
	THINKING ABNORMAL	0	0	2(7.7%)	0	0	2(1.7%)

(1) WITHIN A BODY SYSTEM PATIENTS MAY REPORT MORE THAN ONE ADVERSE EVENT.
 (2) POSSIBLE OR PROBABLE.

COSTART BODY SYSTEM (1)	COSTART TERM	FK463 DOSE LEVEL					TOTAL (N=120)
		12.5 mg/DAY (N=26)	25.0 mg/DAY (N=22)	50.0 mg/DAY (N=26)	75.0 mg/DAY (N=22)	100.0 mg/DAY (N=24)	
NEUROUS SYSTEM	ANXIETY	0	0	1(3.8%)	0	0	1(0.8%)
	NEUROGRASS	0	0	0	0	1(4.2%)	1(0.8%)
SKIN AND APPENDAGES	ANY AE	0	0	3(11.5%)	2(9.1%)	0	5(4.2%)
	RASH	0	0	3(11.5%)	1(4.5%)	0	4(3.3%)
	SWELING	0	0	1(3.8%)	1(4.5%)	0	2(1.7%)
	PRURITUS	0	0	0	1(4.5%)	0	1(0.8%)
SPECIAL SENSES	ANY AE	0	0	2(7.7%)	0	0	2(1.7%)
	OTITIS MEDIA	0	0	1(3.8%)	0	0	1(0.8%)
	TASTE PERVERSION	0	0	1(3.8%)	0	0	1(0.8%)

Medical Officer Comments: No obvious relationship between micafungin dose and related adverse event was noted.

Severe Adverse Events Related to Micafungin

Most adverse events were considered mild-moderate in intensity. Four patients had severe adverse events considered to be related to micafungin. These events are shown in the following table.

BEST POSSIBLE COPY

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 18. Severe Drug-Related Adverse Events (FAS) (Applicant's Table 10, study report, 24 April, 2004))

Patient Number	Dose Level	Event	Day of Onset	Outcome
101001	50.0 mg	Rash	13	Resolved Day 16
101018	50.0 mg	Increased LFTs	7	Discontinued FK463 on Day 9
101020	50.0 mg	Sweating	1	Resolved Day 1
		Anxiety	5	Persistent condition
301004	12.5 mg	Increased LFTs	7	Persistent condition

Patient base: all patients who received at least 1 dose of FK463 (full analysis set).

LFTs: liver function tests.

Medical Officer Comments: Patient 101001 (listed above) developed a severe rash which resolved without discontinuation of micafungin, arguing against a relationship to micafungin for that event. Because the event was not considered serious, no narrative summary is available from the applicant. Liver function test abnormalities will be discussed below in section on hepatic safety.

Serious Adverse Events

Serious adverse events occurred in a total of 18/120 (15%) patients, and are listed in the following table. The most common serious adverse event was pneumonia, which occurred in 3 patients. Most serious adverse events occurred in one patient each, with the exception of sepsis, diarrhea, gastrointestinal hemorrhage, and convulsion, which each occurred in two patients.

**APPEARS THIS WAY
ON ORIGINAL**

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

Table 19. All Serious Adverse Events (FAS) (Applicant's Table 13.5.3.1, study report, 24 April, 2004)

COSTART BODY SYSTEM (1)	COSTART TERM	FK463 DOSE LEVEL					TOTAL (N=120)
		12.5 mg/DAY (N=26)	25.0 mg/DAY (N=22)	50.0 mg/DAY (N=26)	75.0 mg/DAY (N=22)	100.0 mg/DAY (N=24)	
ANY AE		3 (11.5%)	3 (13.6%)	4 (15.4%)	4 (18.2%)	4 (16.7%)	18 (15.0%)
BODY AS A WHOLE	ANY AE	0	2 (9.1%)	0	2 (9.1%)	2 (8.3%)	6 (5.0%)
	SEPSIS	0	1 (4.5%)	0	0	1 (4.2%)	2 (1.7%)
	ABSCESS	0	0	0	1 (4.5%)	0	1 (0.8%)
	AIDS	0	1 (4.5%)	0	0	0	1 (0.8%)
	ASTHENIA	0	0	0	1 (4.5%)	0	1 (0.8%)
	TUBERCULOSIS REACTIVATED	0	0	0	0	1 (4.2%)	1 (0.8%)
CARDIOVASCULAR SYSTEM	ANY AE	0	0	1 (3.8%)	0	0	1 (0.8%)
	DEEP THROMBOPHLEBITIS	0	0	1 (3.8%)	0	0	1 (0.8%)
DIGESTIVE SYSTEM	ANY AE	2 (7.7%)	0	0	1 (4.5%)	1 (4.2%)	4 (3.3%)
	DIARRHEA	1 (3.8%)	0	0	0	1 (4.2%)	2 (1.7%)
	GASTROINTESTINAL HEMORRHAGE	1 (3.8%)	0	0	1 (4.5%)	0	2 (1.7%)
	GASTROENTERITIS	0	0	0	0	1 (4.2%)	1 (0.8%)
	VOMITING	0	0	0	0	1 (4.2%)	1 (0.8%)
HEMIC AND LYMPHATIC SYSTEM	ANY AE	0	0	0	1 (4.5%)	0	1 (0.8%)
	LEUKOPENIA	0	0	0	1 (4.5%)	0	1 (0.8%)
METABOLIC AND NUTRITIONAL DISORDERS	ANY AE	1 (3.8%)	0	0	0	1 (4.2%)	2 (1.7%)
	DEHYDRATION	1 (3.8%)	0	0	0	0	1 (0.8%)
	HYPOKALEMIA	0	0	0	0	1 (4.2%)	1 (0.8%)
NERVOUS SYSTEM	ANY AE	0	0	1 (3.8%)	1 (4.5%)	0	2 (1.7%)
	CONVULSION	0	0	1 (3.8%)	1 (4.5%)	0	2 (1.7%)
	COMA	0	0	0	1 (4.5%)	0	1 (0.8%)
RESPIRATORY SYSTEM	ANY AE	1 (3.8%)	0	2 (7.7%)	2 (9.1%)	1 (4.2%)	6 (5.0%)
	PNEUMONIA	1 (3.8%)	0	1 (3.8%)	1 (4.5%)	0	3 (2.5%)
	PULMONARY EMBOLUS	0	0	0	1 (4.5%)	0	1 (0.8%)
	PULMONARY TUBERCULOSIS REACTIVATED	0	0	1 (3.8%)	0	0	1 (0.8%)
	RESPIRATORY FAILURE	0	0	0	0	1 (4.2%)	1 (0.8%)
UROGENITAL SYSTEM	ANY AE	0	1 (4.5%)	0	0	0	1 (0.8%)
	KIDNEY FAILURE	0	1 (4.5%)	0	0	0	1 (0.8%)

(1) WITHIN A BODY SYSTEM PATIENTS MAY REPORT MORE THAN ONE ADVERSE EVENT.

BEST POSSIBLE COPY

Drug-Related Serious Adverse Events

Only 1 patient had a serious adverse event considered to be related to micafungin. This patient received 12.5 mg/day micafungin and developed diarrhea, and is described in narrative summary below.

Narrative Summaries for Patient with Serious Drug-Related Adverse Events

Patient 301021 was a 32 year old black female with HIV and a CD4 count of 68 cells/mm³, who received micafungin 12.5 mg/day for 15 days for esophageal candidiasis. Baseline conditions included anemia, cachexia, night sweats, cough, and folliculitis. The patient developed moderate diarrhea and dehydration, described as potentially life-threatening, on day 1. Both adverse events (diarrhea and dehydration) resolved with intravenous rehydration and an antidiarrheal agent by day 8. At the end-of-therapy, the patient was noted to have persistent esophageal mucosal lesions and symptoms of EC (i.e. treatment failure). The patient was found dead on day 24. Primary cause of death was listed as HIV wasting, with esophageal candidiasis listed as a contributing factor. The death was considered unrelated to micafungin.

Medical Officer Comments: Diarrhea is frequently associated with HIV wasting and this patient had diarrhea at baseline, so it would be difficult to attribute the diarrhea solely to micafungin, although it may have contributed to its worsening. The patient continued

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

micafungin despite the diarrhea, and whether the diarrhea would have improved by discontinuation of micafungin is unknown, but would have been helpful in determining causality.

Discontinuations due to Adverse Events

Sixteen of 120 (13.3%) patients had adverse events resulting in micafungin discontinuation. No relationship between micafungin dose and adverse events resulting in discontinuation was observed. Two patients had an adverse event considered related to micafungin which resulted in micafungin discontinuation (patient 5014004 with allergic reaction, and patient 101018 with abnormal liver function tests). These patients are described in narrative summaries below.

Table 20. Adverse Events Resulting in Micafungin Discontinuation (FAS) (Applicant's Table 13.5.4.1 Study Report, 24 April, 2004)

COSTART BODY SYSTEM (1)	COSTART TERM	FKM63 DOSE LEVEL					TOTAL (N=120)
		12.5 ng/DAY (N=26)	25.0 ng/DAY (N=22)	50.0 mg/DAY (N=26)	75.0 mg/DAY (N=22)	100.0 mg/DAY (N=24)	
ANY AE		2 (7.7%)	2 (9.1%)	5 (19.2%)	3 (13.6%)	4 (16.7%)	16 (13.3%)
BODY AS A WHOLE	ANY AE	0	1 (4.5%)	1 (3.8%)	2 (9.1%)	2 (8.3%)	6 (5.0%)
	ABSCESS	0	0	0	1 (4.5%)	0	1 (0.8%)
	AIDS	0	1 (4.5%)	0	0	0	1 (0.8%)
	ALLERGIC REACTION	0	0	0	0	1 (4.2%)	1 (0.8%)
	ASTHENIA	0	0	0	1 (4.5%)	0	1 (0.8%)
	SEPSIS	0	0	1 (3.8%)	0	0	1 (0.8%)
	TUBERCULOSIS REACTIVATED	0	0	0	0	1 (4.2%)	1 (0.8%)
CARDIOVASCULAR SYSTEM	ANY AE	0	0	1 (3.8%)	0	0	1 (0.8%)
	DEEP THROMBOPHLEBITIS	0	0	1 (3.8%)	0	0	1 (0.8%)
DIGESTIVE SYSTEM	ANY AE	1 (3.8%)	0	1 (3.8%)	0	1 (4.2%)	3 (2.5%)
	DIARRHEA	0	0	0	0	1 (4.2%)	1 (0.8%)
	GASTROENTERITIS	0	0	0	0	1 (4.2%)	1 (0.8%)
	GASTROINTESTINAL HEMORRHAGE	1 (3.8%)	0	0	0	0	1 (0.8%)
	LIVER FUNCTION TESTS ABNORMAL	0	0	1 (3.8%)	0	0	1 (0.8%)
	VOMITING	0	0	0	0	1 (4.2%)	1 (0.8%)
NERVOUS SYSTEM	ANY AE	0	0	1 (3.8%)	1 (4.5%)	0	2 (1.7%)
	CONVULSION	0	0	1 (3.8%)	1 (4.5%)	0	2 (1.7%)
	CONFUSION	0	0	0	1 (4.5%)	0	1 (0.8%)
RESPIRATORY SYSTEM	ANY AE	1 (3.8%)	0	1 (3.8%)	1 (4.5%)	1 (4.2%)	4 (3.3%)
	PNEUMONIA	1 (3.8%)	0	1 (3.8%)	1 (4.5%)	0	3 (2.5%)
	RESPIRATORY FAILURE	0	0	0	0	1 (4.2%)	1 (0.8%)
UROGENITAL SYSTEM	ANY AE	0	1 (4.5%)	0	0	0	1 (0.8%)
	KIDNEY FAILURE	0	1 (4.5%)	0	0	0	1 (0.8%)

BEST POSSIBLE COPY

Medical Officer Comments: Except for convulsions which occurred in 2 patients, and pneumonia, which occurred in 3 patients, other adverse events in this category occurred in only 1 patient each. Brief narrative summaries for these patients are provided below. Patients in whom micafungin was discontinued, and died during the study are described under the section on deaths below.

Narrative Summaries for Patients who Discontinued Micafungin due to Adverse Events

Patient 101023 was a 29 year-old black female with HIV, and a CD₄ count of 22 cells/mm³. The patient was not receiving antiretroviral therapy. Other conditions at baseline included anemia, cough, rash, weight loss, and pulmonary tuberculosis. The patient received micafungin 50 mg/day for 5 days for EC. Micafungin was discontinued on day 6 due to confusion, and a seizure. This adverse event was considered unrelated to micafungin.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Medical Officer Comments: No further information was provided in the narrative summary regarding etiology of seizure other than the patient did not have meningismus or focal neurologic deficits at that time.

Patient 401012 was an 18 year old black female with HIV, and a CD⁴ count of 60 cells/mm³. She was not receiving antiretroviral therapy. Conditions at baseline included hypotension, weight loss, anorexia, and anemia, and seizures for which she received phenytoin. She received micafungin 75 mg/day for 2 days. Micafungin was discontinued on day 3 due to a seizure, which resolved without residual effects. The seizure was considered unrelated to micafungin. This patient also experienced a pulmonary embolus, reported on day 2.

Medical Officer Comments: This patient had a history of seizures at baseline, so it seems unlikely that this events was related to micafungin.

Patient 101010 was a 26 year-old black female with HIV, and a CD₄ count of 40 cells/mm³. The patient was not receiving concomitant antiretroviral therapy. Baseline conditions included lymphadenopathy, asthma, anemia, hypotension, weight loss, and an unspecified lung disorder. She received micafungin 50 mg/day for 10 days. Micafungin was discontinued on study day 10 due to sepsis. Sepsis was not considered related to micafungin, and was ongoing at the end-of-study (2 weeks post-treatment). Other adverse events in this patient included bronchitis, nausea, and vomiting (day 3), and diarrhea (day 10).

Medical Officer Comment: I would agree that sepsis is not likely related to micafungin, although the source of sepsis is not provided in the patient narrative.

Patient 101018 was a 35 year-old black female with HIV and a CD₄ count of 87 cells/mm³. The patient was not receiving antiretroviral therapy. Concurrent baseline conditions included anemia, lymphadenopathy, hypotension, cachexia, nausea, diarrhea, tachycardia, hyperventilation, vomiting, abdominal pain, and fever. She received micafungin 50 mg/day for esophageal candidiasis for 9 days. Micafungin was discontinued after the 9th dose due to increased AST, and ALT, which were considered **possibly related** to micafungin. Other adverse events included increased alkaline phosphatase. The patient was also receiving isoniazid, rifampin, pyrazinamide and ethambutol, cotrimoxazole (bactrim), and paracodein. The table below shows hepatic laboratory values for this patient.

Hepatic Laboratory Values for Patient 101018

Study Day	AST (U/L)	ALT (U/L)	Total Bilirubin (mg/dL)	Alkaline phosphatase (U/L)
Baseline	32	6	0.4	49
Day 7	648	205	0.6	133
Day 10	370	208	0.6	305
Day 19	41	43	0.6	141

Medical Officer Comments: Although this case is confounded by use of antituberculous medications, some of which have been associated with transaminase elevation (isoniazid,

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

rifampin, and pyrazinamide), AST and ALT, levels improved within a day of stopping micafungin. Therefore I would concur with the investigator in concluding that the transaminase elevations were possibly related to micafungin.

Patient 301009 was a 42 year-old black female with HIV, and a CD₄ count of 17 cells/mm³. The patient was not receiving antiretroviral therapy. Baseline conditions included gastritis, duodenitis, anemia, and syphilis. The patient received micafungin 12.5 mg/day for esophageal candidiasis for 4 days. On day 4, micafungin was discontinued due to gastrointestinal bleeding and anemia, with the hemoglobin dropping from 11 mg/dL to 3 mg/dL at that time. The narrative summary states that the gastrointestinal bleeding was due to diffuse gastritis. Micafungin was not considered related to these events. Diarrhea was also reported on study day 4.

Medical Officer Comments: This patient had baseline gastritis and anemia, so the gastrointestinal bleeding and resultant anemia was not likely related to micafungin. A review of the laboratory database revealed only mild thrombocytopenia and baseline, and during treatment. Platelet count was $123 \times 10^9/L$, a level unlikely to precipitate gastrointestinal bleeding.

Patient 101003 was a 22 year-old black female with HIV, and a CD₄ count of 15 cells/mm³. She was not receiving antiretroviral therapy. Baseline conditions included fever, cachexia, anemia, pneumonia, diarrhea, and lymphadenopathy. She received micafungin 50 mg/day for 1 day. Micafungin was discontinued on day 2 due to development of a pulmonary embolism, which was considered unrelated to micafungin.

Medical Officer Comments: This patient did not have any known conditions predisposing to deep venous thrombosis, and secondary pulmonary embolism, except for HIV, which has been associated with the lupus anticoagulant, which is associated with venous and arterial thrombosis. Given the 2 day time course between starting micafungin and development to pulmonary embolus, I would agree that this event was not likely related to micafungin.

Patient 501004 was a 36 year-old black female with HIV, and a CD₄ count of 10 cells/mm³. Baseline conditions included subcutaneous nodules, lymphadenopathy, anemia, and cachexia. She was not receiving antiretroviral therapy. For EC, micafungin was administered at a dose of 100 mg/day for 12 days, and was discontinued on day 12 due to an allergic reaction described as erythema multiforme. A skin biopsy was not obtained. Concurrent medications included pregamol, vitamin B and vitamin C. Urticaria was also reported on study day 12. The investigator considered erythema multiforme to be **probably related** to micafungin.

Medical Officer Comments: Erythema multiforme can be a serious condition involving the skin and mucous membranes, and requiring systemic steroids for treatment. This reaction was most likely related to micafungin because the patient was not receiving any other medications associated with erythema multiforme, although this condition has been associated with other infections such as Herpes simplex, but no other infections are noted in the narrative summary.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

No further information was available as to whether the skin lesions resolved after stopping micafungin.

Patient 501009 was a 23 year-old female with HIV, and a CD₄ count of 13 cells/mm³. The patient was not receiving antiretroviral therapy. Baseline conditions included hypocalcemia, anemia, electrolyte abnormalities, tachycardia, hypokalemia, and gastroenteritis. She received micafungin 100 mg/day for 8 days for treatment of EC. The patient developed a fever on day 5, and was hospitalized on day 7 due to severe vomiting and diarrhea. Micafungin was discontinued on day 8 due to severe diarrhea. The patient was also noted to have a urinary tract infection, pyelonephritis, and gastroenteritis, headache and neck pain. Diarrhea resolved on day 11, and was considered unrelated to micafungin. Additional medications received starting day 8 included augmentin, Imodium, septran (trimethoprim sulfamethoxazole), amoxil and ciprobay (ciprofloxacin), loperamide, maxolon, pregamol, slow K (potassium), titralac, and panado.

Medical Officer Comments: It would be difficult to attribute the diarrhea or vomiting to micafungin given the patient's underlying gastroenteritis, urinary tract infection and pyelonephritis.

Deaths

A total of 13 deaths occurred among 120 patients (10.8%) in this study. Three patients died during treatment with micafungin; while 10 died during the post-treatment period. None of the deaths were attributed to micafungin. The primary cause of death for these patients is shown in the table below. Brief narrative summaries are also provided in the section below.

APPEARS THIS WAY
ON ORIGINAL

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

Table 21. Summary of Deaths During Study (Applicant's Table 11, study summary, 24 April, 2004)

Patient Number	Age/ Sex	Related to Study Drug	Related to Fungal Infection	Study Day	Primary Cause of Death
12.5 mg/day					
301015	44/M	No	No	11	Pneumonia
301024	31/F	No	No	22	Progress of AIDS
301021	32/F	No	Yes	24	HIV wasting
25.0 mg/day					
201017	37/M	No	No	22	Probable septicemia
201007	39/M	No	No	9	Renal failure
201019	34/M	No	No	5	Terminal AIDS
50.0 mg/day					
101014	38/M	No	No	6	Bilateral pneumonia
101006	30/M	No	No	5	Pulmonary tuberculosis Immune deficiency
75.0 mg/day					
401007	30/M	No	No	13	AIDS
401015	43/F	No	No	5	Bilateral pneumonia
100.0 mg/day					
501020	30/M	No	No	3	Tuberculosis meningitis
501010	25/F	No	No	22	Septicemia
501021	34/F	No	No	9	Septicemia

Patient base: all patients who received at least 1 dose of FK463 (full analysis set).

During treatment through 30 days posttreatment.

AIDS: acquired immune deficiency syndrome. HIV: human immunodeficiency virus.

M=male, F=female.

Medical Officer Comments: Except for one death attributed to renal failure, all of the deaths in this study were related to infection (tuberculosis, pneumonia, sepsis, or progression of AIDS, or AIDS wasting syndrome). This is not unexpected in this population of severely immunosuppressed patients with advanced HIV disease, who were not receiving antiretroviral therapy.

Narrative Summaries for Patients who died during the Study

Patient 301015 was a 44 year-old black male with HIV. A CD₄ count was not obtained, and he was not receiving antiretroviral therapy. At baseline, the patient had pneumonia, anemia and elevated liver enzymes. Alkaline phosphatase was > 2.5 x ULN. The patient received micafungin 12.5 mg/day for 10 days. The patient was discontinued due to lack of efficacy at 10 days (day 7 evaluation revealed persistent symptoms of EC). On day 10, the patient developed fever and tachypnea, and was diagnosed with pneumonia. The patient died on day 11 due to pneumonia. The death was not considered related to micafungin.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Patient 301024 was a 31 year-old "colored" HIV-positive female with a CD₄ count of 73 cells/mm³. She was not receiving antiretroviral therapy. Baseline conditions included lymphadenopathy, anemia, and thrombocytopenia. She received micafungin 12.5 mg/day for EC for a total of 14 days. The only adverse event reported was a severe ear infection which resolved on day 20. The patient was admitted to hospice care during the 2-week post-treatment period due to increased weakness, and died on day 22. The cause of death was progression of AIDS, and was not considered related to micafungin.

Patient 301021 was a 32 year-old black female with HIV and a CD₄ count of 8 cells/mm³. See narrative summary for this patient in the section above on serious drug-related adverse events.

Patient 201017 was a 37 year-old black male with HIV and a CD₄ count of 116 cells/mm³. This patient was not receiving antiretroviral therapy, but was receiving isoniazid, rifampin, and pyrazinamide for pulmonary tuberculosis at baseline. He received micafungin 25 mg/day for 13 days for EC. During micafungin treatment, the patient developed nausea and vomiting (day 8), fever (day 2), and "septicemia" (day 7). The nausea was considered possibly related to micafungin by the investigator. The patient received amoxicillin, gentamicin, and penicillin for treatment of "septicemia". Micafungin was stopped on day 13 because the patient refused to continue treatment. On day 15, he was noted to have increasing dyspnea, fever, hypotension, and tachycardia. His condition continued to deteriorate, and he died on day 22. Primary cause of death was probably septicemia, and secondary causes included pulmonary tuberculosis, pneumonia, and AIDS. The death was considered unrelated to micafungin.

Patient 201007 was a 39 year-old black male with HIV and a CD₄ count of 22 cells/mm³. He was not receiving antiretroviral therapy, and had no other significant baseline conditions listed, although at baseline, serum creatinine was 3.3 mg/dL. He received micafungin 25 mg/day for 5 days for esophageal candidiasis. Micafungin was discontinued after the 5th dose because of acute renal failure. Serum creatinine on days 3 and 8 was 1.7 mg/dL. Other adverse events included increased liver function tests on day 6 (see table below), and nausea (day 2). Additionally, the patient became leukopenic during the study (WBC 5.8 x 10⁹/L at baseline, and 1.7 x 10⁹/L on day 8), and developed worsening anemia (hemoglobin 9.2 g/dL at baseline and 7.6 g/dL by day 8). Platelet count was 28 x 10⁹ at baseline, and 22 x 10⁹ on day 8. The patient died on day 9 due to acute renal failure and progression of AIDS. The death was considered unrelated to micafungin.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Renal and Hepatic Laboratory Values for Patient 201007

Study Day	AST (U/L)	ALT (U/L)	Total bilirubin (mg/dL)	Alkaline phosphatase (U/L)	BUN mg/dL	Creatinine (mg/dL)
Baseline	83	73	1.1	79	54	3.3
Day 7	280	174	1.2	78	29	1.7
Day 8	48	47	3.2	54	22	1.7

Medical Officer Comments: This patient's renal function improved from baseline by study day 7; however, because no laboratory data is available for the day of micafungin discontinuation, it is not clear whether renal function worsened with micafungin, and then improved after discontinuation. Although not listed as an adverse event, this patient may have had mild hemolysis, given the worsening anemia, and rise in total bilirubin. I would agree that this death was probably not related to micafungin.

Patient 201019 was a 34 year-old black male with HIV and a CD₄ count of 5 cells/mm³. Significant baseline conditions included disseminated tuberculosis, anemia, tremor, molluscum contagiosum, and lymphadenopathy. Medications prior to enrollment included isoniazid, rifampin, and pyrazinamide. He was not receiving antiretroviral therapy. He received micafungin 25 mg/day for 5 days for EC. The patient died on day 5 due to advanced AIDS and disseminated tuberculosis. The death was not considered related to micafungin.

Patient 101014 was a 38 year-old black male previously diagnosed with AIDS. A baseline CD₄ count was not obtained, and the patient was not receiving antiretroviral therapy. Baseline conditions included leukopenia, pneumonia, anorexia, hepatomegaly, and lymphadenopathy. He received micafungin 50 mg/day for 6 days for EC. The patient was hospitalized on day 6 for bilateral pneumonia and persistent anemia. He received penicillin, and cefuroxime, as well as a transfusion of packed red blood cells, but died the same day due to bilateral pneumonia, AIDS, and leukopenia. WBC was $1.7 \times 10^9/L$ at baseline, and $1.6 \times 10^9/L$ on study day 3 hemoglobin was 8.5 g/dL and 7.2 g/dL at baseline and day 3, respectively. The death was considered unrelated to micafungin.

Medical Officer Comment: This patient was leukopenic at baseline, and the WBC did not change significantly by study day 3. However, no additional laboratory values were available to assess the magnitude of leukopenia prior to death in this patient, so it is unknown whether leukopenia worsened significantly during treatment.

Patient 101006 was a 30-year old black male with HIV and pulmonary tuberculosis, cachexia, anemia, dehydration, lymphadenopathy, and asthenia at baseline. No CD₄ count was obtained, and the patient was not receiving antiretroviral therapy. The patient received micafungin 50 mg/day for 2 days, and withdrew from the study at that time. Concomitant medications included isoniazid, rifampin, and pyrazinamide. The patient developed pneumonia and disorientation on day, and died on day 5. The causes of death were pulmonary tuberculosis, immune deficiency and pneumonia. The death was considered unrelated to study drug.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Patient 401007 was a 30 year-old black male with HIV and a CD₄ count of 6 cells/mm³. Baseline conditions included pulmonary tuberculosis, lymphadenopathy, increased AST, anemia, and fever. The patient was not receiving antiretroviral therapy, but was taking antituberculous medications. He received micafungin 75 mg/day for 13 days for EC. Adverse events during treatment included leukopenia (day 3), anemia (day 7), nausea, vomiting, and rash (day 11), and abdominal abscess (day 13). None of these events were considered related to micafungin. The patient died on day 13 due to AIDS and abdominal tuberculosis. The death was not considered related to micafungin.

Patient 401015 was a 43 year-old black female with HIV and a CD₄ count of 6 cells/mm³. Significant conditions at baseline included fever elevated liver function tests, extrapyramidal syndrome, lymphadenopathy, anemia, abdominal pain, pneumonia, and hypotension. She was not receiving antiretroviral therapy. Micafungin was administered at a dose of 75 mg/day for EC for a total of 4 days. Adverse events included fever and cough (day 1), severe asthenia (day 4), bilateral pneumonia (day 5). The patient was started empirically on Rifater® (day 4) for pulmonary tuberculosis, and on bactrim day 5 for pneumonia. She died on day 5 due to bilateral pneumonia and progression of AIDS. The death was considered unrelated to micafungin.

Patient 501020 was a 30 year-old black male with HIV and a CD₄ count of 23 cells/mm³, who was receiving antiretroviral therapy. Baseline conditions included pulmonary tuberculosis, abdominal pain, nausea, vomiting, lymphadenopathy, headache, neck pain, confusion, hypertension, and fever. He received micafungin 100 mg/day for 3 days for EC. On study day 1, the patient developed encephalopathy due to meningitis, which was thought to be related to progressive tuberculosis. The patient died on day 3 due to presumed tuberculous meningitis. The death was not considered related to micafungin.

Patient 501010 was a 25 year-old black male with HIV and a CD₄ count of 70 cells/mm³. Baseline conditions included nausea, hypotension, vomiting, tachycardia, cachexia, ascites, anemia, diarrhea, and lymphadenopathy. He was not receiving antiretroviral therapy. He received micafungin 100 mg/day for 12 days for EC. Adverse events during treatment included fever (day 2), tachypnea (day 4), tremor (day 5), increased alkaline phosphatase (day 7). The patient subsequently developed "septicemia" secondary to gastroenteritis, and died on day 22 due to septicemia, gastroenteritis, and rapid progression of AIDS. The death was considered unrelated to micafungin.

Patient 501021 was a 34 year-old black female with HIV and a CD₄ count of 79 cells/mm³. Conditions at baseline included vomiting, nausea, fever, cachexia, anemia, pneumonia, and tachycardia. She was not receiving antiretroviral therapy. She received micafungin 100 mg/day for 8 days for EC. Adverse events during the study period included phlebitis at the infusion site and hyperkalemia (day 4), sinusitis, dyspnea, wheezing, and sepsis (day 8), and respiratory failure and generalized seizure (day 9). The patient died on day 9 due to septicemia, pneumonia, and bronchiectasis. The death was considered unrelated to micafungin.

Other Significant Adverse Events

Hepatic Adverse Events

Thirteen of 120 (10.8%) patients had a hepatic adverse event in the study, as shown in the table below.

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

Table 22. Hepatic Adverse Events (FAS) (Applicant's Table 12, study report, 24 April, 2004)

Adverse Event	FK463 Dose Level (mg/day)					
	n (%)					
	12.5 (n=26)	25.0 (n=22)	50.0 (n=26)	75.0 (n=22)	100.0 (n=24)	Total (n=120)
Any hepatic event	3 (11.5%)	6 (27.3%)	2 (7.7%)	0 (0.0%)	2 (8.3%)	13 (10.8%)
LFT abnormal	3 (11.5%)	4 (18.2%)	2 (7.7%)	0 (0.0%)	0 (0.0%)	9 (7.5%)
Alk phos increased	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	2 (8.3%)	3 (2.5%)
SGOT increased	0 (0.0%)	2 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.7%)

FK463= micafungin

Patient base: all patients who received at least 1 dose of FK463 (full analysis set).

Alk phos: alkaline phosphatase

LFT: liver function test

SGOT: serum glutamic oxaloacetic transaminase. (AST)

Medical Officer Comments: No apparent dose-relationship was noted for these adverse events. One additional hepatic adverse event was found in Table 13.5.1.1, hepatitis, which occurred in an additional patient who received 100 mg/day micafungin.

Two patients had increased liver function tests considered severe and possibly related to micafungin. **Patient 101018** was described above in the section "Study Drug Discontinuation due to Adverse Events". **Patient 301004** received 12.5 mg/day micafungin for 14 days, as well as zelitrex, pregamol, panado, erythromycin, doxycidine, tramal, isoniazide, septran, and voltaren. Hepatic laboratory values for this patient are shown in the table below.

Hepatic Laboratory Values for Patient 301004

Study day	AST (U/L)	ALT (U/L)	Total Bilirubin (mg/dL)	Alkaline phosphatase (U/L)
Baseline	47	46	0.2	246
Day 7	216	182	0.2	357
Day 16	59	63	0.2	425
Day 31	117	147	0.3	717

Medical Officer Comments: AST and ALT values decreased after micafungin was stopped on day 14, so a relationship to micafungin is certainly possible. Alkaline phosphatase values, however, continued to rise after micafungin was stopped. This patient received a number of concomitant medications known to have potential hepatotoxicity (isoniazid, bactrim, voltaren), thus, attribution of liver function test abnormalities to micafungin alone, would be difficult.

Hepatic Laboratory Values

Mean AST, ALT, and total bilirubin remained within the normal range with minimal change from baseline to end-of-therapy for all dosing groups. However, the mean alkaline phosphatase increased during micafungin treatment in the 100 mg/day group, from a baseline mean of 122 ± 87 U/L to 193 ±

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

230 at EOT, and decreased to 124 ± 88 U/L at the week 2 post-treatment visit. The median alkaline phosphatase increased from 79 U/L (range 34-385) at baseline, to 98 U/L (range 36-1093) at EOT, then decreased to 85 U/L (range 59-374) 2 weeks post-treatment.

Shift tables for alkaline phosphatase are shown below. A total of 8/120 (6.7%) patients (in all treatment groups) had an elevation of alkaline phosphatase at the end of therapy, above the baseline value. One patient had an alkaline phosphatase elevation between 5 and 10 x ULN.

Table 23. Shift of Alkaline phosphatase from baseline to EOT (Applicant's Appendix 14.3.5.1)

----- LABORATORY TEST-ALKALINE PHOSPHATASE (U/L) -----

----- FK463 DOSE LEVEL = 12.5 mg/DAY -----								----- FK463 DOSE LEVEL = 25.0 mg/DAY -----							
----- END OF THERAPY -----								----- END OF THERAPY -----							
BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL		BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL	
NORMAL	20	2	0	0	3	25		NORMAL	19	0	0	0	0	19	
HIGH 1	0	0	0	0	1	1		HIGH 1	1	2	0	0	0	3	
HIGH 2	0	0	0	0	0	0		HIGH 2	0	0	0	0	0	0	
HIGH 3	0	0	0	0	0	0		HIGH 3	0	0	0	0	0	0	
NO DATA	0	0	0	0	0	0		NO DATA	0	0	0	0	0	0	
TOTAL	20	2	0	0	4	26		TOTAL	20	2	0	0	0	22	

ULN-UPPER LIMIT OF NORMAL
 FOR SERUM CREATININE:
 NORMAL- LESS THAN 2 X ULN
 HIGH 1- 2 X ULN TO < 3 X ULN
 HIGH 2- 3 X ULN TO < 4 X ULN
 HIGH 3- 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:
 NORMAL- LESS THAN 2.5 X ULN
 HIGH1- 2.5 X ULN TO < 5.0 X ULN
 HIGH2- 5.0 X ULN TO < 10 X ULN
 HIGH3- 10 X ULN OR GREATER

BEST POSSIBLE COPY

APPEARS THIS WAY
 ON ORIGINAL

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 23. (continued) Shift of Alkaline phosphatase from baseline to EOT (Applicant's Appendix 14.3.5.1) (continued)

-----LABORATORY TEST-ALKALINE PHOSPHATASE (U/L)-----

-----FK463 DOSE LEVEL = 50.0 mg/DAY-----							-----FK463 DOSE LEVEL = 75.0 mg/DAY-----						
-----END OF THERAPY-----							-----END OF THERAPY-----						
BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL	BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	23	1	0	0	2	26	NORMAL	20	1	0	0	0	21
HIGH 1	0	0	0	0	0	0	HIGH 1	1	0	0	0	0	1
HIGH 2	0	0	0	0	0	0	HIGH 2	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0	HIGH 3	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0	NO DATA	0	0	0	0	0	0
TOTAL	23	1	0	0	2	26	TOTAL	21	1	0	0	0	22

ULN-UPPER LIMIT OF NORMAL
FOR SERUM CREATININE:
NORMAL- LESS THAN 2 X ULN
HIGH 1- 2 X ULN TO < 3 X ULN
HIGH 2- 3 X ULN TO < 4 X ULN
HIGH 3- 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:
NORMAL- LESS THAN 2.5 X ULN
HIGH1- 2.5 X ULN TO < 5.0 X ULN
HIGH2- 5.0 X ULN TO < 10 X ULN
HIGH3- 10 X ULN OR GREATER

Table 23. (continued) Shift of Alkaline phosphatase from baseline to EOT (Applicant's Appendix 14.3.5.1) (continued)

-----LABORATORY TEST-ALKALINE PHOSPHATASE (U/L)-----

-----FK463 DOSE LEVEL = 100.0 mg/DAY-----						
-----END OF THERAPY-----						
BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	20	3	0	0	0	23
HIGH 1	0	0	1	0	0	1
HIGH 2	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0
TOTAL	20	3	1	0	0	24

ULN-UPPER LIMIT OF NORMAL
FOR SERUM CREATININE:
NORMAL- LESS THAN 2 X ULN
HIGH 1- 2 X ULN TO < 3 X ULN
HIGH 2- 3 X ULN TO < 4 X ULN
HIGH 3- 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:
NORMAL- LESS THAN 2.5 X ULN
HIGH1- 2.5 X ULN TO < 5.0 X ULN
HIGH2- 5.0 X ULN TO < 10 X ULN
HIGH3- 10 X ULN OR GREATER

Medical Officer Comments: Most increases in alkaline phosphatase were mild, except for the one patient with an increase to at least 10 x the upper limit of normal.

Shift tables for AST from baseline to end-of-therapy are shown below. A total of 11/120 (9.2%) patients had an AST elevation at the end-of-therapy above the baseline value. Four of these patients developed AST levels to 5 to <10x ULN; while 1 patient with a normal AST at baseline, developed an AST value of ≥ 10 x ULN at the end-of-therapy.

BEST POSSIBLE COPY

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 24. Shift of AST from baseline to end-of-therapy (applicant's Appendix 14.3.5.1)

LABORATORY TEST-SCOT (U/L)						
----- FK463 DOSE LEVEL = 12.5 mg/DAY -----						
----- END OF THERAPY -----						
BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	16	2	0	0	4	22
HIGH 1	2	1	1	0	0	4
HIGH 2	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0
TOTAL	18	3	1	0	4	26

LABORATORY TEST-SCOT (U/L)						
----- FK463 DOSE LEVEL = 25.0 mg/DAY -----						
----- END OF THERAPY -----						
BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	16	2	1	0	0	19
HIGH 1	3	0	0	0	0	3
HIGH 2	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0
TOTAL	19	2	1	0	0	22

ULN-UPPER LIMIT OF NORMAL
FOR SERUM CREATININE:
NORMAL- LESS THAN 2 X ULN
HIGH 1- 2 X ULN TO < 3 X ULN
HIGH 2- 3 X ULN TO < 4 X ULN
HIGH 3- 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:
NORMAL- LESS THAN 2.5 X ULN
HIGH1- 2.5 X ULN TO < 5.0 X ULN
HIGH2- 5.0 X ULN TO < 10 X ULN
HIGH3- 10 X ULN OR GREATER

Table 24. Shift of AST from baseline to end-of-therapy (applicant's Appendix 14.3.5.1) (continued)

LABORATORY TEST-SCOT (U/L)						
----- FK463 DOSE LEVEL = 50.0 mg/DAY -----						
----- END OF THERAPY -----						
BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	16	1	1	1	2	21
HIGH 1	2	1	0	0	0	3
HIGH 2	1	0	0	0	0	1
HIGH 3	1	0	0	0	0	1
NO DATA	0	0	0	0	0	0
TOTAL	20	2	1	1	2	26

LABORATORY TEST-SCOT (U/L)						
----- FK463 DOSE LEVEL = 75.0 mg/DAY -----						
----- END OF THERAPY -----						
BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	16	0	1	0	0	17
HIGH 1	4	1	0	0	0	5
HIGH 2	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0
TOTAL	20	1	1	0	0	22

ULN-UPPER LIMIT OF NORMAL
FOR SERUM CREATININE:
NORMAL- LESS THAN 2 X ULN
HIGH 1- 2 X ULN TO < 3 X ULN
HIGH 2- 3 X ULN TO < 4 X ULN
HIGH 3- 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:
NORMAL- LESS THAN 2.5 X ULN
HIGH1- 2.5 X ULN TO < 5.0 X ULN
HIGH2- 5.0 X ULN TO < 10 X ULN
HIGH3- 10 X ULN OR GREATER

BEST POSSIBLE COPY

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 24. Shift of AST from baseline to end-of-therapy (applicant's Appendix 14.3.5.1)

(continued)

----- LABORATORY TEST-SCGT (U/L) -----

----- FR453 DOSE LEVEL = 100.0 mg/DAY -----

----- END OF THERAPY -----

	BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	23	1	0	0	0	0	24
HIGH 1	0	0	0	0	0	0	0
HIGH 2	0	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0	0
TOTAL	23	1	0	0	0	0	24

ULN=UPPER LIMIT OF NORMAL

FOR SERUM CREATININE:

- NORMAL= LESS THAN 2 X ULN
- HIGH 1= 2 X ULN TO < 3 X ULN
- HIGH 2= 3 X ULN TO < 4 X ULN
- HIGH 3= 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:

- NORMAL= LESS THAN 2.5 X ULN
- HIGH1= 2.5 X ULN TO < 5.0 X ULN
- HIGH2= 5.0 X ULN TO < 10 X ULN
- HIGH3= 10 X ULN OR GREATER

Medical Officer Comments: AST elevation was more frequent at the end-of-therapy than was ALT, bilirubin, or alkaline phosphatase. At least one patient developed significant hepatocellular damage, based on an AST of at least 10 x ULN; however, whether this is directly attributable to micafungin cannot be determined by this type of population data.

Shift tables for ALT from Baseline to EOT are shown in the table below. At the end-of-therapy, a total of 7/120 (5.8%) patients had ALT elevation above the baseline level. Three of these patients with a normal ALT at baseline, had AST values between 5 and 10 x ULN at the end-of-therapy.

Table 25. Shift of ALT from Baseline to EOT (Applicant's Appendix 14.3.5.1)

----- LABORATORY TEST-SCPT (U/L) -----

----- FR453 DOSE LEVEL = 12.5 mg/DAY -----								----- FR453 DOSE LEVEL = 25.0 mg/DAY -----							
----- END OF THERAPY -----								----- END OF THERAPY -----							
	BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL		BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	20	1	0	0	0	4	25	NORMAL	19	2	1	0	0	0	22
HIGH 1	0	1	0	0	0	0	1	HIGH 1	0	0	0	0	0	0	0
HIGH 2	0	0	0	0	0	0	0	HIGH 2	0	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0	0	HIGH 3	0	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0	0	NO DATA	0	0	0	0	0	0	0
TOTAL	20	2	0	0	0	4	26	TOTAL	19	2	1	0	0	0	22

ULN=UPPER LIMIT OF NORMAL

FOR SERUM CREATININE:

- NORMAL= LESS THAN 2 X ULN
- HIGH 1= 2 X ULN TO < 3 X ULN
- HIGH 2= 3 X ULN TO < 4 X ULN
- HIGH 3= 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:

- NORMAL= LESS THAN 2.5 X ULN
- HIGH1= 2.5 X ULN TO < 5.0 X ULN
- HIGH2= 5.0 X ULN TO < 10 X ULN
- HIGH3= 10 X ULN OR GREATER

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

Table 25. (continued) Shift of ALT from Baseline to EOT (Applicant's Appendix 14.3.5.1)

----- LABORATORY TEST-SCPT (U/L) -----

----- FK463 DOSE LEVEL = 50.0 mg/DAY -----							----- FK463 DOSE LEVEL = 75.0 mg/DAY -----						
-----END OF THERAPY-----							-----END OF THERAPY-----						
BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL	BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	17	1	2	0	2	22	NORMAL	20	0	0	0	0	20
HIGH 1	1	2	0	0	0	3	HIGH 1	1	0	0	0	0	1
HIGH 2	1	0	0	0	0	1	HIGH 2	1	0	0	0	0	1
HIGH 3	0	0	0	0	0	0	HIGH 3	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0	NO DATA	0	0	0	0	0	0
TOTAL	19	3	2	0	2	26	TOTAL	22	0	0	0	0	22

ULN=UPPER LIMIT OF NORMAL
 FOR SERUM CREATININE:
 NORMAL= LESS THAN 2 X ULN
 HIGH 1= 2 X ULN TO < 3 X ULN
 HIGH 2= 3 X ULN TO < 4 X ULN
 HIGH 3= 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:
 NORMAL= LESS THAN 2.5 X ULN
 HIGH1= 2.5 X ULN TO < 5.0 X ULN
 HIGH2= 5.0 X ULN TO < 10 X ULN
 HIGH3= 10 X ULN OR GREATER

Table 25. (continued) Shift of ALT from Baseline to EOT (Applicant's Appendix 14.3.5.1)

----- LABORATORY TEST-SCPT (U/L) -----

----- FK463 DOSE LEVEL = 100.0 mg/DAY -----						
-----END OF THERAPY-----						
BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	24	0	0	0	0	24
HIGH 1	0	0	0	0	0	0
HIGH 2	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0
TOTAL	24	0	0	0	0	24

ULN=UPPER LIMIT OF NORMAL
 FOR SERUM CREATININE:
 NORMAL= LESS THAN 2 X ULN
 HIGH 1= 2 X ULN TO < 3 X ULN
 HIGH 2= 3 X ULN TO < 4 X ULN
 HIGH 3= 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:
 NORMAL= LESS THAN 2.5 X ULN
 HIGH1= 2.5 X ULN TO < 5.0 X ULN
 HIGH2= 5.0 X ULN TO < 10 X ULN
 HIGH3= 10 X ULN OR GREATER

Shift tables for total bilirubin from baseline to end-of-therapy are shown below. One of 120 patients (0.8%) had an increase in bilirubin from normal to between 2.5 and 5 x ULN at the end-of-therapy.

BEST POSSIBLE COPY

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 26. Shift of Total Bilirubin from Baseline to End-of-therapy (Applicant's Appendix 14.3.5.1)

----- LABORATORY TEST-TOTAL BILIRUBIN (ng/dL) -----

----- FK463 DOSE LEVEL = 12.5 mg/DAY -----							----- FK463 DOSE LEVEL = 25.0 mg/DAY -----						
-----END OF THERAPY-----							-----END OF THERAPY-----						
BASILINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL	BASILINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	22	0	0	0	4	26	NORMAL	21	1	0	0	0	22
HIGH 1	0	0	0	0	0	0	HIGH 1	0	0	0	0	0	0
HIGH 2	0	0	0	0	0	0	HIGH 2	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0	HIGH 3	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0	NO DATA	0	0	0	0	0	0
TOTAL	22	0	0	0	4	26	TOTAL	21	1	0	0	0	22

ULN=UPPER LIMIT OF NORMAL
FOR SERUM CREATININE:
NORMAL- LESS THAN 2 X ULN
HIGH 1- 2 X ULN TO < 3 X ULN
HIGH 2- 3 X ULN TO < 4 X ULN
HIGH 3- 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:
NORMAL- LESS THAN 2.5 X ULN
HIGH1- 2.5 X ULN TO < 5.0 X ULN
HIGH2- 5.0 X ULN TO < 10 X ULN
HIGH3- 10 X ULN OR GREATER

Table 26. (continued) Shift of Total Bilirubin from Baseline to End-of-therapy (Applicant's Appendix 14.3.5.1)

----- LABORATORY TEST-TOTAL BILIRUBIN (ng/dL) -----

----- FK463 DOSE LEVEL = 50.0 mg/DAY -----							----- FK463 DOSE LEVEL = 75.0 mg/DAY -----						
-----END OF THERAPY-----							-----END OF THERAPY-----						
BASILINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL	BASILINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	24	0	0	0	2	26	NORMAL	22	0	0	0	0	22
HIGH 1	0	0	0	0	0	0	HIGH 1	0	0	0	0	0	0
HIGH 2	0	0	0	0	0	0	HIGH 2	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0	HIGH 3	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0	NO DATA	0	0	0	0	0	0
TOTAL	24	0	0	0	2	26	TOTAL	22	0	0	0	0	22

ULN=UPPER LIMIT OF NORMAL
FOR SERUM CREATININE:
NORMAL- LESS THAN 2 X ULN
HIGH 1- 2 X ULN TO < 3 X ULN
HIGH 2- 3 X ULN TO < 4 X ULN
HIGH 3- 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:
NORMAL- LESS THAN 2.5 X ULN
HIGH1- 2.5 X ULN TO < 5.0 X ULN
HIGH2- 5.0 X ULN TO < 10 X ULN
HIGH3- 10 X ULN OR GREATER

BEST POSSIBLE COPY

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 26. (continued) Shift of Total Bilirubin from Baseline to End-of-therapy (Applicant's Appendix 14.3.5.1)

----- LABORATORY TEST-TOTAL BILIRUBIN (mg/dL) -----

----- FK463 DOSE LEVEL = 100.0 mg/DAY -----

----- END OF THERAPY -----

	BASELINE	NORMAL	HIGH 1	HIGH 2	HIGH 3	NO DATA	TOTAL
NORMAL	24	0	0	0	0	0	24
HIGH 1	0	0	0	0	0	0	0
HIGH 2	0	0	0	0	0	0	0
HIGH 3	0	0	0	0	0	0	0
NO DATA	0	0	0	0	0	0	0
TOTAL	24	0	0	0	0	0	24

ULN-UPPER LIMIT OF NORMAL

FOR SERUM CREATININE:

NORMAL- LESS THAN 2 X ULN
HIGH 1- 2 X ULN TO < 3 X ULN
HIGH 2- 3 X ULN TO < 4 X ULN
HIGH 3- 4 X ULN OR GREATER

FOR AST/SGOT, ALT/SGPT, ALK PHOS, TOTAL BILIRUBIN:

NORMAL- LESS THAN 2.5 X ULN
HIGH1- 2.5 X ULN TO < 5.0 X ULN
HIGH2- 5.0 X ULN TO < 10 X ULN
HIGH3- 10 X ULN OR GREATER

Medical Officer Comments: In this study, although a number of patients had increased transaminases or alkaline phosphatase, no patients had hepatic failure or other serious clinical hepatic adverse events.

Renal Function

A total of 5/120 (4.2%) had adverse events referable to the urogenital system, as shown in Table 15 above. These events included urinary tract infection, cystitis, kidney failure, kidney pain, and pyelonephritis, each in one patient. None of these events was considered related to micafungin. One patient (number **201007**) died as a result of renal failure. A narrative summary for this patient was provided in the section "Deaths during Study Period" above.

Mean BUN and creatinine values remained within normal range throughout the study in all dosing groups, and no patient had a shift from baseline serum creatinine to an increased creatinine level.

Infusion-Related Reactions

A total of 7/120 (5.8%) patients experienced chills during micafungin infusion (in 2 cases, chills were considered drug-related); and 18/120 (15.0%) experienced fever. However, fever was considered drug-related in only one patient.

Allergic Reactions

An allergic reaction described as erythema multiforme (and urticaria) occurred in 1 patient (**patient 501004**), described in narrative summary (section on "Study Drug Discontinuations due to Adverse Events). Additionally, rash was reported in 8/120 (6.7%) patients (4 cases were attributed to micafungin), and pruritis and rash was reported in 1 patient.

Clinical Review

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

Micafungin sodium for Esophgeal Candidiasis

Mycamine (Micafungin sodium)

Medical Officer Comments: As in other studies reviewed for this NDA, allergic reactions, including rash, and pruritis were reported with micafungin, and in many cases were attributed to micafungin. The case of erythema multiforme was discussed above.

Cardiovascular Adverse Events

A total of 20/120 (16.7%) patients had a cardiovascular adverse event. Cardiovascular events for all micafungin treatment groups were pooled and are shown in the table below. None of these adverse events were serious. Phlebitis and tachycardia were the most frequent events in this category.

Table 27. Cardiovascular Adverse Events (FAS) (adapted from Applicant’s Table 13.5.1.1.)

COSTART Term	Micafungin Total N=120
Phlebitis	5 (4.2)
Tachycardia	5 (4.2)
Chest pain	3 (2.5)
Vasodilatation	3 (2.5)
Hypertension	2 (1.7)
Hypotension	2 (1.7)
Palpitation	2 (1.7)
Deep thrombophlebitis	1 (0.8)
Syncope	1 (0.8)
Vascular headache	1 (0.8)

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

Medical Officer Comment: Phlebitis was seen more frequently in the studies which used higher doses of micafungin (150 mg), and may be a dose-related adverse event. These events are concerning because micafungin is known to cause vascular irritation in animals, and phlebitis and thrombophlebitis were fairly common adverse events in studies with healthy volunteers who received micafungin. Theoretically if a drug causes vascular irritation, and results in blood clotting, more serious adverse events such as deep venous thrombosis, pulmonary embolus, or even myocardial infarction and stroke could occur. Pulmonary embolus was reported in one patient in this study in a different patient than the one with deep thrombophlebitis reported above. Myocardial infarction and stroke were not reported as adverse events in this study.

Vasodilatation could be considered a histamine-mediated reaction, which were observed in animal studies. Hypotension could be considered part of a symptom complex related to vasodilatation or infusion reactions, but it can also be associated with sepsis.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Hematological Adverse Events

A total of 7/120 (5.8%) patients had a hematological adverse event, including 4 patients with anemia, 2 with leukopenia, and 2 with lymphadenopathy. None of these events were considered related to micafungin, and only 1 event, leukopenia, was serious.

The mean and median hemoglobin value did not differ significantly from baseline to end-of-therapy and to the 2 week post-treatment visit for patients in any of the micafungin dosing groups. Measures of central tendency were not reported by the applicant for hematocrit, WBC, or platelet count.

Medical Officer Comments: Although the mean and median hemoglobin for the population is not very sensitive screen for changes that occur uncommonly, it is notable that neither hemolysis nor hemolytic anemia was reported in this study.

Laboratory Evaluations

No significant differences were observed in mean or median values for sodium, potassium, magnesium, calcium measured at baseline, days 3,7, 14 (or end-of-therapy), and 2 weeks post-treatment for patients in any of the micafungin dosing groups.

Medical Officer Comments: the measures of central tendency applied to a population are not very sensitive for evaluating safety signals, and are influenced by outliers. However, only a few adverse events were reported in this category under metabolic and nutritional disorders. These included hypokalemia (2 patients), hyperkalemia (2 patients), hypernatremia (1 patient), and hypoglycemia (1 patient). None of these events were considered related to micafungin, however, hypokalemia was reported as a serious adverse event in 1 patient.

Vital Signs

No significant differences from baseline, day 3, 7, 14 (or end-of-therapy), and 2 weeks post-treatment, were noted in mean or median systolic and diastolic blood pressures, heart rate, or temperature in patients in any of the micafungin dosing groups.

Safety Conclusions:

1. There was no apparent relationship between adverse events and micafungin dose.
2. The most common adverse reactions were fever (15%), diarrhea (14.2%), headache (13.3%), vomiting (12.5%), and nausea (10.8%).
3. The most common adverse events considered related to micafungin were vomiting (6.7%), abnormal liver function tests (5.8%), nausea (5.0%), and rash (3.3%).
4. Serious adverse events occurred in 18/120 (15%) of patients overall. Pneumonia was the most common serious adverse event, occurring in 3 (2.5%) patients. Only one serious adverse event was considered drug-related (diarrhea in a single patient).

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

5. Micafungin was discontinued in 16/120 patients (13.3%) due to adverse events. Pneumonia was the most common adverse event leading to discontinuation, occurring in 3 patients.

6. Thirteen of 120 (10.8%) patients died during the study, most during the 2 week post-treatment period. Most deaths were due to pneumonia, tuberculosis, or septicemia. None of the deaths were considered related to micafungin.

7. No serious hepatic adverse events occurred in this study. However, abnormal liver function tests and increased AST and alkaline phosphatase were commonly reported adverse events.

8. Renal failure was reported as a serious adverse event in one patient, who died. However, this patient had baseline renal insufficiency.

9. There were 2 serious vascular adverse events- deep venous thrombophlebitis and pulmonary embolism. Phlebitis was a commonly reported adverse event.

10. Rash was a common drug-related adverse event. One patient had an allergic reaction described as erythema multiforme, which is potentially serious or life-threatening.

11. Leukopenia and anemia were common adverse events, not unexpectedly in patients with advanced HIV. One case of leukopenia was serious. No cases of thrombocytopenia, hemolytic anemia, or hemolysis were reported as adverse events in this study.

12. The safety profile of micafungin in this study was similar to that observed in the two pivotal studies for this NDA, 03-7-005 and FG463-21-09, and to the overall micafungin safety database.

10.1.4 Supportive Study 98-0-047

An open-label non-comparative study of FK463 (Micafungin) in the Treatment of Candidemia of Invasive Candidiasis

Medical Officer Comments: This study was reviewed previously by Dr. Ekopimo Ibia for NDA 21-506. Thus, a study summary with emphasis on patients who had esophageal candidiasis, is provided in this review.

Study Objectives: To evaluate safety and efficacy of micafungin in the treatment of patients with confirmed candidemia or invasive candidiasis caused by both *Candida albicans* and non-*C. albicans* organisms.

Primary Efficacy Endpoint

The primary efficacy endpoint was the investigator's global assessment of treatment success, defined as complete or partial response. An independent review was also performed by .

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

to provide an independent assessment of baseline diagnosis, disease status, efficacy outcomes, and cause of death with regard to candidiasis.

Medical Officer Comments: The primary outcome measure in this study was less stringent than that used in the two pivotal studies for this indication, 03-7-005 and FG463-21-09, where a more objective measure, endoscopic response was the primary endpoint.

Secondary Efficacy Endpoints

Secondary Efficacy Endpoints included clinical response at end-of-therapy (complete, partial, stabilization, or progression); mycological response at end-of-therapy (eradication, presumed eradication, or persistence); relapse; and the use of additional antifungal medications during the 6 week post-treatment period.

Study Design

This was an open-label, noncomparative, multinational study in adults and pediatric patients, conducted under 2 protocols, 98-0-047 (non-European protocol), and FG463-21-02 (European protocol). The study was conducted at 62 sites worldwide, including the U.S. (30 sites), Canada (7 sites), Brazil (6 sites), South Africa (5 sites), Peru (3 sites), Italy (2 sites), United Kingdom (2 sites), France (2 sites), and 1 site each in Chile, Guatemala, Germany, Sweden, and Poland. The study took place from February 27, 1999 to December 27, 2002.

Protocol Overview

Adults and pediatric patients with a confirmed diagnosis of candidemia or invasive candidiasis were enrolled. Patients ≥ 18 years old were enrolled at European sites in protocol FG463-21-02. Patients were classified as follows:

De novo: patient newly diagnosed with candidiasis who received ≤ 48 hours of prior systemic antifungal therapy

Efficacy failure: patients with confirmed candidiasis who received more than 5 days of prior systemic antifungal therapy with no response. These patients could receive micafungin alone, or micafungin plus other systemic antifungal therapy.

Inclusion Criteria included documentation of candidemia or invasive candidiasis by typical signs and symptoms, confirmed by fungal culture or histology. Females of childbearing age were required to have a negative pregnancy test; and all patients (or legal representative) were required to sign informed consent.

Exclusion Criteria included pregnancy, nursing, abnormal liver function tests (AST or ALT ≥ 10 x upper limit of normal (ULN), or bilirubin > 5 x ULN, or alkaline phosphatase > 5 x ULN). Additionally, patients with life expectancy of < 5 days, with hypersensitivity or serious reaction to echinocandins, with prior antifungal therapy in violation of entry criteria (≤ 48 hours for *de novo* patient and ≥ 5 days for efficacy failure patients) were excluded. Requirement for systemic antifungal therapy for conditions other than candidemia or invasive candidiasis, and previous enrollment in the

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

study were also exclusionary criteria; and any patient with a concomitant medical condition considered by the investigator or medical monitor to constitute an unacceptable risk to the patient, was excluded.

Micafungin Dosing

Micafungin was administered as a daily intravenous infusion over 1 hour. Initially all patients were to receive an initial dose of 50 mg/day (1 mg/kg for patients weighing \leq 40 kg). However, under protocol amendment number 4, patients with infections caused by germ-tube negative *Candida*, or by a non- *C. albicans* species, received an initial dose of 100 mg/day (2 mg/kg/day for patients weighing \leq 40 kg). The micafungin dose could be increased in 50 mg increments after 5 days of therapy at a specific dose. The incremental dose increase was 25 mg prior to amendment number 4. The maximum dose in the European protocol was 200 mg/day. *De novo* patients received micafungin alone; while efficacy failure patients received either micafungin alone, or in addition to their current antifungal therapy.

Duration of Therapy

Micafungin was administered for a minimum of 5 days and a maximum of 6 weeks.

Assessments and Procedures

A physical examination, clinical laboratory evaluations (serum chemistry and hematology), and assessment of fungal infection were evaluated at baseline, scheduled times during treatment, and 6 weeks post-treatment. Baseline physical examination included vital signs and ophthalmic examination.

Safety assessment was based on adverse events and laboratory profiles. All adverse events through 72 hours after the last administration of study drug were recorded, and followed as long as necessary until the event stabilized

Statistical considerations

At least 100 evaluable patients were planned, and case report forms from 357 patients were collected. A total of 353 patients were included in the Full Analysis Set, and 288 patients in the Per Protocol set, as defined below:

Full Analysis Set (FAS): All enrolled patients who received at least 1 dose of micafungin. This population was included in the safety analysis.

Per Protocol Set (PPS): All enrolled patients who received at least 5 doses of micafungin, and who had confirmed candidemia, and proven or probable invasive candidiasis (liver, spleen, or disseminated only) at baseline. The applicant used this population for efficacy analysis.

Results

Patient Disposition

A total of 357 patients were enrolled, and 353 patients were included in the FAS (4 patients did not receive a dose of micafungin); while 288 patients were considered evaluable and included in the PPS, as shown in Table 1 below. In the FAS, 270/353 patients received micafungin monotherapy, and 83/353 (23.5%) received micafungin in combination with other antifungal therapy.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Table 1. Summary of Study Population (Applicant's Table 1, study report, 24 April, 2004)

	De Novo	Efficacy Failure		Total
		FK463 & Other	FK463 Alone	
All Enrolled Patients	219	83	55	357
Full Analysis Set	215 (98.2%)	83 (100.0%)	55 (100.0%)	353 (98.9%)
Per Protocol Set	187 (85.4%)	58 (69.9%)	43 (78.2%)	288 (80.7%)

Patient base: all enrolled patients, irrespective of whether FK463 was administered (all enrolled patients); all patients who received at least 1 dose of FK463 (full analysis set); all patients who received at least 5 doses of FK463 and have proven or probable (liver, spleen, or disseminated only) invasive candidiasis at baseline (per protocol set).

De novo: patients must have had less than 48 hours of systemic antifungal therapy.

Efficacy failure: patients must have had documented clinical and microbiological evidence of continuing disease despite >5 days of therapy with systemic antifungal agents prior to study entry; patients received either a regimen of FK463 alone or FK463 was added to their prior systemic antifungal regimen.

Medical Officer Comments: It is notable that for NDA 21-506, a total of 254 patients were enrolled, and 250 patients were included in the FAS, and 209 in the PPS.

Study Completion

A total of 221/357 (61.9%) patients completed the study; 105/357(29.4%) enrolled patients died, 17/357 (4.8%) were lost to follow-up, and 14/357 (3.9%) patients did not complete the study due to other reasons, including 4 patients did not meet enrollment criteria, 4 patients withdrew consent, 2 patients were non-compliant with follow-up, and 2 patients were not evaluable (1 of the latter did not receive a dose of micafungin). Patient status at the end of the study is shown in Table 2 below.

Table 2. Patient Status at end-of-Study (Applicant's Table 2, study report, 24 April, 2004)

	De Novo (n=219)	Efficacy Failure		Total (n=357)
		FK463 & Other (n=83)	FK463 Alone (n=55)	
Completed Study	139 (63.5%)	52 (62.7%)	30 (54.5%)	221 (61.9%)
Death†	57 (26.0%)	29 (34.9%)	19 (34.5%)	105 (29.4%)
Lost to Follow-up	13 (5.9%)	1 (1.2%)	3 (5.5%)	17 (4.8%)
Other	10 (4.6%)	1 (1.2%)	3 (5.5%)	14 (3.9%)

Patient base: all enrolled patients.

† Includes death of one de novo patient who never received study drug (Patient Number 359485).

Medical Officer Comments: None of the deaths in this study were related to study drug as determined by the investigator.

Reasons for Treatment Discontinuation

A total of 222/353 (62.9%) patients completed therapy; while 131/353 (37.1%) patients discontinued therapy. Most treatment discontinuations were due to adverse events (20.1%). Reasons for treatment discontinuation are shown in Table 3 below.

Table 3. Reasons for Micafungin Discontinuation (FAS) (Applicant's Table 3, study report, 24 April, 2004)

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

	De Novo (n=215)	Efficacy Failure		Total (n=353)
		FK463 & Other (n=83)	FK463 Alone (n=55)	
Completed Therapy	141 (65.6%)	47 (56.6%)	34 (61.8%)	222 (62.9%)
Discontinued Therapy	74 (34.4%)	36 (43.4%)	21 (38.2%)	131 (37.1%)
Adverse Event	38 (17.7%)	20 (24.1%)	13 (23.6%)	71 (20.1%)
Lack of Efficacy	20 (9.3%)	10 (12.0%)	5 (9.1%)	35 (9.9%)
Administrative	16 (7.4%)	6 (7.2%)	3 (5.5%)	25 (7.1%)

Patient base: all patients who received at least 1 dose of FK463 (full analysis set).

Medical Officer Comments: The adverse events resulting in treatment discontinuation were considered drug-related in 24/353 (6.8%) patients in this study; and most adverse events leading to micafungin discontinuation were due to the patient's underlying condition.

Patient Demographics

Most patients were male and Caucasian, with a mean age of 39 ± 21.1 years. Patient demographic characteristics are summarized in Table 4 below. A total of 250 adult patients (≥ 16 years old), and 38 pediatric patients (< 16 years old) were included in the PPS. Of the 38 children, 6 patients were < 1 month old, 13 patients were between 1 month to 1 year old, 14 patients were from 2-11 years old, and 5 patients were from 12-15 years old.

Four pediatric patients in this study, aged 3, 4, 6, and 7 years old, had esophageal candidiasis.

Table 4. Baseline Patient Characteristics (FAS) (Applicant's Table 4, study report, 24 April, 2004)

	De Novo (n=215)	Efficacy Failure		Total (n=353)
		FK463 & Other (n=83)	FK463 Alone (n=55)	
Sex				
Male	124 (57.7%)	42 (50.6%)	35 (63.6%)	201 (56.9%)
Female	91 (42.3%)	41 (49.4%)	20 (36.4%)	152 (43.1%)
Race				
Caucasian	135 (62.8%)	59 (71.1%)	36 (65.5%)	230 (65.2%)
Mestizo	48 (22.3%)	1 (1.2%)	5 (9.1%)	54 (15.3%)
Black	26 (12.1%)	17 (20.5%)	8 (14.5%)	51 (14.4%)
Oriental	2 (0.9%)	3 (3.6%)	4 (7.3%)	9 (2.6%)
American Indian	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Other†	3 (1.4%)	3 (3.6%)	2 (3.6%)	8 (2.3%)
Age (years)				
Mean ± SD	43.5 ± 19.47	28.1 ± 22.98	40.8 ± 18.39	39.4 ± 21.12
Range	0.0 to 92.0	0.0 to 76.0	0.1 to 73.0	0.0 to 92.0
Weight (kg)				
n	213	82	55	350
Mean ± SD	62.1 ± 28.99	50.7 ± 33.83	61.4 ± 23.50	59.3 ± 29.74
Range	3.4 to 265.0	0.60 to 119.6	1.30 to 106.3	0.6 to 265.0
APACHE II Scores‡				
n	164	40	39	243
Mean ± SD	11.7 ± 5.51	13.6 ± 6.15	13.1 ± 5.85	12.2 ± 5.70
Range	0.0 to 34.0	3.0 to 34.0	5.0 to 31.0	0.0 to 34.0

Patient base: all enrolled patients who received at least 1 dose of FK463 (full analysis set).

Medical Officer Comments: Some imbalances between treatment groups were noted, including gender differences in efficacy failure patients who received micafungin alone (63.6% male and 36.4% female), racial differences (22.3% Mestizo patients in the de novo, compared to 1.2% and 9.1% in efficacy failure patients who received micafungin plus another antifungal agent, or micafungin alone, respectively; and 20.5% blacks among the efficacy failure patients who

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

received micafungin plus another antifungal agent, compared to those who received micafungin alone, 14.5%, or de novo patients who received micafungin (12.1%). Patient demographics for patients with EC were not provided separately.

Underlying Disease at Baseline

Most patients in this study had HIV, 29.7% (105/353), or were receiving antineoplastic chemotherapy, 19.8% (70/353). Underlying conditions are summarized in Table 5 below.

Table 5. Underlying Disease or Condition (FAS) (Applicant’s Table 6, study report, 24 April, 2004)

	De Novo (n=215)	Efficacy Failure		Total (n=353)
		FK463 & Other (n=83)	FK463 Alone (n=55)	
Bone Marrow (or Other Progenitor Cell) Transplant				
Allogeneic	5 (2.3%)	16 (19.3%)	6 (10.9%)	27 (7.6%)
Autologous	3 (1.4%)	1 (1.2%)	2 (3.6%)	6 (1.7%)
Antineoplastic Chemotherapy	24 (11.2%)	28 (33.7%)	18 (32.7%)	70 (19.8%)
HIV	90 (41.9%)	5 (6.0%)	10 (18.2%)	105 (29.7%)
Bacterial Infection/ Antibiotic Use	16 (7.4%)	1 (1.2%)	2 (3.6%)	19 (5.4%)
Neoplasm	9 (4.2%)	1 (1.2%)	2 (3.6%)	12 (3.4%)
Post-Surgical Infection	13 (6.0%)	1 (1.2%)	0 (0.0%)	14 (4.0%)
Solid Organ Transplant	6 (2.8%)	2 (2.4%)	6 (10.9%)	14 (4.0%)
Corticosteroid Therapy	5 (2.3%)	1 (1.2%)	0 (0.0%)	6 (1.7%)
Heart Disorder	5 (2.3%)	0 (0.0%)	0 (0.0%)	5 (1.4%)
Liver Disease	3 (1.4%)	2 (2.4%)	1 (1.8%)	6 (1.7%)
Immune Disorder	2 (0.9%)	0 (0.0%)	1 (1.8%)	3 (0.8%)
Kidney Disorder	4 (1.9%)	0 (0.0%)	0 (0.0%)	4 (1.1%)
Aplastic Anemia	1 (0.5%)	1 (1.2%)	0 (0.0%)	2 (0.6%)
Premature Infant	1 (0.5%)	14 (16.9%)	1 (1.8%)	16 (4.5%)
Other†	28 (13.0%)	10 (12.0%)	6 (10.9%)	44 (12.5%)

† Patient base: all enrolled patients who received at least 1 dose of FK463 (full analysis set).

BEST POSSIBLE COPY

***Medical Officer Comments:** A total of 91/99 (91.9%) of patients in the PPS with EC had HIV disease at baseline. Among the other 8 patients with EC, 2 patients had a solid organ transplant, and one patient each had underlying corticosteroid use, bacterial infection/antibiotic use, disseminated strongyloidosis, aplastic anemia, achalasia, and myelofibrosis. CD₄ count data was collected for only 6 patients overall in this study. Among those 6 patients, the CD₄ mean was 15 cells/mm³ ± 15 cells/mm³; the median CD₄ count was 8 cells/mm³, with a range of 2-41 cells/mm³. Thus, for those patients that had a CD₄ count determination, we can conclude they were severely immunocompromised. For the rest of the HIV population in this study, we can assume patients were at least moderately immunocompromised, because EC is generally seen only in patients with CD₄ counts < 200 cells/mm³.*

There were some imbalances between treatment groups in this study. More HIV patients (41.9%) of the de novo patients had underlying HIV disease, compared to 6% in efficacy failure patients who received micafungin plus another antifungal agent, and 18.2% who received micafungin alone. Additionally, there were more allogeneic transplant patients in the efficacy failure group who received micafungin plus another antifungal agent than those who received micafungin alone (10.9%), or who were de novo patients (2.3%). However, because

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

most of the EC patients were de novo patients who received micafungin alone, 88.9% (88/99, as shown in table 6 below, the demographic imbalances in this study should have no effect on outcomes in the subset of patients with EC.

Baseline Candida Infection

Most patients 172/288(59.7%) had *Candida albicans* at baseline; while 120/288 (41.7%) had a non-*C.albicans* species isolated at baseline. The primary site of *Candida* infection in the PPS is summarized in Table 6 below.

Table 6. Primary Site of Candida Infection at Baseline (PPS)(Applicant’s Table 7, study synopsis, 24 April, 2004)

	De Novo (n=187)	Efficacy Failure		Total (n=288)
		FK463 & Other (n=58)	FK463 Alone (n=43)	
Site of Candida Species Infection				
Blood	72 (38.5%)	29 (50.0%)	25 (58.1%)	126 (43.8%)
Esophageal	88 (47.1%)	2 (3.4%)	9 (20.9%)	99 (34.4%)
Disseminated†				
proven	5 (2.7%)	16 (27.6%)	5 (11.6%)	26 (9.0%)
probable	0 (0.0%)	5 (8.6%)	0 (0.0%)	5 (1.7%)
Abscess	6 (3.2%)	1 (1.7%)	1 (2.3%)	8 (2.8%)
Peritoneal	5 (2.7%)	1 (1.7%)	1 (2.3%)	7 (2.4%)
Liver				
proven	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (0.3%)
probable	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (0.3%)
Oropharyngeal	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Lungs	3 (1.6%)	0 (0.0%)	0 (0.0%)	3 (1.0%)
Other‡	7 (3.7%)	3 (5.2%)	1 (2.3%)	11 (3.8%)

† Patient base: all patients who received at least 5 doses of FK463 and have proven or probable (liver, spleen, or disseminated only) invasive candidiasis at baseline (per protocol set).

Medical Officer Comments: *Most patients with esophageal candidiasis (EC) (88/99, 88.9%) were enrolled as de novo patients; while 11/99 (11.1%) were efficacy failure patients. Two of the latter received micafungin alone; while 9 received micafungin in combination with another antifungal agent. Notably, candidemia was the most common site of Candida infection in this study, with 126/288 (43.8%) patients having candidemia, and 26/288 (9.0%) having disseminated candidiasis. Overall, 99/288 (34.3%) of PPS patients had EC in this study.*

It should be noted that in NDA 21-506, a total of 97 patients in the PPS had esophageal candidiasis at baseline, 88/97 (90.7%) were de novo patients and 9/97 (9.3%) were efficacy failure patients.

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

Esophageal Candidiasis at Baseline

Esophageal candidiasis was documented endoscopically, and confirmed by histology or cytology. As shown in the table below, most patients with EC, 91/99 (91.9%) patients had *C. albicans* at baseline; while 7 patients had *C. glabrata*, 5 had *C. krusei*, and 4 had *Candida species*. Most of the latter organisms were co-isolated with *C. albicans*.

Table 7. Baseline *Candida* species in Patients with Esophageal candidiasis (Applicant’s Table 11, study report, 24 April, 2004)

Candida Species	De Novo (n=88)	Efficacy Failure		Total (n=99)
		FK463 & Other (n=2)	FK463 Alone (n=9)	
<i>C. albicans</i>	84 (95.5%)	1 (50.0%)	6 (66.7%)	91 (91.9%)
<i>C. glabrata</i>	5 (5.7%)	0 (0.0%)	2 (22.2%)	7 (7.1%)
<i>C. krusei</i>	3 (3.4%)	0 (0.0%)	2 (22.2%)	5 (5.1%)
<i>Candida sp. NOS†</i>	3 (3.4%)	1 (50.0%)	0 (0.0%)	4 (4.0%)

† Patient base: all patients who received at least 5 doses of FK463 and have proven or probable (liver, spleen, or disseminated only) invasive candidiasis at baseline (per protocol set); primary site = proven esophageal.

Medical Officer Comments: Most de novo patients (95.5%) had *C. albicans* at baseline; while 5/11 (45.5%) efficacy failure patients had non- *C. albicans* species.

Esophageal lesions were graded as not present, mild, moderate, or severe. Baseline endoscopic grade for patients with EC is summarized in the table below.

Table 8. Esophageal Mucosal Grade at Baseline (Applicant’s Table 12, study report, 24 April, 2004)

Esophageal Lesion Grade	De Novo (n=88)	Efficacy Failure		Total (n=99†)
		FK463 & Other (n=2†)	FK463 Alone (n=9)	
Mild	14 (15.9%)	1 (50.0%)	1 (11.1%)	16 (16.2%)
Moderate	33 (37.5%)	0 (0.0%)	1 (11.1%)	34 (34.3%)
Severe	38 (43.2%)	0 (0.0%)	4 (44.4%)	42 (42.4%)
Not Reported	3 (3.4%)	1 (50.0%)	3 (33.3%)	7 (7.1%)

† Patient base: all patients who received at least 5 doses of FK463 and have proven or probable (liver, spleen, or disseminated only) invasive candidiasis at baseline (per protocol set); primary site = proven esophageal.

Medical Officer Comments: Seven (7) of 99 (7.1%) patients did not have baseline endoscopic grade reported. Most de novo EC patients, 47/88 (53.4%), had moderate to severe disease at baseline; while only 1/2 efficacy failure patients who received combination therapy had a baseline endoscopic grade recorded as mild, and 4/9 (44.4%) efficacy failure patients who received micafungin alone had severe EC.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Efficacy

Drug Exposure

For adult patients in the PPS set overall, the mean daily dose of micafungin was 72.1 ± 29.1 mg, and the mean maximum daily dose was 86.8 ± 46.7 mg. The mean maximum daily dose of micafungin was lower in *de novo* patients (76.6 ± 39.7 mg) than in efficacy failure patients (114.4 ± 48.7 for those who received micafungin plus another antifungal agent, and 104.7 ± 57.4 mg in those who received micafungin alone) The mean duration of therapy in adults overall was 21.9 ± 14.3 days, ranging from 5 to 102 days. The maximum dose of micafungin in the study was 400 mg administered for one day in a single patient. Among pediatric patients in the PPS, the overall mean duration of therapy was 31.5 ± 31.4 days, ranging from 5 to 162 days. The overall mean daily dose was 1.5 ± 0.85 mg/kg. The maximum daily dose received in children was 7.2 mg/kg micafungin. The table below summarizes micafungin dosing for each of the treatment groups for adult and pediatric patients in the Per Protocol Set.

**APPEARS THIS WAY
ON ORIGINAL**

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

Table 9. Summary of Micafungin Dosing (PPS) (adapted from Applicant's Tables 18 and 19, study report, 24 April, 2004)

Parameter	N	Duration of micafungin treatment (days) (mean ± SD)	Daily Dose (mean ± SD) (mg/day)	Maximum daily dose (mg) (mean ± SD)	Average cumulative dose (mg) (mean ± SD)
Adults					
<i>De novo</i> (N= 173)	173	19.7 ± 10.5	65.2 ± 23.5	76.6 ± 39.7	1332.9 ± 1027.3
Efficacy failure (micafungin + other antifungal agent) (N=40)	40	31.3 ± 23.3	89.1 ± 30.5	114.4 ± 48.7	2811.4 ± 2094.7
Efficacy failure (micafungin alone) N=27	27	21.9 ± 13.3	85.8 ± 38.5	104.6 ± 57.4	2193.2 ± 2372.4
Total Adult Patients	250	21.9 ± 14.3	72.1 ± 29.1	86.8 ± 46.7	1696.8 ± 1599.4
Children					
<i>De novo</i> (N=14)	14	17.7 ± 12.4	1.1 ± 0.3	1.3 ± 0.4	22.2 ± 20.5
Efficacy failure (micafungin + other antifungal agent) (N=18)	18	41.3 ± 41.2	1.6 ± 0.9	2.0 ± 1.5	72.2 ± 94.8
Efficacy failure (micafungin alone) (N=6)	6	34.2 ± 16.0	2.3 ± 1.1	3.1 ± 1.8	78.5 ± 47.1
Total Pediatric Patients	38	31.5 ± 31.4	1.5 ± 0.9	1.9 ± 1.4	54.8 ± 72.2

Medical Officer Comments: *Micafungin dosing and exposure was not analyzed separately in patients with EC.*

Primary Efficacy Endpoint- Global Response to Therapy

Overall, treatment success (complete or partial response) was reported in 91/99 (91.9%) of patients with EC. In the *de novo* treatment group, 82/88 (93.2%) patients with EC were considered treatment successes. In the efficacy failure group, 8/9 (88.9%) of those who received micafungin alone were considered treatment success; while the 1 patient who received micafungin plus another antifungal agent was a treatment failure, as shown in the table below.

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

Table.10 Investigator Global Assessment at EOT for Patients with EC (PPS) (Applicant's Table 26, study report 24 April, 2004)

	De Novo (n=88)	Efficacy Failure		Total [95% CI] (n=99)
		FK463 & Other (n=2)	FK463 Alone (n=9)	
Success	82 (93.2%)	1 (50.0%)	8 (88.9%)	91 (91.9%) [86.6%, 97.3%]
Complete response	58 (65.9%)	0 (0.0%)	6 (66.7%)	64 (64.6%)
Partial response	24 (27.3%)	1 (50.0%)	2 (22.2%)	27 (27.3%)
Failure	6 (6.8%)	1 (50.0%)	1 (11.1%)	8 (8.1%)
Stabilization	3 (3.4%)	0 (0.0%)	0 (0.0%)	3 (3.0%)
Progression	3 (3.4%)	1 (50.0%)	1 (11.1%)	5 (5.1%)
Not Evaluable	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Patient base: all patients who received at least 5 doses of FK463 and have proven or probable (liver, spleen, or disseminated only) invasive candidiasis at baseline (per protocol set); primary site = esophagus.

Medical Officer Comments: It is notable, that only two-thirds of the patients considered treatment successes in the de novo group, and in the efficacy failure group who received micafungin alone actually had a complete response to therapy; while one-third had a partial response.

The actual dose of micafungin received in these patients is not clear from the study report which states: "Treatment success was achieved in most of the esophageal candidiasis patients, 91.9% (91/99) at doses of 50 to 100 mg/day. The dose of micafungin was increased to improve therapeutic effect in 66/99 (66.7%) of patients with EC, and 59/66 (89.4%) patients had treatment success. The maximum dose ranged from 75 to 150 mg/day for these patients (3 patients were treated with a maximum dose of 125 mg/day, and 5 patients were treated with a maximum dose of 150 mg/day). "For the 33/99(33.3%) patients who did not have a dose increase, 32 patients received 50 mg/day (or 1 mg/kg/day), and 1 patient received 100 mg/day. Among patients who failed, 7 patients received 75-125 mg/day, and one patient received 50 mg/day micafungin.

Because a complete response was seen in only 64.6% patients, who received micafungin doses between 50 and 100 mg/day, these findings support the regulatory decision to have the applicant submit study 03-7-005 for review with this NDA. Study 03-7-005 utilized 150 mg/day micafungin in comparison with fluconazole 200 mg/day in the treatment of EC, and efficacy as measured by clinical cure was > 90% in both treatment groups.

In the independent reviewer's analysis of overall response at end-of-therapy, 90/100 (90.0%) patients with esophageal candidiasis were considered treatment successes, 67/100 (67%) patients had complete response to therapy, and 23/100 (23%) had a partial response to therapy. In the *de novo* group, 85/92 (92.4%) patients were considered treatment successes, and in the efficacy failure group, 5/7 (71.4%) patients who received micafungin alone were successes, and 0/1 patient in the micafungin plus other antifungal agent group achieved treatment success.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Medical Officer Comments: Note that the denominators (number of patients in treatment groups) differed in the independent reviewer's analysis. There was no significant difference between the Applicant's and independent reviewer's analysis for the de novo patients; but treatment success in the efficacy failure group was somewhat lower as judged by the independent reviewers. The independent reviewers were John Rex, M.D., and Luis Ostrosky-Zeichner, M.D. Dr. Rex is an internationally recognized authority in the treatment of fungal infections, and was also an investigator for this study. There was however, no reason to suspect any bias in his report.

Primary Treatment Outcome in Pediatric Patients

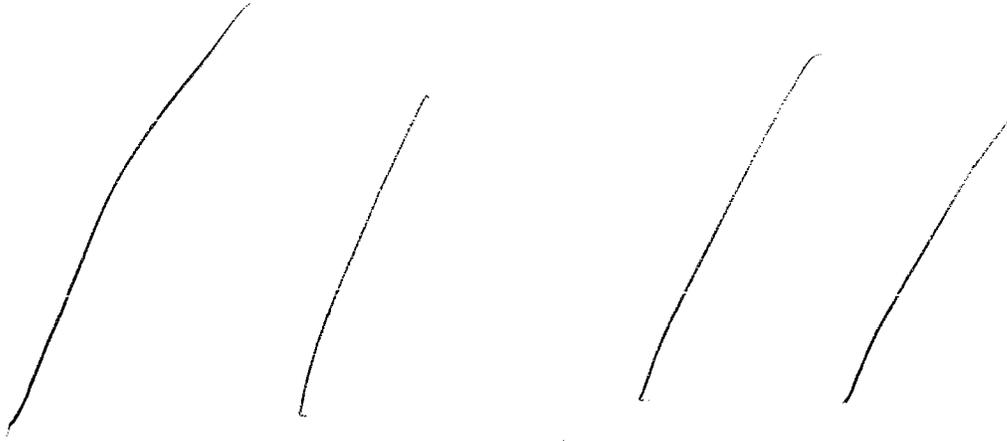


Table 12. Treatment Success for Patients with EC by *Candida* species at Baseline (Applicant's Table 38)

Candida Species	De Novo (n=88)	Efficacy Failure		Total (n=99)
		FK463 & Other (n=2)	FK463 Alone (n=9)	
Any <i>Candida</i> sp.	82/88 (93.2%)	1/2 (50.0%)	8/9 (88.9%)	91/99 (91.9%)
<i>C. albicans</i>	78/84 (92.9%)	0/1	5/6 (83.3%)	83/91 (91.2%)
<i>C. glabrata</i>	4/5 (80.0%)	--	2/2 (100.0%)	6/7 (85.7%)
<i>C. krusei</i>	3/3 (100.0%)	--	2/2 (100.0%)	5/5 (100.0%)
<i>Candida</i> sp. NOS	3/3 (100.0%)	1/1 (100.0%)	--	4/4 (100.0%)

Patient base: all patients who received at least 5 doses of FK463 and have proven or probable (liver, spleen, or disseminated only) invasive candidiasis at baseline (per protocol set); primary site = esophageal.

Medical Officer Comments: The mean dose of micafungin used for treatment of non-*C. albicans* isolates was generally higher than that used for treatment of *C. albicans* infections.

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

Secondary Efficacy Endpoints

Endoscopic Evaluation of Esophageal Mucosa at End-of-Therapy

A total of 91/99 (91.9%) patients had endoscopic evaluation at baseline, and 79/99 (79.8%) patients had endoscopy performed at the end of therapy. Overall, 72/99 (72.7%) patients had endoscopic clearing or improvement; while 61.6% (61/99), had clearing and 11.1% (11/99) had improvement at the end-of-therapy. Six of 99 (6.1%) patients had no change, and 1/99 (1.0%) had worsening at the EOT. These data are shown in the table below.

Table 13. Esophageal Mucosal Lesions at End-of-Therapy (PPS)(Applicant’s Table 39, study report, 24 April, 2004)

Baseline Status	End of Therapy Status	De Novo (n=88)	Efficacy Failure		Total (n=99)
			FK463 & Other (n=2)	FK463 Alone (n=9)	
Not Assessed	No Symptoms at Baseline	3 (3.4%)	2 (50.0%)	3 (33.3%)	8 (8.1%)
Mild	Cleared	12 (13.6%)	1 (50.0%)	1 (11.1%)	14 (14.1%)
	Worse	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Not Done	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
Moderate	Cleared	24 (27.3%)	0 (0.0%)	1 (11.1%)	25 (25.3%)
	Improved	3 (3.4%)	0 (0.0%)	0 (0.0%)	3 (3.0%)
	Unchanged	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Not Done	5 (5.7%)	0 (0.0%)	0 (0.0%)	5 (5.1%)
Severe	Cleared	21 (23.9%)	0 (0.0%)	1 (11.1%)	22 (22.2%)
	Improved	8 (9.1%)	0 (0.0%)	0 (0.0%)	8 (8.1%)
	Unchanged	4 (4.5%)	0 (0.0%)	1 (11.1%)	5 (5.1%)
	Not Done	5 (5.7%)	0 (0.0%)	2 (22.2%)	7 (7.1%)

Patient base: all patients who received at least 5 doses of FK463 and have proven or probable (liver, spleen, or disseminated only) invasive candidiasis at baseline (per protocol set) and had systemic esophageal candidiasis at baseline.

Medical Officer Comments: Thirteen patients in the PPS did not have an end-of-therapy endoscopic assessment. Each of these patients was considered a treatment success by the investigator. If these patients are counted as endoscopic failures, along with patients that were worse or unchanged at EOT, a total of 72/99 (72.7%) patients would be considered having endoscopic success at the end-of-therapy.

Relapse at 6-weeks Post-treatment for Patients with Esophageal Candidiasis

Of the 91/99 (91.9%) patients who had a successful response (complete or partial) at the end of therapy 9/99 (9.1%) patients experienced a relapse of EC, by 6 weeks post-therapy. Additionally, 5/99 (5.1%) patients treated for EC developed a new fungal infection during the 6-week post-treatment period. These infections are listed in the following table.

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

Table 14. Emergent* Fungal Infections in the Post-Treatment Period in EC Patients (adapted from applicant's Table 7, appendix 14.7, study report)

Patient number	Patient Classification	Baseline organism	Outcome at End of therapy	Last study day of micafungin	Onset of infection (study day)	Primary Site and organism for new infection
172877	Efficacy failure/micafungin alone	<i>C. albicans</i>	Success (complete)	Day 33	Day 41	OPC <i>C. albicans</i>
314480	<i>De novo</i>	<i>C. albicans</i>	Success (complete)	Day 18	Day 44	EC <i>Candida species</i>
314495	<i>De novo</i>	<i>C. albicans</i>	Success (partial)	Day 16	Day 30	EC <i>Candida species</i>
323472	<i>De novo</i>	<i>C. albicans</i>	Success (complete)	Day 21	Day 60	CNS <i>Cryptococcus neoformans</i>
324473	<i>De novo</i>	<i>C. albicans</i>	Failure (stabilization)	Day 7	Day 8	EC <i>C. lipolytica</i>

*Emergent = new site of infection or different fungal organism

Medical Officer Comments: *The applicant did not provide further information (eg. micafungin dose and duration of treatment) in the study summary regarding the patients who had a relapse of EC or an emergent fungal infection during the 6 week post-treatment period. Relapse of EC in patients with advanced HIV disease is not unusual unless the underlying immune deficiency is treated with antiretroviral therapy, or if the patient received antifungal prophylaxis, particularly for recurrent EC. In this study, 6 weeks post-treatment was used as the time point for evaluation of relapse in comparison to the other studies which evaluated EC relapse for this NDA (2- and 4-weeks in protocol 03-7-005, 2-weeks in FG463-21-09, and 2 weeks in 97-7-003). The relapse rate of 9.9% in this study is lower than that seen in the other studies for this NDA, which may be due to differences in the time of relapse evaluation, and in differences in determining the incidence of relapse (eg. in studies 03-0-005 and FG463-21-09, patients who died, were lost to follow-up, or received systemic antifungal therapy were counted as having EC relapse in the medical officer and statistical reviewer's analyses).*

Use of Antifungal Agents Post-Treatment

The use of antifungal agents was common in the post-treatment period. In the FAS, 135/353 (38.2%) patients received systemic and/or non-systemic antifungal agents for treatment or empirical therapy. In addition, 95/353 (26.9%) patients received systemic (67 patients) and/or non-systemic (41 patients) antifungal therapy for prophylaxis or maintenance therapy in the 6 week post-treatment period.

Medical Officer Comments: *The use of antifungal agents in the post-treatment period confounds the evaluation of relapse. Further analysis of antifungal therapy use in EC patients*

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

during this timeframe was not presented in the applicant's study report, and was not determined for this review.

Other Secondary Endpoints

A complete clinical response at the end-of-therapy was reported in 67/99 (67.7%) patients with EC. Mycological eradication was documented in 58/99 (58.6%) patients, and presumed eradication in 10/99 (10.1%); while mycological persistence was observed in 19/99 (19.2%) of patients at the end-of-therapy.

Efficacy Conclusions

1. Micafungin was effective for treatment of esophageal candidiasis in this study population. Overall treatment success (complete or partial response) was reported in 91/99 (91.9%) patients in the PPS; while complete treatment success was reported in 64/99 (64.6%) of patients. The secondary endpoints generally supported the primary outcome measure, overall treatment success.
2. The exact dose and duration of micafungin used in this study was variable. In general, patients who had *Candida albicans* isolated at baseline started at 50 mg/day micafungin; and patients with non-*C. albicans* isolated at baseline started at 100 mg/day micafungin. In approximately two-thirds of patients, the micafungin dose was increased incrementally during the treatment period.
3. Because only 4 pediatric patients (< 16 years old) were enrolled in this study, no firm conclusions can be drawn about efficacy of micafungin for EC in children.

Safety Evaluation

Patients enrolled in this study were included in the overall micafungin safety database of 2402 patients, used for safety analysis in the Integrated Summary of Safety for NDA 21-754.; and micafungin safety in this supportive study was not evaluated separately for this review

10.1.5 Normal laboratory values

In this review, US units were used for laboratory values when available, otherwise SI (standard international) units were used.

Normal Laboratory Values (Applicant's Appendix 12.1.7, 120-day Safety Update)

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

LABORATORY TEST	SI UNITS	HEBM LOW VALUE IN SI UNITS	HEBM HIGH VALUE IN SI UNITS	HEI UNITS	CONVERSION FACTOR TO US UNITS	HEBM LOW VALUE IN US UNITS	HEBM HIGH VALUE IN US UNITS
ALBUMIN	g/L	40	60	g/dL	0.1	4	6
ALKALINE PHOSPHATASE	U/L	30	120	U/L	1	30	120
AMYLASE	U/L	0	130	U/L	1	0	130
ABSOLUTE NEUTROPHIL COUNT	10 ⁶ /L	3150	6200	cells/mm ³	1	3150	6200
ATYPICAL LYMPHOCYTES	fraction	0	0.01	%	100	0	1
NEUTROPHIL BANDS	fraction	0.03	0.05	%	100	3	5
BAEOPHILS	fraction	0	0.0075	%	100	0	0.75
BAEOPHILS, ABSOLUTE UNITS	10 ⁶ /L	15	50	cells/mm ³	1	15	50
NYELOBLAST	fraction	0	0.01	%	100	0	1
BUN	mmol/L	3	6.5	mg/dL	2.801	8.403	18.2055
CALCIUM	mmol/L	2.2	2.56	mg/dL	4	8.8	10.24
CHLORIDE	mmol/L	95	105	mmol/L	1	95	105
CREATINE PHOSPHOKINASE	U/L	0	150	U/L	1	0	150
CREATININE CLEARANCE	ml/s	1.24	2.08	ml/min	60	74.4	124.8
CREATININE	umol/L	50	110	mg/dL	0.0113	0.565	1.243
DIRECT BILIRUBIN	umol/L	0	4	mg/dL	0.0585	0	0.234
ECGINOMYELS	fraction	0.01	0.03	%	100	1	3
ECGINOMYELS, ABSOLUTE UNITS	10 ⁶ /L	50	250	cells/mm ³	1	50	250
GST	U/L	0	30	U/L	1	0	30
GLUCOSE	mmol/L	3.9	6.1	mg/dL	16.015	70.2585	109.892
BICARBONATE	mmol/L	22	28	mmol/L	1	22	28
HEMATOCRIT	fraction	0.33	0.49	%	100	33	49
HDL	mmol/L	0.8	2.35	mg/dL	38.6698	30.9358	90.874

LABORATORY TEST	SI UNITS	HEBM LOW VALUE IN SI UNITS	HEBM HIGH VALUE IN SI UNITS	HEI UNITS	CONVERSION FACTOR TO US UNITS	HEBM LOW VALUE IN US UNITS	HEBM HIGH VALUE IN US UNITS
HEMOGLOBIN	g/L	115	180	g/dL	0.1	11.5	18
POTASSIUM	mmol/L	3.5	5	mmol/L	1	3.5	5
LEN	U/L	50	150	U/L	1	50	150
LDL	mmol/L	1.3	4.0	mg/dL	38.6698	50.2707	159.482
LYMPHOCYTES	fraction	0.25	0.33	%	100	25	33
METANUCLCYTES	fraction	0	0	%	100	0	0
MAGNESIUM	mmol/L	0.8	1.2	mg/dL	2.43	1.944	2.916
MONOCYTES	fraction	0.03	0.07	%	100	3	7
MONOCYTES, ABSOLUTE UNITS	10 ⁶ /L	285	500	cells/mm ³	1	285	500
ODIUM	mmol/L	135	147	mmol/L	1	135	147
PLATELETS	10 ⁹ /L	130	400	10 ⁹ /L	1	130	400
PHOSPHATE	mmol/L	0.8	1.6	mg/dL	3.1	2.48	4.96
NEUTROPHILS	fraction	0.54	0.62	%	100	54	62
PROTHROMBIN TIME	seconds	9	12	seconds			
RED BLOOD CELL	10 ¹² /L	3.5	5.9	10 ¹² /L	1	3.5	5.9
RETICULOCYTE COUNT	fraction	0.001	0.024	%	100	0.1	2.4
SETRIC	10 ⁹ /L	10	75	10 ⁹ /L	1	10	75
SPT	U/L	0	35	U/L	1	0	35
SPT	U/L	0	35	U/L	1	0	35
TOTAL BILIRUBIN	umol/L	2	18	mg/dL	0.0585	0.117	1.053
TOTAL CHOLESTEROL	mmol/L	0	6.85	mg/dL	38.6698	0	264.888
TRANSFERRIN	g/L	1.7	3.7	mg/dL	100	170	370
TOTAL PROTEIN	g/L	60	80	g/dL	0.1	6	8

BEST POSSIBLE COPY

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

LABORATORY TEST	SI UNITS	HEBM LOW VALUE IN SI UNITS	HEBM HIGH VALUE IN SI UNITS	SI UNITS	CONVERSION FACTOR TO US UNITS	HEBM LOW VALUE IN US UNITS	HEBM HIGH VALUE IN US UNITS
TRIGLYCERIDES	mmol/L	0	1.8	mg/dL	88.574	0	159.433
URIC ACID	umol/L	120	420	mg/dL	0.0168	2.016	7.056
WHITE BLOOD CELLS	10 ⁹ /L	3.2	9.8	10 ⁹ /L	1	3.2	9.8

10.2 Line-by-Line Labeling Review



21 Page(s) Withheld

 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

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

Rx only

Manufactured for:
Fujisawa Healthcare, Inc.
Deerfield, IL 60015-2548

March 2005

MYCAMINE is a trademark of Fujisawa Pharmaceutical Company Ltd., Osaka, Japan.

10.3. ODS Consultations

10.3.1 ODS Consultation on Hepatic Safety of Micafungin

Dr. John Senior's consultation regarding the hepatic safety of micafungin follows below:

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 31 January 2005

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmaco-epidemiology and Statistical Science (OPSS), HFD-030

TO: Renata Albrecht, M.D., Director, Division of Special Pathogen and Immunologic Drug Products (DSPIDP), HFD-590

MARY SINGER, M.D., MEDICAL REVIEWER, HFD-590

VIA: Mark Avigan, M.D., Director, Division of Drug Risk Evaluation (DDRE), HFD-430; Office of Drug Safety (ODS), HFD-400
Paul Seligman, M.D., Director, (OPSS), HFD-030

SUBJECT: ODS CONSULTATION #D040713 REGARDING HEPATOTOXICITY POSSIBLY INDUCED BY USE OF MICAFUNGIN (MYCAMINE, FUJISAWA) FOR TREATMENT OF ESOPHAGEAL CANDIDIASIS (NDA 21-754)

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Documents reviewed:

- 1) Consultation request from HFD-590 to OPSS/ODS/DDRE dated 26 October 2004, assigned #D040713 for desired completion date of 25 January 2005
 - 2) Packages of material (37 volumes) from Fujisawa Pharmaceuticals providing:
 - a) 120-day safety update to NDA 21-754 submitted 24 August 2004: 17 volumes
 - b) Response to September 10 request for information, submitted 22 September: 3 volumes
 - c) Clinical protocols for 8 studies for NDA 21-506 and 21-754: 2 volumes
 - d) Response to October 13 request for information, submitted 25 October: 1 volume
 - e) Response to October 20 request for information, submitted 29 October: 1 volume
 - f) Response to October 27 request for information, submitted 12 November: 1 volume
 - g) Response to December 14 request for information, submitted 22 December: 12 volumes
 - 3) Medical literature (PubMed) on echinocandin toxicity 21 January 2005
 - 4) DSS, DFS listings for reviews entered to 21 January 2005 for micafungin, NDA 21-754
 - 5) Additional two cases of possible micafungin-induced injury received by fax 24 January 2005
-

In view of the huge amount of material submitted in the 37 volumes cited above, plus the original New Drug Application (NDA) submission, I asked Dr. Mary Singer what critical questions I should address in this consultation. She suggested on 13 January 2005 that it would be most helpful for me to focus my attention on the cases that were reviewed by a special panel of experts. Division 590 on 27 October 2004 had requested Fujisawa to have a panel of external expert hepatologists review all deaths due to hepatic failure and serious events of hepatic failure in the safety database. That panel included

They were asked to review 19 cases of "liver damage" and "hepatic failure" to assess the relation of the adverse event to study drug administration. Of the 19 patients, 14 had been treated with micafungin, 4 with fluconazole, and 1 with neither ("placebo"), but panelists were blinded to what treatment the patients had. They were asked to assess whether the adverse hepatic events were not related, possibly related, or related to study drug, as follows:

Not Related	Adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has much more likely alternative etiology).
Possibly Related	Adverse event has a strong temporal relationship to study drug and another etiology is equally or less likely.
Related	Adverse event has a strong temporal relationship to study drug or recurs on rechallenge, and another etiology is unlikely or significantly less likely.

Fujisawa assembled information on the 19 cases, including for each a patient profile and narrative, plus laboratory, radiology, liver biopsy and autopsy reports if available. Treatment with micafungin, fluconazole, or neither was not stated. The 19 cases, along with a copy of the current Investigator Brochure, were sent to each of the panelists during the week of 8 November. They reviewed the cases individually, and then "met" by telephone conference on 23 November 2004 to discuss each of the cases and to reach their consensus on the association of study drug with the occurrence of the hepatic

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

events, with their reasons for arriving at the decisions. Their final report of the review was sent to the sponsor that day by Dr. — who said that, from their review and deliberations, there appeared to be no clear signal of hepatotoxicity from micafungin, but they emphasized that the underlying medical conditions in these patients were extraordinarily complex. The patients were receiving many other types of medications, were immuno-compromised, and had serious underlying diseases including AIDS, malignancies, and pre-existing end-stage liver disease. Of the 19 cases, they felt that 13 were not related, 6 possibly related, and none probably related to study drug. The report of the external panel of expert hepatology reviewers was then forwarded to HFD-590 on 1 December 2004, which then requested on 14 December additional information, including as item 10 a request for a copy of the package of information given to the expert panel, exactly as sent, with the data on the 19 patients and the Investigator Brochure. Fujisawa responded on 22 December, and sent the material requested as volume 8 of a total of 12 volumes.

Comment: The accurate attribution of causality of adverse events as drug-induced has been one of the most difficult problems in medicine to resolve, despite many attempts over the past 35 years or so. Most of the initial attempts considered the problem in general, for any drug-induced adverse reaction (Irey, 1971; Feinstein, 1974; Karch and Lasagna, 1975; Kramer, et al., 1979; Naranjo, et al., 1981), but special efforts were subsequently undertaken in France (Danan, et al., 1987, 1988; Bénichou, et al., 1990, 1993) to address the question of drug-induced liver injury (DILI), and soon after in other European countries (Maria and Victorino, 1997; Aithal, et al., 2000; Lucena, et al., 2001). More recently, with the formation of the Drug-Induced Liver Injury Network (DILIN) funded by the National Institutes of Health (NIH) in 2003, particular attention has been aimed at moving beyond simply opinion-based overview decisions as to the quantitative likelihood of drug-induced causality of the liver reactions. It has been recognized for many years (Goodman, 2002) that there are no pathognomonic histologic changes to make a certain diagnosis that an hepatic disorder is caused by exposure to a drug, as opposed to being caused by a non-drug or disease etiology. At most it can be said that a given set of findings on liver biopsy or autopsy may be “compatible with” or “consistent with” drug causation. There are no laboratory tests that are diagnostic, either. The diagnosis of DILI therefore is one of exclusion, requiring that other possible causes be ruled out, before concluding that it may have been the drug that caused the problem. Time relationships of exposure to drug are critical, for the reaction must follow the exposure, although by how much time is still debatable. Generally, it is widely believed that if the reaction subsides when exposure to drug is stopped (dechallenge), that is some evidence in favor of drug-causation; even stronger evidence is reappearance of the reaction if drug administration is resumed (rechallenge), but that is less and less frequently done intentionally because of the danger of a more severe, irreversible reaction, as well as for ethical and legal liability reasons. To go beyond what the expert panel of hepatologists did when reviewing the 19 cases, let us consider in more detail the semi-quantitative methods developed initially in France, and now widely used throughout the world (Lee, 2000; Kaplowitz, 2001; Kaplowitz, et al., 2003) and under active investigation by the DILIN group.

French investigators (Danan and Bénichou, 1987-1993) worked for years to develop national and international consensus on what information would be needed and how to weight that information to make a reasonably certain diagnosis of DILI. They developed a method for typing a given liver reaction as principally hepatocellular or cholestatic, or mixed, based on the ratio (R) of relative rise in serum activity of alanine aminotransferase (ALT) to alkaline phosphatase (ALP) at the time of onset of

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

the hepatic reaction, or first set of clearly abnormal laboratory findings, both expressed as multiples of the upper limit of the normal range for each measure.

DETERMINING THE TYPE OF ACUTE LIVER INJURY

International Consensus (1990), *J Hepatol* **11**: 272-6.

<ul style="list-style-type: none"> Ratio (R) of serum activities of ALT/ ALP, in xULN, measured together at time liver injury first recognized 	
<ul style="list-style-type: none"> <i>Hepatocellular</i> 	<ul style="list-style-type: none"> $R \geq 5$, OR ($ALT > 2xULN$ and ALP in normal range)
<ul style="list-style-type: none"> <i>Cholestatic</i> 	<ul style="list-style-type: none"> $R \leq 2$, OR ($ALP > 2xULN$ and ALT in normal range)
<ul style="list-style-type: none"> <i>Mixed</i> 	<ul style="list-style-type: none"> $2 < R < 5$ AND ($ALT > 2xULN$ and $ALP > ULN$)

- Note: ALT, alanine amonotransferase; ALP, alkaline phosphatase; xULN, multiples of the upper limit of the normal range.

They then assembled teams of experts from Europe and the United States to define terminology, establish standards and definitions, and decide what clinical information was critical to making the best decisions about drug causality. The time of drug exposure and course of the hepatic reaction were agreed to be essential factors, with positive weight for reaction following drug exposure, then subsiding when exposure was stopped, and reappearance if drug exposure was resumed. Negative weights were applied if the timing was wrong. Other possible causes for acute liver injury were important to determine, including acute viral hepatitis A or B (much less often acute hepatitis C), ischemic hepatitis following shock or heart failure, recent heavy alcohol consumption, acute cholelithiasis, autoimmune hepatitis, and less often other disease causes such as acute onset of Wilson's disease, infections with other viruses (cytomegalic, herpes simplex, Ebstein-Barr). Also considered were other drugs that might have been taken concomitantly, and the known history of hepatotoxicity of the drugs, both the one in question and the concomitant medications. Weights for each factor, ranging from +3 to -3 points were assigned, by consensus of the experts, resulting in a total score that could range from -8 to +14. Scores of 0 or less were taken to exclude the possibility of drug-induced injury, 1 or 2 unlikely, 3-5 possible, 6-8 probable, and 9-14 as highly probable.

Because both Danan and Bénichou at that time were employed by the pharmaceutical firm of Roussel-Uclaf, the system of scoring was called "RUCAM," Roussel-Uclaf Causality Assessment Method. The simplified RUCAM scoring system, as published in 1993 (Danan, et al.; Bénichou, et al.), and still in use ten years later (Danan, 2003):

Criteria for Causal Assessment of Drug-induced Hepatocellular Liver Injury

1. Temporal relationship of start of drug to start of illness

- | | |
|--|----|
| 1. Initial treatment: onset in 5-90 days; subsequent treatment course: 1-15 days | +2 |
| 2. Initial treatment <5 or >90 days; subsequent treatment course: > 15 days | +1 |
| 3. After stopping drug: onset within 15 days, or within 15 days after subsequent treatment | +1 |
| 4. Otherwise | 0 |

5.

2. Course

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

ALT decreases \geq 50% from peak within 8 days	+3
ALT decreases \geq 50% from peak within 30 days	+2
If the drug is continued or decrease \geq 50% from peak >30 days, or inconclusive	0
Against causative role for drug	-2

3. Risk factors

Alcohol use, 1; No alcohol use, 0	0 or 1
Age \geq 55 years, +1; Age < 55 years, 0	0 or 1

4. Concomitant drug

No concomitant drug administered	0
Concomitant drug with suggestive or compatible time of onset	-1
Concomitant known hepatotoxin with suggestive or compatible time of onset	-2
Concomitant drug with positive rechallenge or validated diagnostic test	-3

5. Non-drug causes: Six are primary: recent hepatitis A, B, or C, acute alcoholic hepatitis (AST \geq 2x ALT), biliary obstruction, recent hypotension (especially if heart disease).

Secondary group: Underlying other disease; possible CMV, EBV or HSV infection

All primary and secondary causes reasonably ruled out:	+2
All 6 primary causes ruled out	+1
4 or 5 primary causes ruled out	0
Fewer than 4 primary causes ruled out (maximum negative score for items 4 and 5: -4)	-2
Non-drug cause highly probable	-3

6. Previous information on hepatotoxicity of the drug in question

Package insert or labeling mention	+2
Published case reports but not in label	+1
Reaction unknown	0

7. Rechallenge

Positive (ALT doubles with drug in question alone)	+3
Compatible (ALT doubles with same drugs as given before initial reaction)	+1
Negative (Increase in ALT but \leq 2 X ULN, same conditions as when reaction occurred)	-2
Not done, or indeterminate result	0

Total (range of algebraic sum: -8 to +14)

Note: Item 4 and 5 cannot exceed a score of -4

**Interpretation: Highly probable, >8; Probable, 6-8; Possible, 3-5;
Unlikely, 1-2; Excluded, \leq 0**

Applying the RUCAM to a given case still requires experience and skill, as well as a consistent approach to how the items are defined. One of the problems in scoring the likelihood that a given hepatic abnormality is a DILI has been the amount and quality of information available to whomever is

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

attempting to judge possible causality. This led the DILIN Causality Committee to list information that is needed in order to exclude non-drug causes of a given hepatic reaction. Items felt to be critical were:

DILIN DATA COMPLETENESS CHECKLIST CRITICAL INFORMATION FOR DECIDING ON CAUSE OF LIVER INJURY

- | | | | |
|----|---|--------|----------------|
| 1 | Were details of drug exposure including dose, drug start and stop date recorded? | No ___ | Yes ___ |
| 2 | Was lifetime history of medication use from the same therapeutic class of agents recorded? | No ___ | Yes ___ |
| 3 | Was timing of clinical liver disease recorded? | No ___ | Yes ___ |
| 4 | Were key history and PE data present? | No ___ | Yes ___ |
| 5 | Was assessment for prior liver disease performed? | No ___ | Yes ___ |
| 6 | Were doses, start and stop dates of competing prescription medications recorded? | No ___ | Yes ___ |
| 7 | Were doses, start and stop dates of OTC and complementary/alternative agents recorded? | No ___ | Yes ___ |
| 8 | Was baseline EtOH history known? | No ___ | Yes ___ |
| 9 | Was baseline ALT recorded? | No ___ | Yes ___ |
| 10 | Were serial ALT values recorded? | No ___ | Yes ___ |
| 11 | Was baseline total bilirubin recorded? | No ___ | Yes ___ |
| 12 | Were serial total bilirubin values recorded? | No ___ | Yes ___ |
| 13 | Was baseline AP recorded? | No ___ | Yes ___ |
| 14 | Were serial AP values recorded? | No ___ | Yes ___ |
| 15 | Was baseline PT (INR) recorded? | No ___ | Yes ___ |
| 16 | Were serial PT (INR) values recorded? | No ___ | Yes ___ |
| 17 | Were data for anti-HAV IgM recorded? | No ___ | Yes ___ |
| 18 | Were data for HBsAg recorded? | No ___ | Yes ___ |
| | <i>If HBsAg was positive for >6 months, please be sure to also answer questions 30 and 31.</i> | | |
| 19 | Were data for anti-HBc IgM recorded? | No ___ | Yes ___ |
| 20 | Were data for HCV RNA recorded? | No ___ | Yes ___ |
| | <i>If HCV RNA was positive for >6 months, please be sure to also answer question 32.</i> | | |
| 21 | Were data for autoimmune hepatitis (ANA, immunoglobulins) recorded? | No ___ | Yes ___ |
| 22 | Was serum ceruloplasmin, if under 50, recorded? | No ___ | Yes ___ |
| 23 | Was history of hypotension or CHF recorded? | No ___ | Yes ___ |
| 24 | Were liver ultrasound, CT, or MRI data recorded? | No ___ | Yes ___ |
| 25 | Was ERCP performed, and if so, are data available? | No ___ | Yes ___ |
| 26 | Were liver biopsy data present? | No ___ | Yes ___ |
| 27 | Were data on rechallenge available? | No ___ | Yes ___ |
| | <i>Data related to chronic HIV, HBV or HCV:</i> | | |
| 28 | If the patient had a history of HIV disease, was baseline CD4 recorded? | No ___ | Yes ___ NA ___ |
| 29 | If HIV was positive, were serial CD4 and HIV RNA values recorded? | No ___ | Yes ___ NA ___ |
| 30 | If HBsAg positive >6 months, prior HBV DNA, HBeAg, anti-HBe, treatment recorded? | No ___ | Yes ___ NA ___ |
| 31 | If HBsAg was positive for >6 months, were data on anti-HDV available? | No ___ | Yes ___ NA ___ |
| 32 | If HCV RNA positive >6 months, were prior HCV RNA, ALT, and treatment recorded? | No ___ | Yes ___ NA ___ |

Note: PE, physical examination; ALT, alanine transaminase; ; ALP, alkaline phosphatase; ; PT, prothrombin time; INR, international ratio; Serious = hospitalized, disabling, life threatening, or fatal; HAV, hepatitis A virus; IgM, immunoglobulin M; HBV, hepatitis B virus; ; HCV, hepatitis C virus; RNA, ribonucleic acid assay for HCV; ANA, antinuclear antibodies; EtOH, , ethanol; CHF, congestive heart failure; CT, computed tomography; MRI, magnetic resonance imaging.

Comment: Several of these items contain two or more questions, which cannot be well answered by a simple yes or no, and the quality of information for each is not assessed, just whether or not some information was available or recorded. Nevertheless, it is valuable for scoring the RUCAM to have as much information as possible. It may be unlikely that many cases will have all the information listed above, but it is perhaps useful to make some effort to quantitate how much information was indeed available for each of the cases to be adjudged. It has been the experience of all who attempt to use spontaneously reported data, such as reports to MedWatch, that there is much information missing.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

The DILIN group recently (January 2005) called Dr. Danan, now working at Aventis in Paris, to resolve some questions of definition, so that in the future they can apply the method to scoring putative DILI cases in both retrospective review of cases associated with drugs known to cause hepatotoxicity of different types (isoniazid, phenytoin, Augmentin: clavulanic acid + amoxicillin), and valproic acid), and to prospective study of DILI cases from any drug. Use of the RUCAM is still something of an art, and obtaining accurate and reproducible results both within raters at different times and between raters at any time is still a work in progress. Proper use of the RUCAM requires that considerable amounts of good information be gathered. Simple failure to rule out 3 or more of the 6 primary disease causes of acute liver injury generates a -2 score for item 5, which will negate a +2 score for initial onset within 5-90 of first drug exposure. If nothing is known about the course after stopping the drug (dechallenge), and if there are no risk factors of age 55 or more or use of alcohol, no rechallenge is done, no concomitant drug likely to have caused the reaction was known to have been given, and no labeling or literature information available, then a RUCAM score of 0 will be generated, which is taken as excluding DILI. The RUCAM demands that adequate information be obtained, and allows an interpretation of "excluded" simply by failing to gather and record adequate information. This will need to be borne in mind as we proceed.

Finally, after assessing the quantity of information available, and using that information to score the likelihood that a DILI has occurred, a global assessment can be attempted, using a five-point scale:

Based on your assessment of the information available and RUCAM scoring, how likely do you assess the hepatic abnormalities to be drug-induced?

- Definite More than 95%
- Very likely >75-95%
- Probable >50-75%
- Possible 25-50%
- Unlikely <25%

Therefore, we shall try to apply these methods to assessing the apparent likelihood of causation of the selected cases as drug-induced injury, and then compare the findings to the consensus arrived at by the expert panel. As requested by Dr. Singer on 13 January 2005, we shall start by considering cases #1008, 10665008, 10745035, 063786, 262780, 262788, 287679, 0203501, and 474177, cases thought to be relatively less confounded, or in younger patients. Then, I shall consider the other 10 cases of the 19 reviewed by the special panel of experts.

In the tables below, I shall summarize patient identification information, acute liver disease, other concomitant or underlying diseases, concomitant medications, quantity and quality of information available, the RUCAM score, and my global assessment as an estimated percent likelihood that the drug may have caused the liver injury observed or diagnosed. This will not be an estimation of whether the drug may have caused the death of the patient, only the acute liver disease. I shall use the DILIN 32-question checklist of data completeness, and apply the information available in the patient profile and narrative provided for each case by the sponsor, as reviewed by the expert panel of external hepatologists. Finally, after reviewing all 19 cases, I shall compare the consensus report by Dr. Maddrey sent on 23 November 2004, and comment on agreements or disagreements.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
---------	---------------------	---------------------	-------------	-------------	-------	--------

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL					
#1008 M48b — Pretoria, South Africa	-3	40	19	125	0.35	HIV: asthenia, diarrhea, cachexia. CD4 = 290/μL inv esophageal candidiasis. tuberculosis	micafungin to — (14) cotrimoxazole betaclopramide loperamide flumazenil	9 + 20 – 3 NA very poor	+2 onset -2 <3 R/Os = 0 inadequate information	50%, possible
	7	49	19	132	0.76					
	14	2068	322	122	0.76	died — (15), of aggravated tuberculosis				
	hepatocellular injury nausea (7), vomiting (8), confusion (13), hepatorenal failure (13)									

Comment: death may have resulted from the advanced underlying disease, but did micafungin cause the acute terminal liver failure?

Note: M, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL					
#10665008 F31b — Pretoria, South Africa	-1	47	28	103	0.29	HIV: severe cachexia. CD4 = 34/μL inv esophageal candidiasis. reactivated tuberculosis	fluconazole to — (21) Voltaren Panadol Cifran Rifafour Maxolon	8 + 21 – 3 NA very poor	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	30%, possible
	7	49	22	163	0.23					
	16	44	15	128	0.76	died — (21), of pneumonia – Pneu. carinii				
	21	4002	1274	294	3.74					
	hepatocellular injury nausea (16), anxiety (16), hepatic failure (21)									

Comment: death may have resulted from the tuberculosis, but did fluconazole or other drug cause the acute terminal liver failure?

Note: F, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL					
#10745035 M34b — Pretoria, South Africa	-3	121	65	264	0.94	HIV: lymphadenopathy, cachexia, diarrhea, anemia CD4 = 97/μL inv esophageal candidiasis. reactivated tuberculosis alcohol abuse	micafungin to — (5), stop because liver failure Rifinah DS-24 Voltaren Bactrim herbal cough syrup	6 + 22 – 4 NA very poor	+2 onset -2 <3 R/Os +1 alcohol -1 other drug = 0 inadequate information	25%, possible
	5	66	29	208	8.25	died — (17), of reactivated tuberculosis				
	?? alcoholic hepatic injury jaundice (5), severe hepatic failure (4-21)									

Comment: death may have resulted from tuberculosis, but did micafungin or other drug aggravate advanced alcoholic liver disease?

Note: M, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL					
#063786 M58c — location not stated	1	158	102	332	30.5	end-stage liver disease, corticosteroid therapy invasive lung aspergillosis. died — (8), of hepatic failure from unknown liver disease	micafungin to — (7) Solumedrol Prevacid Ambisome Haldol	7 + 20 – 5 NA very poor	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	15%, unlikely
	7	266	132	472	43.0					
	?? previous liver disease jaundice (5), severe hepatic failure (4-21)									

Comment: death may have resulted from tuberculosis, but did micafungin or other drug aggravate advanced unknown liver disease?

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease					underlying diseases	medications	information	RUCAM	global
	Sday	AST	ALT	ALP	TBL					
#262780 M4c — location not stated	1	32	38	335	1.70	leukemia, bone marrow transplant invasive lung aspergillosis.	micafungin to — (29) ABELCET itraconazole Tylenol Foscarnet Zithromax Actigall Many, many others	10 + 17 – 5 NA poor	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	25%, possible
	9	25	35	345	2.40	died — (31), of interstitial pneumonia, with multiorgan failure				
	16	20	33	236	4.10					
	23	35	57	314	2.20					
	30	196	178	581	9.80					
	cholestatic liver disease nausea (5), vomiting (5), itch (18), bilirubin elevation (24), hepatic failure (27)									

Comment: death may have resulted from tuberculosis, but did micafungin cause or aggravate cholestatic liver disease?

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable..

patient	acute liver disease	underlying diseases	medications	information	RUCAM	Global
#262788 M16b — Memphis, TN	Sday AST ALT ALP TBL -2 87 58 156 5.7 9 118 49 279 21.1 10 134 56 353 24.8 cholestatic liver disease bilirubin elevation (2), hepatic failure (2), renal failure (4)	acute myelogenous leukemia, allogenic marrow transplant invasive lung aspergillosis. probable liver candidiasis died (10), of respiratory distress syndrome autopsy confirmed	micafungin to (10) fluconazole Myclex Ambisome many others	10 + 17 - 5 NA poor	-2 <3 R/Os -1 other drug = -3 inadequate information	<5%, very unlikely

Comment: death may have resulted from lung disease, but cholestatic liver disease preceded micafungin, so very unlikely M-DILI.

Note: M, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#287679 F51c — location not stated	Sday AST ALT ALP TBL 1 50 59 946 7.08 7 57 26 1217 9.65 14 134 63 2601 11.7 20 159 112 3188 19.6 cholestatic liver disease pre-existing disease; pain(13), ascites (19), jaundice (30)	pancreatic carcinoma Candida albicans septicemia. died (30), of hepatic failure secondary to spread of pancreatic cancer	micafungin to (19) amphotericin B vancomycin Panadol Tazocin others	11 + 16 - 5 NA fair	-2 <3 R/Os -3 panc. CA -1 other drug = -6 inadequate information	<1%, ruled out

Comment: death resulted from pancreatic cancer, and cholestatic liver disease preceded micafungin, so very unlikely M-DILI.

Note: F, female; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#0203501 F36o — U MN Minnea- polis MN	Sday AST ALT ALP TBL 1 37 43 81 0.9 4 27 37 65 0.6 12 20 17 69 1.5 16 5970 754 173 10.5 hepatocellular liver injury anorexia (6), liver large (10), confusion and renal failure (15), coagulation disorder (16), liver failure(16), cardiac arrest (17), GI bleed (18)	acute myelogenous leukemia, allogenic marrow transplant no fungal infection proved mitral regurgitation resistant bacteremia died (19), of gastro- intestinal hemorrhage, after liver failure with coagulation disorder	fluconazole to (15) IV heparin (?flush) acetaminophen Ativan Halcion tobramycin many others	13 + 14 - 5 NA fair	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	40% possible

Comment: death resulted from GI bleeding, but did fluconazole cause the acute liver failure and coagulation disorder?.

Note: F, female; o, Oriental; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#474177 M40c — Mainz, Germany	Sday AST ALT ALP TBL 1 85 66 696 5.17 7 79 29 638 11.9 14 99 52 691 14.5 21 134 66 657 19.4 28 444 510 1680 25.0 34 419 381 1470 40.4 35 363 298 1442 41.8 cholestatic liver disease jaundice (5), pruritus (16), renal failure (33), shock, coma, hepatic failure (36),	leukemia, unspecified probable lung aspergillosis. alcohol abuse died (), of leukemia	micafungin to (34) amphotericin B Distranervin cyclophosphamide Cytarabine Haldol Ambisome Caspofungin many others	10 + 17 - 5 NA poor	-2 <3 R/Os -1 other drug = -3 inadequate information	<5%, very unlikely

Comment: death may have resulted from terminal bleed, but cholestatic liver disease preceded micafungin, so very unlikely M-DILI.

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Comment: For these 9 cases, chosen by Dr. Mary Singer for me to review first, there are none that show a RUCAM score that suggests even possible drug causation of the liver disease, but mainly because the data available to insert into the RUCAM system are so inadequate. Without sufficient data, the RUCAM can yield misleading interpretations that the likelihood of DILI is excluded. On the other hand, the exercise of examining carefully just what information is and is not available may allow better-informed global assessments that may lead to different conclusions with higher levels of likelihood that the drugs in question may have at least aggravated severely any pre-existing liver disease or may have induced liver disease in otherwise very sick people. With these thoughts clearly in mind, let us now consider the other 10 cases of the 19 reviewed by the expert panel.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#384301 M52c — Ottawa, ON CA	Sday AST ALT ALP TBL 1 25 33 163 17.9 4 24 23 387 25.8 7 45 28 188 21.5 8 66 33 134 24.2 cholestatic liver disease jaundice, liver failure (-??), hemorrhage (8), hepatic failure (9)	Hodgkin's lymphoma no fungal infection proved. renal insufficiency, Cr 3.15 sepsis, V tach (3), severe acidosis (6), Died — (9), of hepatic failure. Autopsy confirmed dx	no antifungal agent ("placebo") ← to — (8) cefotaxime vancomycin acyclovir Ativan many others	10 + 17 – 5 NA poor	onset before -2 <3 R/Os -3 other cause = not DILI incompatible inadequate information	<1%, not DILI

Comment: death resulted from lymphoma infiltration of the liver, preceding administration of "placebo", so not-DILI.

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#2194007 M77c — Stanford Palo Alto CA	Sday AST ALT ALP TBL 1 546 117 25 2.0 5 234 17 66 2.9 8 113 17 95 8.1 12 116 22 149 16.3 hepatocellular disease shocked liver failure (-??), hemorrhage (8), hepatic failure (9)	massive blood loss, aortic aneurysm repair (-1) no fungal infection proved. renal insufficiency, Cr 3, diabetes, respiratory distress, Died — (9), in shock, with nepatorenal, respiratory failure	micafungin — to — (13) Kefzol midazolam dopamine insulin many others	10 + 17 – 5 NA poor	onset before -2 <3 R/Os -3 other cause = not DILI incompatible inadequate information	<1%, not DILI

Comment: death resulted from hypotensive shock, ischemic liver disease, preceding administration of micafungin, so not-DILI.

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#20785 F30c — U MN Minnea -polis MN	Sday AST ALT ALP TBL 8 32 30 236 0.7 15 35 38 257 0.7 28 35 26 257 0.6 54 16 12 150 2.5 66 27 203 3.4 80 44 244 34.6 93 64 844 51.3 cholestatic liver disease abd. pain (18), confusion (37) hepatic failure (78)	acute myelogenous leukemia, post marrow transplant probable lung aspergillosis. died — (94), of veno occlusive disease, sepsis, liver failure, renal failure	micafungin — (77) amphotericin B itraconazole Percocet Tylenol Ativan Dilantin CellCept Many others	12 + 15 – 5 NA fair	+2 onset -2 <3 R/Os -1 other drug -3 other cause = -4 inadequate information	<10%, unlikely

Comment: death may have resulted from veno-occlusive disease, but did micafungin aggravate the terminal liver failure?

Note: F, female; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#33885 F62b —	Sday AST ALT ALP TBL -1 44 41 652 2.7 7 82 55 540 2.3 14 5836 783 1155 3.2	duodenal carcinoid tumor septicemia, Candida glab. diabetes, cachexia, sepsis, pancreatitis, hypotension,	micafungin — to — (13) fluconazole	10 + 17 – 5 NA	+2 onset -2 <3 R/Os -1 other drug -3 other cause	40%, possibly worsened

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

location not stated	hepatocellular injury added ascites (6), confusion (14), vomiting (15), renal failure (15), hypotension (15)	renal failure, cholestatic liver disease from carcinoid died (15), sepsis, multiorgan failure	APAP propoxyphen cefoxitin vancomycin many others	poor	= -4 inadequate information	
---------------------	--	---	---	------	--------------------------------	--

Comment: death may have resulted from sepsis, but did micafungin add hepatocellular injury to carcinoid cholestatic liver disease?

Note: F, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#585271 M73c Warsaw, Poland	Sday AST ALT ALP TBL 1 36 19 112 0.72 5 29 16 8 439 118 928 2.18 mixed liver injury severe liver damage (8), renal insufficiency (8)	mantle cell lymphoma, chemotherapy pulmonary aspergillosis and candidiasis, pneumonia diabetes, coronary disease Died (22), heart failure. Autopsy confirmed.	micafungin to (8) metformin fluconazole Ambroxol many others	8 + 19 - 5 NA very poor	+2 onset -2 <3 R/Os -1 other drug -3 other cause = -4 inadequate information	<10%, unlikely

Comment: death resulted from cardiac failure, which may have caused ischemic liver injury

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#059777 M0.7h Washington, DC	Sday AST ALT ALP TBL -1 10 9 135 5.7 3 18 9 115 23.3 10 52 3 305 51.1 17 101 81 290 8.9 24 202 232 330 6.4 31 61 146 315 2.9 46 54 78 284 1.5 84 37 58 218 0.7 98 27 10 91 0.3 116 10 33 163 162 26 153 1.1 ?cholestatic liver injury jaundice, hepatomegaly (2), renal insufficiency (1), acute hemolysis? (9)	acute myelogenous leukemia, chemotherapy Klinefelter syndrome sinus aspergillosis, sinusitis fever, pancytopenia, failure to thrive, systolic murmur survived, recovered	micafungin 22Aug00 to 13Dec00 (114) Ambisome Nystatin Tylenol Ativan Midazolam Bactrim RBCs, platelets dopamine itraconazole many, many others	9 + 16 - 5 NA poor	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	25%, possibly made worse

Comment: infant, 8 months, with preexisting jaundice, possibly increased markedly by micafungin, but adapted and recovered

Note: M, male; h, Hispanic; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#287674 M48c Capetown South Africa	Sday AST ALT ALP TBL 1 22 18 74 0.59 7 51 26 87 0.59 14 257 356 110 8.42 21 54 65 117 25.7 hepatocellular injury vomiting (3), jaundice (15), hepatic failure (14)	Lymphoma chemotherapy Candida rugosa septicemia hypotension (13), Afib (14), anemia and renal failure (14), pneumothorax (17), bleeding gastric ulcer, hematemesis, edema (28) died (28), heart failure	micafungin to (27) warfarin (-4 to 14) Panadol Amphotericin B Mycostatin many others	10 + 17 - 5 NA poor	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	30%, possible

Comment: death resulted from hypotensive shock, ischemic liver disease.

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#372501 M39c Ontario Canada	Sday AST ALT ALP TBL 3 31 37 62 0.47 8 35 59 58 0.64 16 17 24 45 5.08 19 21 18 51 14.3 24 58 35 64 28.7 26 60 45 62 36.9 33 118 110 53.9 39 129 226 65.5	acute biphenotypic leukemia marrow transplant (6) HBsAg carrier possible fungal infection (26) persistent leucopenia, anemia, thrombocytopenia (21-35) renal insufficiency (27-43)	fluconazole to (26); LE cyclophosphamide ciprofloxacin methotrexate acyclovir ceftazidime vancomycin	14 + 15 - 3 NA fair	+2 onset -2 <3 R/Os -2 neg dechall -1 other drugs -3 other cause = -6 limited information	<1%, not F-DILI

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

	veno-occlusive disease jaundice (13), veno-occlusive disease (16), liver failure (32)	died (43), hepatic failure, venoocclusive disease	Abelcet (26-34) dopamine many others		
--	--	--	--	--	--

Comment: death resulted from veno-occlusive liver disease, probably from chemotherapy; liver disease not from fluconazole

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; LE, lack of efficacy; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#423004 F40c Portland, Oregon	Sday AST ALT ALP TBL -1 39 55 177 0.6 3 122 289 171 0.7 6 91 134 120 1.6 12 110 110 81 1.6 17 33 25 111 2.4 hepatocellular injury abdominal pain, asthenia (7), anorexia (12), 'hepatic failure' (17), abnormal thinking (18- 34)	chronic myelogenous leukemia marrow transplant pulmonary Candida albicans and Aspergillus sp. chest pain (8), lung edema (9) pericardial effusion (9), heart failure, congestive (10), renal failure (13), GVHD (32) died ← (34), pulmonary mycosis	fluconazole to 26Sep00 (17): LE ursodiol cyclophosphamide Decadron acetaminophen ciprofloxacin methotrexate vancomycin Solumedrol dobutamine many others	10 + 17 - 5 NA poor	+1 onset -2 <3 R/Os -1 other drugs = -2 inadequate information	25%, possible

Comment: death resulted from cardiopulmonary disease, probably from chemotherapy; liver injury relatively mild (not liver failure)

Note: F, female; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; LE, lack of efficacy; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#3103 F26c " " location not stated	Sday AST ALT ALP TBL -2 27 30 312 0.9 1 27 20 140 0.8 7 24 18 190 1.1 14 16 17 152 0.8 28 18 9 163 0.8 ? obstructive liver disease nausea (5), 'liver damage' (11), vomiting (16), liver biopsy, laparoscopy (42)	HIV, non-Hodgkins lymphoma esophageal Candida alb. fever, cough many liver abscesses(15), liver bx(42), non-Hodgkins lymphoma in hilar nodes survived	micafungin 3May02 to 16May02 (14) acetaminophen (-1 to 24) isoniazid (2-24) metronidazole ceftriaxone many others	9 + 18 - 5 NA very poor	incompatible excluded inadequate information	<1% not M-DILI

Comment: no significant liver disease; isolated elevated alkaline before micafungin given

Note: F, male; c, Caucasian; Sday, days since first dose; AST, ALT, serum aspartate, alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

Comment: In the majority of these cases (10 of the 19), there did not seem to be clear causation of the hepatic injury by the administered antifungal treatment, which in 8 of the cases was micafungin (#3103, 20785, 63786, 262788, 287679, 474177, 585271, 2194007), in 1 case was fluconazole (#372501) and in 1 case none (#384301). Nine other cases seem possibly to have had liver injury caused or aggravated by the drug, 6 by micafungin (#1008, 33885, 262780, 287674, and 10745035) and 3 by fluconazole #203501, 423004, 10665008). There were no cases in this series in which it can be stated with confidence that the antifungal drug definitely or even probably caused the liver injury, mainly because of multiple confounding possible other causes from underlying or concomitant diseases, or by the plethora of other drugs that were given. This was further made difficult by the generally inadequate provision of sufficient clinical information to make the differential diagnosis of drug-induced, as opposed to disease-induced, other drug-induced, and certainly no information at all on the possibilities of drug-drug interactions that might have caused the problems. Many of the patients considered were actually dying of terribly serious diseases when antifungal treatment was started, and there are almost no data on effects of withdrawing the drug to see if improvement in the

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

liver injury might follow, and no patients were observed long enough for rechallenge effects to be observed.

We are stuck, therefore, with relying upon opinions as to whether the hepatic injuries seen were related to drug administration or not, and even experts do not always agree, as we have seen, and will now consider more closely. After considering independently the data provided, I rated each case for adequacy of information to make a diagnosis of DILI, an estimate of the RUCAM score, and my estimated likelihood that the hepatic reaction was drug induced, before looking at the panel consensus ratings. In the following table, I list my ratings and the expert panel's:

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

COMPARISON OF CAUSALITY ATTRIBUTION RATINGS BY JRS AND THE EXPERT PANEL

Note: M, micafungin; F, fluconazole; N, neither; NR, not related; P, possibly related; R, related; U, unlikely

Case #	Underlying diseases	Liver Disease/Injury	Drug	JRS	Panel
# 1008, M48b, South Africa	HIV cachexia, tuberculosis; Esophageal candidiasis	Hepatocellular injury without jaundice, 14 days, moderately severe	M	P 50% concur	PR
# 3103, F26c, location not stated	Non-Hodgkin's lymphoma Esophageal candidiasis	Obstructive liver disease, hilar lymphoma, elevated ALP before micafungin given	M	U <1% concur	NR
# 20785, F30c, Minneapolis MN	Acute myelogenous leukemia; Probable lung aspergillosis	Cholestatic liver disease, before drug given, but worse after 80 days, ?leukemic infiltrate	M	U <10% concur	NR
# 33885, F62b, location not stated	Duodenal carcinoid tumor; Candida septicemia	Hepatocellular injury, at 14 days, added to carcinoid cholestatic disease	M	P 40% disagree*	NR
<i>*Comment: Panel thought NR, but JRS noted preexisting liver disease, probably worsened by micafungin</i>					
# 59777, M 0.7h Washington DC	Acute myelogenous leukemia; Sinus aspergillosis ; survived	Cholestatic liver injury, transient, aggravating mild preexisting abnormality, recovered	M	P 25% disagree*	NR
<i>*Comment: Panel thought data inadequate, but JRS noted preexisting liver disease, probably worsened by micafungin.</i>					
# 63786, M58c location not stated	End-stage liver disease ???; Invasive lung aspergillosis	Previous liver disease of unknown type, with slight increase in jaundice, 7 days	M	U 15% concur	NR
# 262780, M4c location not stated	Leukemia, marrow transplant; Lung aspergillosis	Cholestatic liver injury or aggravation, some preexisting cholestasis	M	P 25% concur	PR
# 262788, M16b Memphis TN	Acute myelogenous leukemia; Lung aspergillosis; liver C alb	Cholestatic liver injury aggravation, 9 days, some preexisting cholestasis	M	U <5% concur	NR
# 287674, M48c, South Africa	Lymphoma chemotherapy; Candida rugosa septicemia	Hepatocellular injury with jaundice, 14 days, Liver tests normal before	M	P 30% concur	PR
# 287679, F51c location not stated	Pancreatic CA, metastases; Candida alb septicemia	Cholestatic liver disease, pre-existing, before drug given	M	U <1% concur	NR
# 474177, M40c Mainz, Germany	Leukemia, NOS Probable lung aspergillosis	Alcoholic liver disease, with cholestasis, somewhat worsened after 21 days on drug	M	U <1% disagree*	PR
<i>*Comment: Panel thought PR, but JRS noted preexisting liver disease, probably worsened by drugs given for leukemia.</i>					
# 585271, M73c Warsaw, Poland	Mantle cell lymphoma Lung aspergillosis & candida	Mixed liver injury, probable tumor in liver, preexisting before micafungin given	M	U <10% concur	NR
# 2194007, M77c Palo Alto CA	Massive blood loss, aneurysm Repair; no fungal infection	Hepatocellular disease, probably ischemic liver injury	M	U <1% concur	NR
#10745035, M34b South Africa	HIV cachexia, tuberculosis; Esophageal candidiasis	Aggravation of prior alcoholic liver disease, with jaundice and hepatic failure, 5 day	M	P 25% concur	PR
FLUCONAZOLE CASES					
# 203501, F36o Minneapolis MN	Acute myelogenous leukemia; No fungal infection proved	Hepatocellular injury with jaundice, 16 days coagulation disorder, gastrointestinal bleeding	F	P 40% disagree*	NR
<i>*Comment: Panel divided, maybe aggravation, but data unreadable; JRS thought fluconazole may have caused liver failure</i>					
# 372501, M39c, Ontario, Canada	Acute biphenotypic leukemia Possible fungal infection	Veno-occlusive disease, from chemotherapy, with progressive liver failure	F	U <1% concur	NR
# 423004, F40c, Portland OR	Chronic myelogenous leukemia Pulmonary aspergillus sp.	Hepatocellular injury, perhaps added to Leukemic infiltrate before drug	F	P 25% disagree*	NR
<i>* Comment: Panel thought NR; JRS thought quite possibly fluconazole-induced aggravation, not liver failure</i>					
#10665008, F31b South Africa	HIV severe cachexia, tbc; Esophageal candidiasis	Hepatocellular injury with jaundice, 21 days Severe	F	P 30% concur	PR
NEITHER MICAFUNGIN OR FLUCONAZOLE					
# 384301, M52c Ottawa, Canada	Hodgkin's lymphoma No fungal infection proved	Cholestatic liver disease before drug given, due to tumor in liver, not DILI	N	U <1% concur	NR

Comment: It may be seen that my independent assessments concurred with the consensus of the panel of experts in 5 of 6 cases in which they thought the liver abnormalities were possibly related to administration of study drug. The exception was #474177, the 40-year-old German man with a history of alcohol abuse who had significantly abnormal liver tests before starting on micafungin, and then

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

slowly progressed to worsening of all his liver tests as he died of leukemia complications or the many antineoplastic and other drugs he received. Micafungin was stopped after 34 days, and he lived only 4 days more, so not “dechallenge” effects could be observed. My estimates also were in concurrence in 9 of the 13 cases in which the panel thought the liver reactions were unrelated to study drug, with disagreements for cases #33885, 59777, both of whom received micafungin, and for cases #203501 and 372501 who received fluconazole. It was my thinking in all 4 cases that the antifungal treatment had added to or aggravated pre-existing liver disease, with some degree of likelihood, but insufficient information to be more certain.

The concept of drug-induced injury adding to or aggravating pre-existing liver disease was seen in some of the cases in which there was concurrence of our thinking (#262780), although this is not a widely held view. There is considerable controversy about whether or not a relatively uncommon or unpredictable (“idiosyncratic”) hepatic injury is more likely to occur in patients with previous liver disease, or whether it simply appears so because such people are less well able to withstand or to recover from additional liver injury if it is induced by a drug.

Another point that was noted in review of these cases was that there were several cases of serum bilirubin elevations that seemed out of proportion to the serum enzyme indicators of liver injury, often in cases in which there was underlying liver disease not likely caused by micafungin (e.g., see cases #63786, 262788, 474177, 384301, 2194007, 20785, 59777, 287674, and 372501 among the 19 cases summarized above). All of the echinocandins were plagued by some degree of red blood cell hemolysis problems during their development, and molecular manipulations were used to find less hemolytic antifungal compounds. Merck found that L-671,329 was less hemolytic than was aculeacin (Frompting and Abruzzo, 1989); and L-743,872 (MK-0991, (later called caspofungin) less hemolytic than amphotericin B (Bartizal, et al., 1997). Efforts in the Fujisawa laboratories in which FR131535 was found less hemolytic than FR901379 (Fujie, et al., 2001), led to FK-463 (micafungin). In evaluating the cases of possibly micafungin-induced hepatotoxicity, whether in a previously normal liver, or in aggravation of some underlying liver disease, a contribution of micafungin-accelerated hemolysis should be considered as at least partly responsible for rises in serum total bilirubin concentrations.

The finding of significant but rare hepatotoxicity associated with caspofungin, a recently approved member of this new class of echinocandin agents, is of interest and possible pertinence to this consideration of micafungin. The class of echinocandins (caspofungin, anidulafungin, micafungin) all have a central, large, cyclic hexapeptide nucleus with N-terminal fatty acyl and an amino group connecting the 3-OH-proline moiety to the δ -amino- γ -hydroxyornithine to form the ring. The three new drug agents differ mainly in their patterns of hydroxylations, which is extensive and confers the water solubility of the compounds (Wiederhold and Lewis, 2003), and in their α -aminoacyl side chains. The agents were developed to be safer than earlier antifungal agents that caused collateral damage to host cells (amphotericin B) and drug interactions (the -conazoles). Caspofungin (CANCIDAS, Merck) is a large, complex, semisynthetic molecule that inhibits 1,3- β -D-glucan synthase required for fungal cell wall synthesis, approved in January 2001 for treatment of invasive aspergillosis. It is of interest that although 8 cases of caspofungin hepatotoxicity have been reported to AERS, only one case is even mentioned in the published literature, in an acute leukemic patient who had moderate but reversible hepatotoxicity (Aliff, et al., 2003). No cases of micafungin-induced liver injury have been reported as yet.

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

In addition to the 19 cases discussed above that had been selected for special review, Dr. Mary Singer found two more, patients who had died after being treated with micafungin, and whose test results suggested acute liver injury. She sent copies of the narratives and patient profile summaries of data by fax on 24 January, and requested my opinion about them, in brief for the planned meeting at 4 p.m. that day, and more fully thereafter. On cursory inspection, both cases appeared to show acute rises in serum tests of liver injury and function, and of renal function, after starting treatment with micafungin. The information provided for the two cases is summarized below, in similar format to that used for the 19 cases previously reviewed above.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#10745031 M34b	Sday AST ALT ALP TBL -3 101 85 217 1.05 7 649 305 519 4.27 hepatocellular injury not stated; lab tests suggest acute liver injury (7)	HIV: no retroviral therapy, CD4 = 148/ μ L inv esophageal candidiasis. anemia, renal insufficiency renal failure worsened (7) died (10), of acute renal failure	micafungin to (9) Bactrim Immodium Lasix others	8 + 21 - 3 NA very poor	+2 onset -2 <3 R/Os = 0 inadequate information	50%, possible
Comment: death may have resulted from renal failure, but did micafungin cause the acute terminal liver injury also?						

Note: M, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#10445008 M45c	Sday AST ALT ALP TBL -1 50 74 547 0.41 8 179 227 646 0.82 14 43 81 741 1.18 26 5670 1760 249 4.05 hepatocellular injury mild transient injury (8), then more severe acute liver injury (26) when the therapy started	HIV: no retroviral therapy, cachexia, CD4 = 13/ μ L inv esophageal candidiasis. neurotoxoplasmosis disseminated tuberculosis; died (26), of reactivated tuberculosis	micafungin to (14) Cisapride (3) Oxaciline (13) Riphampacine (20) Isoniazide (20) Pyrazinamide (20) many, many others	8 + 21 - 3 NA very poor	-1 onset? -2 <3 R/Os = -3 inadequate information	15%, unlikely
Comment: death may have resulted from tuberculosis, but did micafungin cause mild liver injury, anti-tbc therapy severe injury?						

Note: M, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

Comment: The first case (#10745031) had findings 3 days before micafungin was started of modest serum ALT, AST, and ALP elevations but top-normal serum bilirubin, plus definite evidence of renal insufficiency (both UN and creatinine were elevated). After 7 days of micafungin, the renal indicators had worsened, but the serum AST, ALT, ALP and TBL were dramatically increased. It seems likely that the patient had some degree of tuberculous infiltrate in his liver, and that it is quite possible that micafungin induced an acute aggravation of the mild underlying liver problem, which clinically seemed overshadowed by the renal failure to which his death was attributed by the clinical staff. The data are insufficient for any more probable attribution of the acute liver injury to micafungin administration. The second case (#10445008) is interesting in the timing of the treatments. After micafungin was started, he showed a moderate mixed hepatocellular and cholestatic liver injury without rise in serum bilirubin, which subsided except for the cholestasis by Day 14 when the micafungin was stopped. After treatment with Oxaciline for phlebitis on Day 13, and initiation of anti-tuberculosis therapy with isoniazide, rifampin, and pyrazinamide on Day 20, he showed a dramatic rise in the serum transaminase activities suggesting acute superimposed hepatocellular injury with probable jaundice (bilirubin 4.05 mg/dL) on Day 26. Either the Oxaciline or the anti-tuberculosis regimen were more

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

likely responsible for the severe hepatocellular injury noted on Day 26, 2 days before his death. The information available is inadequate to infer more.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

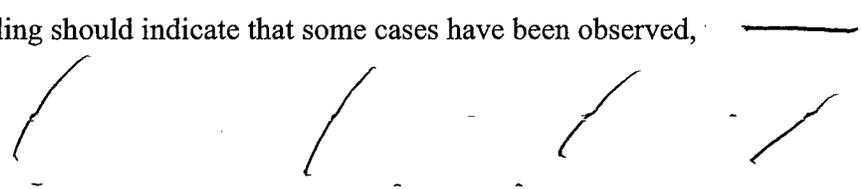
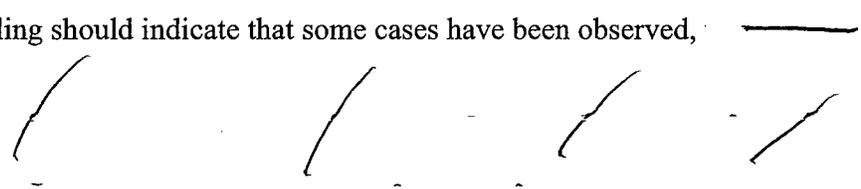
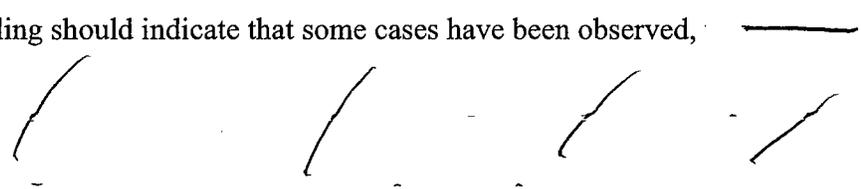
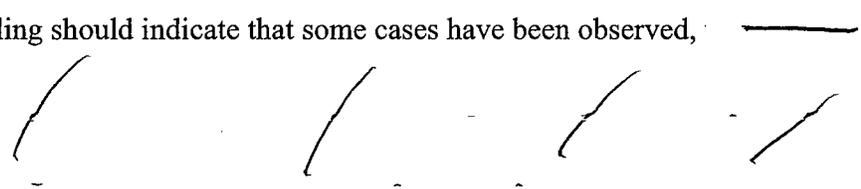
Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Recommendations:

1. These cases in which there appear to be possible causation of liver injury following use of micafungin cannot be entirely dismissed, even though many of the cases can be "thrown out" as not related. As noted by the expert panel, these are extremely difficult cases to assess and there were many confounding factors, both other drugs and concurrent diseases. To make matters worse, drug-induced liver injury is a diagnosis of exclusion, and lack of good information to exclude other causes is not proof that they may be excluded.
2. Other cases must be looked for in patients treated with this micafungin, as well as the other two echinocandins, caspofungin and anidulafungin. Systemic fungal diseases usually occur in otherwise very sick patients who are on other therapies and have underlying problems, which may make them more vulnerable to or less able to recover from additional liver injury that may be caused by agents such as micafungin.
3. The labeling should indicate that some cases have been observed,    
4. It may be shown that more patients are saved by micafungin treatment of their fungal infections than are injured, and the echinocandins may be safer than the previously available agents, but they should not be considered totally safe. Physicians should weigh carefully the relative benefits and risks of them, in managing these extremely serious and complex diseases.

John R. Senior, M.D.

cc: ODS PID#D040163
M. Avigan, ODS/DDRE
P. Seligman, OPSS
S. Birdsong, DDRE
M. Truffa, DDRE
R. Albrecht, HFD-590
M. Singer, HFD-590

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

References

Aithal PG, Rawlins MD, Day CP. Clinical diagnostic scale: a useful tool in the evaluation of suspected hepatotoxic adverse drug reactions. *J Hepatol*. 2000 Dec;33(6):949-52. [PMID: 11131457]

Aliff TB, Maslak PG, Jurcic JG, Heaney MI, Cathcart KN, Sepkowitz KA, Weiss MA. Refractory *Aspergillus* pneumonia in patients with acute leukemia: successful therapy with combination caspofungin and liposomal amphotericin. *Cancer*. 2003 Feb 15;97(4):1025-32. [PMID: 12569602]

Barrett D. From natural products to clinically useful antifungals. *Biochim Biophys Acta*. 2002 Jul 18;1587(2-3):224-33. [PMID: 12084464]

Bartizal K, Gill CJ, Abruzzo GK, Flattery AM, Kong L, Scott PM, Smith JG, Leighton CE, Bouffard A, Dropinski JF, Balkovec J. In vitro preclinical evaluation studies with the echinocandin antifungal MK-0991 (L-743,872). *Antimicrob Agents Chemother*. 1997 Nov;41(11):2326-32. [PMID: 9371328]

Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol*. 1990 Sep;11(2):272-6. [PMID: 2254635]

Bénichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol*. 1993 Nov;46(11):1331-6. [PMID: 8229111]

Carver PL. Micafungin. *Ann Pharmacother*. 2004 Oct;38(10):1707-21. [PMID: 15340133]

Chiou CC, Groll AH, Walsh TJ. New drugs and novel targets for treatment of invasive fungal infections in patients with cancer. *Oncologist*. 2000;5(2):120-35. [PMID: 10794803]

Danan G, Bénichou C, Begaud B, Biour M, Couzigou P, Evreux JC, Lagier G, Berthelot P, Benhamou JP. Critères d'imputation d'une hépatite aiguë à un médicament. Résultats de réunions de consensus. [*Criteria of imputation of acute hepatitis to a drug. Results of consensus meetings.*] *Gastroenterol Clin Biol*. 1987 Aug-Sep;11(8-9):581-5. [PMID: 3308618]

Danan G. Causality assessment of drug-induced liver injury. Hepatology Working Group. *J Hepatol* 1988 Aug;7(1):132-6. [PMID: 3053889]

Danan G, Bénichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol*. 1993 Nov;46(11):1323-30. [PMID: 8229110]

Danan G. Atteintes hépatiques aiguës médicamenteuses. Qu'apportent les échelles diagnostiques ? [*Drug-induced acute hepatic injury. What is the value of diagnostic scales?*] *Gastroenterol Clin Biol*. 2003 May;27(5 Suppl):B21-5. [PMID: 12843933]

Denning DW. Echinocandin antifungal drugs. *Lancet*. 2003 Oct 4;362(9390):1142-51. [PMID: 14550704]

Feinstein AR. Clinical biostatistics. 28. The biostatistical problems of pharmaceutical surveillance. *Clin Pharmacol Ther*. 1974 Jul;16(1):110-23. [PMID: 4843239]

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Fromtling RA. Micafungin sodium (FK463). *Drugs Today (Barc)*. 2002 Apr;38(4):245-57. [PMID: 12532193]

Fromtling RA, Abruzzo GK. L-671,329, a new antifungal agent. III. In vitro activity, toxicity and efficacy in comparison to aculeacin. *J Antibiot (Tokyo)*. 1989 Feb;42(2):174-8. [PMID: 2647704]

Fujie A, Iwamoto T, Sano B, Muramatsu H, Kasahara C, Furuta T, Hori Y, Hino M, Hashimoto S. FR131535, a novel water-soluble echinocandin-like lipopeptide : synthesis and biological properties. [PMID: 11212120].

Goodman ZD. Drug hepatotoxicity. *Clin Liver Dis*. 2002 May;6(2):381-97. [PMID:12122862]

Higashiyama Y, Kohno S. Micafungin: a therapeutic review. *Expert Rev Infect Ther*. 2004 Jun;2(3):345-55. [PMID: 15482200]

Hutchinson TA, Leventhal JM, Kramer MS, Karch FE, Lipman AG, Feinstein AR. An algorithm for the operational identification of adverse drug reactions. II. Demonstration of reproducibility and validity. *JAMA*. 1979 Aug 17;242(7):633-8. [PMID: 449003]

Irey NS. Registry of tissue reactions to drugs. *Mil Med*. 1971 Apr;136(4):346-8. [PMID: 5005419]

Irey NS. Tissue Reactions to Drugs. Teaching Monograph, American Journal of Pathology 1976; 82:617-47.

Irey NS. Diagnostic problems in drug-induced diseases. *Ann Clin Lab Sci*. 1976 May-Jun;6(3): 272-7. [PMID:942185]

Irey NS. When is a disease drug induced? Chapter 1 *in* Pathology of Drug-Induced and Toxic Diseases, R. H. Riddell, ed., Churchill Livingstone, New York, 1982.

Jarvis B, Figgitt DP, Scott LJ. Micafungin. *Drugs*. 2004;64(9):969-84. [PMID: 15101786]

Kaplowitz N. Causality assessment versus guilt-by-association in drug hepatotoxicity. *Hepatology*. 2001 Jan;33(1):123-3. [PMID: 11124850]

Kaplowitz N, Lewis JH, Watkins PB. Did this drug cause my patient's hepatitis? [letter] *Ann Intern Med*. 2003 Jan 21;138(2):159-60. [PMID: 12529106]

Karch FE, Lasagna L. Adverse drug reactions. A critical review. *JAMA*. 1975 Dec 22; 234(12):1236-41. [PMID: 1242749]

Karch FE, Smith CL, Kerzner B, Mazzullo JM, Weintraub M, Lasagna L. Adverse drug reactions - a matter of opinion. *Clin Pharmacol Ther*. 1976 May;19(5, Part 1):498-92. [PMID: 1277705]

Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational identification of adverse drug reactions. I. Background, description, and instructions for use. *JAMA*. 1979 Aug 17;242(7):623-32. [PMID: 449002]

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Lee WM. Assessing causality in drug-induced liver injury. [editorial] *J Hepatol*. 2000 Dec;33(6): 1003-5. [PMID:11131436]

Lee WM, Senior JR. Recognizing drug-induced liver injury: current problems, possible solutions. *Toxicol Pathol*. 2005 Jan;33(1):155-64. [PMID: pending]

Leventhal JM, Hutchinson TA, Kramer MS, Feinstein AR. An algorithm for the operational identification of adverse drug reactions. III. Results of tests among clinicians. *JAMA*. 1979 Nov 2;242(18):1991-4. [PMID: 480646]

Lucena MI, Camargo R, Andrade RJ, Perez-Sanchez CJ, Sanchez de la Cuesta F. Comparison of two clinical scales for causality assessment in hepatotoxicity. *Hepatology*. 2001 Jan;33(1): 123-30. [PMID: 11124828]

Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* 1997 Sep;26(3):664-9. [PMID: 9303497]

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981 Aug; 30(2):239-45. [PMID: 7249508]

Petratis V, Petratiene R, Sarafandi AA, Kelaher AM, Lyman CA, Casler HE, Sein T, Groll AH, Bacher J, Avila NA, Walsh TJ. Combination therapy in treatment of experimental pulmonary aspergillosis: synergistic interaction between an antifungal triazole and an echinocandin. *J Infect Dis*. 2003 Jun 15;187(12):1834-43. [PMID: 12792859]

Petratis V, Petratiene R, Groll AH, Rousillon K, Hemmings M, Lyman CA, Sein T, Bacher J, Bekersky I, Walsh TJ. Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits. *Antimicrob Agents Chemother*. 2002 Jun;46(6):1857-69. [PMID: 12019101]

Schaffner F, Raisfeld IH. Drugs and the liver: a review of metabolism and adverse reactions. *Adv Intern Med* 1969;15:221-51. [PMID: 4908619]

Senior JR. ODS consultation #D040163 regarding hepatotoxicity possibly induced by use of anidulafungin for treatment of esophageal candidiasis. 25 March 2004. *in* CDER Document File System, —

Sivak O, Bartlett K, Risovic V, Choo E, Marra F, Batty DSJr, Wasan KM. Assessing the antifungal activity and toxicity profile of amphotericin B lipid complex (ABLC; Abelcet) in combination with caspofungin in experimental systemic aspergillosis. *J Pharm Sci*. 2004 Jun;93(6):1382-9. [PMID: 15124198]

Van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, Bunin N, Wall DA, Hiemenz JW, Sato Y, Lee JM, Walsh TJ. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation, *Clin Infect Dis*. 2004 Nov 15;39(10):1407-16. [PMID: 15546073]

Wiederhold NP, Lewis RE. The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy. *Expert Opin Investig Drugs*. 2003 Aug;12(8):1313-33. [PMID: 12882619]

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Yokote T, Akioka T, Oka S, Fujisaka T, Yamano T, Hara S, Tsuji M, Hanafusa T. Successful treatment with micafungin of invasive pulmonary aspergillosis in acute myeloid leukemia, with renal failure due to amphotericin B therapy. *Ann Hematol.* 2004 Jan;83(1):64-6. [PMID: 14661114]

10.3.2 ODS Consultation regarding Postmarketing Safety of Micafungin in Japan

The ODS consultation regarding micafungin adverse events reported in the Japanese postmarketing database follows below:

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE		ODS POSTMARKETING SAFETY REVIEW	
FOOD AND DRUG ADMINISTRATION			
TO: Mary Singer, M.D., M.P.H., Medical Officer Renata Albrecht, M.D., Director Division of Special Pathogens and Immunologic Drug Products (DSPIDP) HFD-590	FROM: Adrienne M. Rothstein, Pharm.D. Safety Evaluator Melissa M. Truffa, R.Ph. Safety Evaluator Team Leader DDRE (HFD-430)	ODS PID #: D040821	DATE Completed: February 18, 2005
DATE REQUESTED: Dec. 9, 2004	REQUESTOR/Phone #: Mary Singer, M.D., M.P.H., 301-827-2371		
DRUG (Generic): micafungin sodium	NDA # 021754, 021506	SPONSOR: Fujisawa Pharmaceutical Company, Ltd.	
DRUG NAME (Trade): MYCAMINE™	THERAPEUTIC CLASSIFICATION: echinocandin antifungal agent		
EVENT: Review of Japanese postmarketing experience for serious hepatic, renal, hematologic, hypersensitivity and cardiac events.			
Executive Summary			
<p>DSPIDP is reviewing New Drug Applications for micafungin, which has been marketed in Japan since approval in October 2002. DDRE was asked to provide a safety review of postmarketing events from Japan to assist DSPIDP in their assessment of the MYCAMINE applications and the adequacy of the proposed labeling. DDRE reviewed the 2nd and 3rd PSUR prepared by Fujisawa, an English translation of the Funguard® label in Japan, and the draft Mycamine™ (micafungin sodium) package insert. In addition, the MedWatches for serious postmarketed hepatic, hematologic, and skin events received through August 31, 2004 were reviewed. The events of concern identified by DSPIDP were hepatic, renal, hematologic, hypersensitivity and cardiac events. As a result of this comprehensive review, DDRE has the following recommendations for your consideration:</p> <p>Although most of the Japanese postmarketed cases were extremely complex with multiple concomitant medications and disease states that could predispose to hepatic events, the role of micafungin in the</p>			

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

etiology of these events could not entirely be ruled out. Therefore, we recommend that hepatic events be listed as a **PRECAUTION** including the following: Laboratory abnormalities in liver function tests have been seen in patients treated with micafungin. In some patients with serious underlying conditions who were receiving multiple concomitant medications along with micafungin, clinically significant hepatic abnormalities have occurred. Isolated cases of clinically significant hepatic dysfunction or worsening hepatic failure have been reported in patients:

Patients who develop abnormal liver function tests during MYCAMINE therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing MYCAMINE therapy.

Based on the review of the Japanese postmarketing data and the current Japanese labeling, we recommend that renal impairment be listed as a **PRECAUTION** including the following:

Patients who develop abnormal renal function parameters during MYCAMINE therapy should be monitored for evidence of worsening renal function and evaluated for the risk/benefit of continuing MYCAMINE therapy

The sponsor should consider adding a **WARNING** about the possibility of anaphylactoid reactions during micafungin infusions with recommendations to discontinue MYCAMINE and administer appropriate treatments if this reaction occurs.

Under **ADVERSE REACTIONS**, consider creating a separate paragraph to list the following **Additional Adverse Events from Japanese Postmarketing Sources:**

- Hepatic: hyperbilirubinemia, hepatic function abnormal, hepatic disorder, and hepatocellular damage
- Renal: acute renal failure and renal impairment.
- Hematologic: decreased white blood cell count, hemolytic anemia.
- Vascular: shock

Under **ADVERSE REACTIONS**, the sponsor should remove from adverse events to be consistent with the current version of MedDRA. The sponsor should consider

Under **ADVERSE REACTIONS**, the sponsor should remove from the description of events from clinical trials. Under **DOSAGE AND ADMINISTRATION**, the sponsor should

In addition to the above mentioned labeling recommendations, consider reviewing the clinical data for occurrences of QTc prolongation and hemolytic uremic syndrome. Following the approval of MYCAMINE in the U.S., close monitoring of the following adverse events should be performed: QTc prolongation, hyponatremia, hemolytic uremic syndrome, and serious skin reactions.

Materials Reviewed

These comments are based on a review of the micafungin 2nd PSUR prepared by Fujisawa (data lock

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

period: 08 Apr 2003 – 08 Oct 2003), 3rd PSUR (data lock period: 09 Oct 2003 – 08 Apr 2004), an English translation of the Funguard® (micafungin sodium) Japanese label (7th version, dated July 2004), and the draft Mycamine™ (micafungin sodium) package insert from the 120-day safety update to the NDA submissions (submitted on 24 August 2004). At the request of DSPIDP, the sponsor provided MedWatches for hepatic events, hematologic events and toxic epidermal necrolysis received through August 31, 2004, which were also reviewed for this summary.

U.S. and Japanese Drug Information for Micafungin Sodium

	United States	Japan
Drug Name	MYCAMINE	FUNGUARD
Approval Date	To be determined	08 October 2002
Indication	Treatment of patients with esophageal candidiasis and prophylaxis of <i>Candida</i> infections in patients undergoing hematopoietic stem cell transplantation (HSCT)	Infections caused by <i>Aspergillus</i> sp. and <i>Candida</i> sp., including fungemia, respiratory mycosis, and gastrointestinal mycosis
Daily Dose	Treatment of Esophageal Candidiasis: <u>Adults:</u> 150 mg daily Prophylaxis of <i>Candida</i> infections in patients undergoing HSCT: <u>Adults:</u> 50 mg daily	<u>Adults:</u> 50-150 mg, up to 300 mg daily for severe or refractory infections For patients weighing ≤ 50 kg, dose NTE 6mg/kg/d
Patient Population	Adults	Safety of micafungin in children not established (no clinical experience in Japan).
Maximum Daily Dose	Micafungin has been safely administered in repeated daily doses up to 896 mg (8 mg/kg) in adults	Safety of daily doses up to 300 mg not fully established. No clinical experience in Japan with daily doses > 150 mg, limited clinical experience in foreign countries with daily doses of 300 mg.

Events of Concern:

I. HEPATIC (n=27)

Sponsor Proposed U.S. Labeling:

As noted in the **ADVERSE REACTIONS** section in the proposed U.S. label, increased alkaline phosphatase was reported in — of patients randomized to micafungin in a Phase 3 study comparing micafungin to fluconazole for the treatment of esophageal candidiasis. Less common hepatic events were increases in aspartate aminotransferase and alanine aminotransferase in 0.8% and 0.4% of patients randomized to micafungin, respectively. In a Phase 3 study comparing micafungin to fluconazole for the prophylaxis of *Candida* infections in patients undergoing HSCT commonly reported adverse events in patients randomized to micafungin were hyperbilirubinemia (2.8% of patients), abnormal liver function tests (0.7%), —, and increases in alanine aminotransferase (0.9%), aspartate aminotransferase (0.7%), and —. There were Japanese post-marketing reports of

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

hyperbilirubinemia, hepatic function abnormal, hepatic disorder, and hepatocellular damage listed in the section.

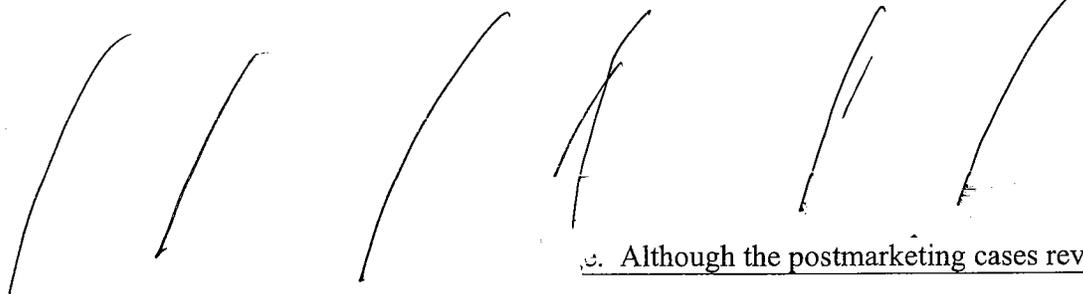
Japanese Labeling:

The Funguard labeling has a **PRECAUTION (CAREFUL ADMINISTRATION)** that use of Funguard in patients with hepatic impairment may aggravate hepatic impairment. There is also an **IMPORTANT PRECAUTION** noting that hepatic function disorder or jaundice may develop in patients receiving Funguard. Additionally, hepatic lesions were noted in the high dose treatment group in animal studies. Under **CLINICALLY SIGNIFICANT ADVERSE REACTIONS**, hepatic function disorder with increased AST, ALT, GGT, or ALP, etc., or jaundice are listed with a recommendation that patients should be carefully monitored by periodic examination. Appropriate measures such as discontinuation of treatment should be taken if abnormalities are observed. Increased LDH was also listed as an adverse reaction from clinical trials in Japan at an incidence of 0.1% - <5%. In foreign clinical studies, increased AST (6.7% of patients), increased ALT (5.8%), increased ALP (5.6%), bilirubinemia (1% - <5%) were reported in patients treated with micafungin.

Due to the number of serious hepatic events for this product, a cumulative review was performed of all Japanese postmarketing serious hepatic events that the sponsor reported receiving through 31 August 2004. Serious hepatic events that were fatal or life-threatening in nature and any serious adverse event of hepatitis, fulminant hepatitis, hepatic failure, and liver damage were reviewed and the DDRE safety evaluator determined a causal relationship between the use of micafungin and the reported events (see Appendix 1). Almost all of the cases were extremely complex, with multiple concomitant medications and disease states that could predispose to hepatic events. The role of micafungin in the etiology of these events is therefore impossible to ascertain in most cases, but cannot be ruled out in a number of cases. Specifically, this review identified 6 serious events of hepatic failure, the causal role of micafungin was assessed as possibly related in 1 case and unlikely in 4; there was not enough information to make a causal assessment in the last case. There was 1 case of hepatitis, which was considered not related to micafungin. There were 3 serious events of hepatocellular damage; the causal relationship to micafungin was possible in 1 and unlikely in 2 cases. There were 2 serious events of liver disorder; both were considered possibly related to micafungin. There were 5 serious events of hyperbilirubinemia; the causal relationship to micafungin was possible in 2 and unlikely in 3 cases. For the 10 serious events of hepatic function abnormal, the causal relationship to micafungin was possible in 4 and unlikely in 5 cases; there was not enough information to assess the last case. See Appendix 1 for a concise description of these cases and a causal assessment of the hepatic events.

Summary of Hepatic Events:

Under **ADVERSE REACTIONS**, the proposed U.S. MYCAMINE label



Although the postmarketing cases reviewed

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

of micafungin, his serum creatinine increased and micafungin was discontinued. The concomitant medications were unknown. A causal assessment could not be made. Thus, there were 5 cases of renal impairment possibly related to micafungin.

c. Hemolytic Uremic Syndrome: (n=3)

There were no cases of hemolytic uremic syndrome (HUS) reported in PSUR-2¹. In PSUR-3², there was 1 serious case of HUS possibly related to micafungin. The 120-day safety update was reviewed and 2 additional cases were identified, one of which was possibly related to micafungin. All 3 serious events of HUS occurred in teenagers who were receiving imipenem/cilastatin concomitantly.

Hemolytic anemia has been associated with imipenem/cilastatin, although hemolytic uremic syndrome is not specifically listed as an adverse reaction.³ The first case of HUS occurred in a 15 y/o male with AML, sepsis and pneumonia. The patient developed an increased T.bili level, decreased hemoglobin, and decreased platelets about 2 days after micafungin (100 mg daily), 1 day after ceftazidime, and less than 1 day after imipenem/cilastatin (1 g daily) were initiated. Hematuria was observed the next day.

About a week later, HUS was diagnosed. Micafungin and imipenem/cilastatin were discontinued and the event was improving. In the second case, a 16 y/o female with AML received a peripheral blood stem cell transplant with TBI and tacrolimus. Ten days later, the patient developed febrile neutropenia and was treated with micafungin (50 mg daily) and antibiotics. A week later, imipenem/cilastatin (500 mg daily) was initiated. Nine days later, HUS was diagnosed based on hematuria and red cell fragmentation in her peripheral blood. Tacrolimus was discontinued of suspected thrombotic microcytic angiopathy. The patient expired 5 days later; the cause of death was renal failure, which may have been aggravated by HUS. The event was possibly related to micafungin. In the last case, a 12 y/o female with AML who was receiving micafungin and imipenem/cilastatin developed HUS.

After an unknown period of time, the patient expired. A causal assessment could not be made based on information provided. Therefore, a causal role of micafungin in the development of HUS is possible in 2 serious cases.

Summary of Serious Renal Events:

For the 2nd and 3rd PSURs, there were a total of 9 events of renal failure, 13 events of renal impairment and 3 events of HUS. For the cases with enough information to make a causal assessment, only 1 event of renal failure, 5 events of renal impairment and 2 events of HUS were considered possibly related to micafungin. In addition, there were 3 serious reports of hyponatremia in PSUR-2, but there was inadequate information to evaluate these cases further.

in the proposed U.S. labeling for Mycamine. Based on the **CLINICALLY SIGNIFICANT ADVERSE REACTIONS** noted in the Japanese labeling, the sponsor should consider listing renal impairment as a **PRECAUTION** in the U.S. label, including the following:

Patients who develop abnormal renal function parameters during MYCAMINE therapy should be monitored for evidence of worsening renal function and evaluated for risk/benefit of continuing MYCAMINE therapy. Consideration should be made to review clinical trial data for events of hemolytic uremic syndrome. Events of hyponatremia and hemolytic uremic syndrome should be closely monitored after the approval of MYCAMINE in the U.S.

III. HEMATOLOGIC (n= 58)

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

Sponsor Proposed U.S. Labeling:

l / / / /

Japanese Labeling:

The current Funguard labeling lists neutropenia (1.5%), thrombocytopenia or hemolytic anemia as **CLINICALLY SIGNIFICANT ADVERSE REACTIONS**. Patients should be carefully monitored by periodic exams with discontinuation of Funguard if abnormalities are observed.

a. Hemolysis: (n=10)

There was 1 serious report of hemolytic anemia in PSUR-2, which occurred in a 70 y/o male with a fungal infection and PMH of aortic aneurysm, rectal cancer and interstitial pneumonia. The patient was receiving 11 concomitant medications at event onset. Based on the information provided, the causal relationship for the event of hemolytic anemia could not be assessed. In PSUR-3 there were 5 serious cases related to hemolysis, including hemolysis (1 event), hemolytic anemia (3), and intravascular hemolysis (1). These cases were not analyzed in the text of the PSUR, so the MedWatches submitted by the sponsor for serious hematologic events were reviewed. In total, the sponsor reported **3 serious cases of hemolysis, 2 serious cases of intravascular hemolysis and 5 serious cases of hemolytic anemia through August 2004**. These 10 cases were examined closely to determine the causal relationship. In all 3 cases of hemolysis, the events were possibly related to micafungin. For intravascular hemolysis, one case was probably and the other was possibly related to micafungin. For hemolytic anemia, the causal relationship to micafungin was probable in 1 case, possible in 3, and unlikely in 1 case.

b. Leukopenia: (n=7)

In PSUR-2 there were 5 serious reports of decreased white blood cell count. Two events were probably, 1 was possibly and 2 were unlikely related to micafungin. In these cases the white blood cell count recovered within a week after the discontinuation of micafungin. In PSUR-3 there was 1 event of leukopenia (follow-up case), 1 of neutropenia, and 1 of agranulocytosis; no cases are described in the text of the PSUR. MedWatches for these events were obtained from the 120-day safety update. **In total there were 5 events of leukopenia, 1 event of neutropenia, and 1 of agranulocytosis received through August 2004**. Leukopenia and neutropenia were commonly reported in U.S. clinical trials and are not unexpected in this patient population requiring systemic antifungal medications.

c. Anemia: (n=20)

In PSUR-2 there were 2 serious events of anemia and follow-up to 1 serious case of aggravated anemia were reported in PSUR-2. Only 1 case was described in the PSUR and was determined to be unlikely related to micafungin. In PSUR-3 there were 8 serious cases of anemia and 1 serious case of aggravated anemia; no cases are described in the text of the PSUR. The 120-day safety update was consulted and **a total of 20 serious events of anemia were identified through August 2004**. Anemia was commonly reported in U.S. clinical trials and is not unexpected in this hospitalized patient population requiring

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

systemic antifungal medications.

d. Thrombocytopenia: (n=14)

There were 3 serious reports of thrombocytopenia and 1 serious report of platelet count decreased in PSUR-2. In these 4 cases the platelet count was low prior to the initiation of micafungin, although a causal relationship was at least possible in 2 cases. In PSUR-3 a total of 2 cases related to thrombocytopenia were received, including 1 event each of idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura. The 120-day safety update was consulted and **a total of 14 serious events related to thrombocytopenia (including thrombocytopenic purpura) were identified through August 2004.** The sponsor reported that 11 serious cases of thrombocytopenia have been received through August 2004. The Japanese labeling was recently updated to list thrombocytopenia as an adverse event. There were 2 serious events of idiopathic thrombocytopenic purpura; there wasn't enough information about either case to make a causal assessment. There was 1 case of thrombotic thrombocytopenic purpura, which was possibly related to micafungin.

e. Suppression of Multiple blood cell lineages: (n=7)

There were no cases of serious adverse events related to suppression of multiple blood cell lineages received in PSUR-2. In PSUR-3, a total of 7 serious events related to suppression of multiple blood cell lineages were received, including 1 event of bone marrow depression and 6 events of pancytopenia. No cases were described in the text of the PSUR. The 120-day safety update was consulted to obtain MedWatches for these serious events. No additional cases were identified from the sponsor through August 2004. Thus, there have been **7 serious events of this nature reported by the sponsor through August 2004,** including 1 event of bone marrow depression and 6 events of pancytopenia. The event of bone marrow depression had an unlikely causal relationship to micafungin. For pancytopenia, the causal relationship to micafungin was unlikely in 4 cases; in the remaining 2 cases, there was not enough information to make a causal assessment.

Summary of Hematologic Events:

The proposed U.S. labeling lists anemia, leukopenia, neutropenia, and thrombocytopenia as common adverse events under **ADVERSE REACTIONS**. Based on the serious events reviewed, leukopenia and thrombocytopenia appear to be reversible with micafungin discontinuation. Hemolytic anemia has rarely been reported from Japanese post-marketed experience. The proposed U.S. labeling appears to be adequate in regards to hematologic events, except to consider adding hemolytic anemia in the listing of adverse events from Japanese postmarketing sources. Unlabeled hematologic adverse events, such as _____, should be closely monitored after the approval of MYCAMINE in the U.S.

IV. HYPERSENSITIVITY (n= 18)

Sponsor Proposed U.S. Labeling:

/ / /

Japanese Labeling:

The current Funguard labeling lists shock and anaphylactoid reactions as **CLINICALLY SIGNIFICANT ADVERSE REACTIONS**. Patients should be carefully monitored and if

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

abnormalities such as decreased blood pressure, oral cavity discomfort, dyspnea, generalized flushing, angioedema, or urticaria, etc. are observed, Funguard should be discontinued. If necessary, appropriate measures such as maintenance of the airway or administration of adrenaline, steroids or antihistamines, etc. should be taken.

a. Allergic Reactions (n=7)

There were **3 serious anaphylactoid reactions** described in PSUR-2. The first case occurred in a 69 y/o female with cancer of the middle ear (s/p surgery and irradiation) with severe marrow depression, pneumonia, acute respiratory insufficiency, and DIC. The patient was receiving 17 drugs and platelets at the time of the event. Thirty minutes after the initiation of micafungin, the patient developed an anaphylactoid reaction, acute circulatory failure and generalized redness. Micafungin was discontinued and the event markedly improved with steroids. The event was probably related to micafungin. In the second case, a 60 y/o male patient with bronchopulmonary aspergillosis, asthma, and bronchitis developed symptoms immediately after the micafungin infusion began. The patient was receiving 10 medications at the time of the event. Micafungin was discontinued and event resolved that same day. The event was probably related to micafungin. In the third case, a 13 y/o female patient with deep mycosis, ALL (s/p BMT), renal failure, sepsis, DIC, and aggravated VOD developed symptoms “in the middle” of micafungin infusion. The patient was receiving 3 medications at the time of the event. Micafungin was discontinued and steroids administered. Her blood pressure normalized in 45 minutes, but the event outcome was unknown. The event was possibly related to micafungin.

In PSUR-3, there were **4 serious events related to allergic reactions, including 2 events of anaphylactic shock and 2 infusion related reactions**. In the first case of anaphylactic shock, a 56 y/o female developed anaphylactic shock and intravascular hemolysis on the day that micafungin was initiated. Micafungin was discontinued and the patient was recovering at last report. The event was possibly related to micafungin. In the second case of anaphylactic shock, a 74 y/o male developed anaphylactic shock on the day that micafungin was initiated. Micafungin was discontinued and the event resolved. The event was possibly related to micafungin. In the first infusion related reaction, a 27 y/o female developed an unspecified infusion related reaction on the day that micafungin was initiated. Micafungin was discontinued and the event resolved. Event possibly related to micafungin. In the second case a 37 y/o female developed an infusion related reaction 4 days after the initiation of micafungin. Micafungin was discontinued 2 days later and the event resolved. Unable to make causal assessment based on line listing.

b. Serious Skin Events: (n= 6)

In PSUR-2 there were **2 serious skin events** reported, including toxic epidermal necrolysis and a serious case of dermatitis medicamentosa. The event of toxic epidermal necrolysis was reported in a 40 y/o female with candidal infection, SLE and UTI. One day after the initiation of micafungin, the patient developed SJS. Micafungin, immunoglobulin, imipenem/cilastatin, and amikacin were discontinued and steroids were administered. One week later, the patient improved. A causative drug cannot be specified, but micafungin cannot be excluded as a cause of the event. One serious event of dermatitis medicamentosa was listed in the report, but there was not enough information to make a causal assessment.

In PSUR-3, there were **3 serious skin events**, including toxic epidermal necrolysis, dermatitis

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

medicamentosa and rash. Toxic epidermal necrolysis was reported in a 77 y/o male with candidal infection, lymphoma and operations for appendicitis and cholelithiasis. The patient was receiving ampicillin/sulbactam, cefozopran, and arbekacin at the time of the event. One week after initiation of micafungin, the patient developed redness on his upper body. Two days later, TEN was diagnosed. Micafungin and ampicillin/sulbactam were discontinued and steroids were administered. At last report, the patient was improving. Event possibly related to micafungin. A 70 y/o male developed dermatitis medicamentosa, increased eosinophil count, and pyrexia. The serious skin event occurred 22 days after initiation of micafungin. Micafungin discontinued and patient recovered. There was not enough information to make a causal assessment. In the third case, a 69 y/o male developed rash and increased bilirubin 26 days after the initiation of micafungin. Micafungin discontinued, but the events did not resolve. There was not enough information to make a causal assessment.

According to a cumulative listing, there was also **1 report of toxic epidermal necrolysis** discussed in PSUR-1 (08 October 2002 to 07 April 2003). The sponsor was contacted and the MedWatch was obtained for this case. This case is confounded by the fact that micafungin, impenem/cilastatin, erythromycin, and clindamycin were all started and stopped around the same time. Twenty days later, the eruptions were almost resolved. One week later, the patient died of MOF. A causative drug could not be specified, but a contributory role of micafungin could not be excluded.

c. Vascular Reactions: (n=5)

There were no reports of vascular reaction in PSUR-2. In PSUR-3, there were **5 serious events of shock**; the verbatim terms for these cases include shock (1 event), acute circulatory failure (3), and circulatory failure (1). For these 5 events of shock, a causal role of micafungin was unlikely in 2 cases and an assessment could not be made for the remaining 3 cases. The first case of acute circulatory failure occurred in a 54 y/o male with reported events of DIC, pneumonia, anemia, jaundice, increased GOT, GPT and BUN. Shock occurred 7 days after initiation of micafungin. The event had a fatal outcome. There was not enough information to make a causal assessment. The second case of acute circulatory failure occurred in a 63 y/o male with asthma. Shock occurred 2 days after initiation of micafungin. The event had a fatal outcome. There was not enough information to make a causal assessment. The third case of acute circulatory failure occurred in a 67 y/o male 83 days after initiation of micafungin. The event was fatal. The event of shock was unlikely related to micafungin. The only case of circulatory failure occurred in a 73 y/o female with reported events of respiratory failure, decreased hemoglobin, and increased ALP, GGT, BUN, creatinine and potassium. Shock occurred 765 days after initiation and 1 month after discontinuation of micafungin. Event had an unlikely causal relationship to micafungin. Finally, a case of shock occurred in a 59 y/o female after unknown duration of micafungin. The event outcome was unknown. There was not enough information to make a causal assessment.

Summary of Hypersensitivity Events:

Under the _____ proposed U.S. label, anaphylactoid reaction was identified _____ In the PSURs reviewed, there were 3 events of anaphylactoid reactions and 2 events of anaphylactic shock that were possibly or probably related to micafungin. The sponsor should consider adding a **WARNING** _____ about the possibility of anaphylactoid reactions during micafungin infusions with _____ recommendations to discontinue MYCAMINE and administer appropriate treatments if anaphylaxis or

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

anaphylactoid reactions occur. In addition, DDRE was able to identify three cases of TEN in which a causative drug could not be specified, but a contributory role of micafungin could not be excluded. Consideration should be made to review clinical trial data for serious skin events and events of this nature should be closely monitored following the approval of MYCAMINE in the U.S.

V. CARDIAC (n= 9)

Sponsor Proposed U.S. Labeling:

/ / / / /

Japanese Labeling:

The current Funguard labeling notes that hypertension and palpitation occurred in 0.1% to <5% of Japanese patients in clinical trials. Additionally, vasodilatation was noted in foreign clinical studies in patients treated with micafungin

a. Arrhythmias (n=4)

In PSUR-2 there was **1 serious report each of supraventricular tachycardia and ventricular tachycardia**, both were unlikely to be related to micafungin. In PSUR-3 there was **1 case each of atrial fibrillation and ventricular tachycardia**; neither could be assessed because they were not described in the text of the report. The event of supraventricular tachycardia occurred in a patient on TPN with no prior cardiac history. Three days after initiation of micafungin, patient developed PSVT with decreased blood pressure and convulsions. The patient was cardioverted and disopyramide was initiated. It was unlikely that the event was related to micafungin. Ventricular tachycardia occurred in a patient receiving 8 other concomitant medications. The patient had a possible prior history of v. tach. Several weeks after an increase in the micafungin dose from 150 mg to 225 mg daily, the patient developed ventricular tachycardia on 12 sequential cycles on the ECG monitor. The heart rate returned to sinus rhythm spontaneously within several seconds without any treatment and the event did not recur (patient monitored by ECG). It was unlikely that the event was related to micafungin.

b. Hypertension: (n=0)

There were no serious reports listed in PSUR-2 or PSUR-3.

c. Acute cardiac failure: (n=5)

In PSUR-2, there was **1 case of acute cardiac failure** in a patient who developed prolonged QTc (QTc 500 msec). The patient was receiving amikacin, itraconazole, allopurinol, panipenem, betamipron, and trimethoprim/sulfamethoxazole at event onset. The cardiac event was possibly related to micafungin. In PSUR-3, there were **2 serious cases of cardiac failure, 1 case of aggravated cardiac failure, and 1 case of congestive cardiac failure**. There was not enough information provided to make a causal assessment of these 4 cases.

Summary of Cardiac Events:

Cardiac events appear to be adequately addressed by the proposed U.S. label. Prolongation of QTc

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

should be evaluated by the sponsor, if not already done.

Overall Summary:

Refer to the summary table below for the distribution of reported adverse events in PSUR-2 and PSUR-3 from April 2003 to April 2004. As depicted below, serious events were commonly reported and comprised 61.3% of all reported adverse events, which is reasonable given the patient population being treated and need to administer micafungin intravenously. Serious adverse events were most commonly reported for the investigations, hepatobiliary, blood and lymphatic, infections and infestations, and respiratory SOCs. The majority of labeling recommendations from DDRE focus on these SOCs.

Summary Table of Adverse Events by System Organ Class from PSURs

System Organ Class	PSUR-2 Total	PSUR-2 Serious	PSUR-2 N/S	PSUR-3 Total	PSUR-3 Serious	PSUR-3 N/S	Percent Serious**
Hepatobiliary	38	20	18	74	43	31	9.6%
Investigations	27	11	16	204	96	108	16.3%
Skin & subcutaneous	16	2	14	16	4	12	0.9%
Blood & lymphatic	12	8	4	37	31	6	5.9%
Metabolism & Nutrition	10	6	4	24	7	17	2.0%
Gastrointestinal	9	7	2	14	10	4	2.6%
Renal & Urinary	7	6	1	20	18	2	3.7%
Cardiac	3	3	0	7	6	1	1.4%
Infections & Infestations	2	2	0	33	32	1	5.2%
Injury, poisoning & procedural complications	2	2	0	5	5	0	1.1%
Musculoskeletal & connective tissue	2	1	1*	1	0	1	0.2%
System Organ Class	PSUR-2 Total	PSUR-2 Serious	PSUR-2 N/S	PSUR-3 Total	PSUR-3 Serious	PSUR-3 N/S	Percent Serious**
Nervous system	2	1	1	13	11	2	1.8%
Respiratory	2	2	0	25	25	0	4.1%
Vascular	2*	1	1	7	5	2	0.9%
General	N/A	N/A	N/A	21	17	4	2.6%
Neoplasms	N/A	N/A	N/A	15	15	0	2.3%
Psychiatric	N/A	N/A	N/A	3	3	0	0.5%
Immune	N/A	N/A	N/A	2	2	0	0.3%
Ear & labyrinth	N/A	N/A	N/A	1	0	1	0%
Total	134	72	62	522	330	192	61.3%

* Error in report text ** Serious AEs as a percentage of total AEs for PSUR-2 & PSUR-3 combined.

Additional Concern: Incompatibility/Decreased Potency

The English translation of the Funguard label and a compatibility study provided by the sponsor notes that incompatibility (immediate precipitation) occurs with vancomycin, aminoglycosides and other drugs commonly used in this patient population. Also, there is decreased potency with ampicillin, trimethoprim/sulfamethoxazole, acyclovir, ganciclovir and acetalozamide. As these medications are likely to be used in this patient population, the

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

Discussion

The Japanese postmarketed safety data reviewed does provide some evidence that micafungin is associated with an increased risk for potentially clinically significant hepatic, renal, hematologic, hypersensitivity and cardiac events. However, the case numbers are limited, except for hepatic events, and almost all the cases are confounded by concomitant drugs and disease conditions which could themselves cause these events of concern. Also, it was difficult to reconcile the events received in the 2nd and 3rd PSUR and the sponsor's listing of serious events through August 2004. An attempt was made to characterize the safety profile of the micafungin based on the post-marketing data provided by the sponsor, although exact counts cannot be verified at this point in time. Regardless, recommendations can be made to expand the MYCAMINE label to provide a better representation of the micafungin safety profile and monitoring recommendations for this product. A recommendation was made to consider a **PRECAUTION** for hepatic events and continually assess the risk/benefit of MYCAMINE therapy in patients who develop worsening hepatic function. A recommendation was made to consider listing renal impairment as a **PRECAUTION**, with a recommendation to continually assess the risk/benefit of MYCAMINE therapy in patients who develop renal dysfunction. DDRE suggests that a **WARNING** be considered for anaphylactoid reactions during micafungin infusions with recommendations to discontinue MYCAMINE and administer appropriate treatments. The sponsor should consider listing the concomitant drugs that are incompatible with or decrease the potency of MYCAMINE. In addition, consideration should be given to reviewing the clinical data for occurrences of QTc prolongation and hemolytic uremic syndrome, if not already conducted.

Reviewer's Signature / Date: /s/	
Division Director Signature / Date: /s/	

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

**APPEARS THIS WAY
 ON ORIGINAL**

Appendix 1. Serious Hepatic Events of Concern*

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	Causality
HEPATIC FAILURE (n=6)					
2003JP007175	Hepatic failure, renal impairment , systemic mycosis, sepsis Fatal	15 y/o Male Aplastic anemia, appendicitis	150 mg daily Suspected candidemia 7 days	<u>Pre-micafungin:</u> AST 25, ALT 50. <u>Maximum Levels:</u> AST 4282, ALT 1387 (1 day after mica. d/c)	Ar flu irr ne ac
Pt died of deep mycosis & sepsis. Hepatic dysfunction appeared and rapidly progressed to hepatic failure when amphi B a therapy. Micafungin d/c and hepatic events resolved. Positive temporal relationship (7 days after initiation), positive dechallenge (discontinuation). Confounders: sepsis, amphotericin B, fluconazole. Possible causal relationship.					
2003JP007545	Hepatic failure, sepsis , renal insufficiency Fatal	56 y/o Male	100 mg Systemic Candidemia 2.5 weeks	<u>Pre-micafungin:</u> Alk Phos 329. <u>Maximum Levels:</u> AST 208, ALT 78, Alk Phos 485 (2 wks after mica. d/c)	im
Prior to micafungin, pt had sepsis with MOF. Pt died of sepsis, hepatic failure and renal failure 2.5 weeks after micafungin d/c. Unlikely causal relationship.					
2003JP007510	Hepatic failure, renal insufficiency , platelet count decreased, CPK decreased Not recovered	82 y/o Male aortic aneurysm rupture, atherosclerosis obliterans, interstitial pneumonia, gastric ulcer, paralytic ileus, renal failure	50 mg Respiratory moniliasis 8 days	<u>Pre-micafungin:</u> T.bili 0.7 <u>Maximum Levels:</u> T.bili 4.9 (2 wks after mica. d/c)	Di di
"Hepatic failure" began 2 weeks after d/c of micafungin. Confounding factors: circulatory insufficiency. Unlikely causal relationship.					
2003JP000750	Hepatic failure , renal insufficiency, multi-organ failure Fatal	54 y/o Male Pneumonia, sepsis, hepatic failure, cirrhosis, esophageal varices, hemorrhagic shock	50 mg Systemic candida 2 days	Not provided.	Ne
Pt with hepatic failure, sepsis, cirrhosis and hemorrhagic shock prior to micafungin initiation. Pt died of his primary disease & micafungin discontinued. Unlikely causal relationship.					
2003JP000963	Hepatic Failure Fatal	79 y/o Male Hepatitis C, cirrhosis, hepatic cancer	150 mg Candidiasis 4 days	<u>Pre-micafungin:</u> T.bili 7.7 <u>Maximum Levels:</u> T.bili 20.3 (1 mo. after mica. d/c)	Ne
Pt with hepatitis C, cirrhosis and hepatic cancer prior to micafungin initiation. Unlikely causal relationship.					
2003JP005939	Hepatic failure Fatal	60 y/o female Hepatitis B, AML	UNK UNK UNK	UNK	Ne
Sponsor classified as definitely not related to micafungin. Unable to assess causal relationship.					

Clinical Review
Mary E. Singer, M.D., Ph.D.
Mycamine (Mycamine sodium)
Mycamine (Mycamine sodium)

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Mycamine Daily Dose, Indication & Duration	Laboratory Results	C
HEPATITIS (n=1)					
2004JP000092	Hepatitis fulminant, lactic acidosis, febrile neutropenia, renal impairment Fatal	58 y/o female Malignant melanoma, sepsis	100 mg Bronchopulmonary aspergillosis 2 weeks	<u>Pre-mycamine:</u> N/A <u>Maximum Levels:</u> AST 18627, ALT 7,444, Alk Phos 163 (2 days after mica. d/c)	Tr
Pt with febrile neutropenia and sepsis fell into a shock state acutely before fulminant hepatitis occurred. Pt was also receiving One day after mycamine discontinued, lactic acidosis and fulminant hepatitis were noted. Pt had no signs of hepatic dysfunction Pt died of fulminant hepatitis. Unlikely causal relationship.					
HEPATOCELLULAR DAMAGE (n=3)					
2003JP006634	Hepatocellular damage Fatal	80 y/o male lung cancer, s/p excision of right upper lung 6 mos. prior, atherosclerosis obliterans	50 mg Fungal infection 8 days	<u>Pre-mycamine:</u> AST 10, ALT 5, Alk Phos 198 <u>Maximum Levels:</u> ALT 68, AST 79, Alk Phos 504, GGT 56 (while on mica) AST 271, ALT 556 (10 days after mica d/c; pt died next day)	va fa
Patient developed aspiration pneumonia and received with mycamine. A week later, pneumonia improved and pt weaned from then developed hepatic damage and mycamine was d/c. CT scan did not show dilation of bile duct. Hepatic damage continued of acute on chronic respiratory failure, 11 days after mycamine d/c. Event possibly related to mycamine based on the report Confounding factors: use of famotidine Possible causal relationship					
2003JP005832	Hepatocellular damage Fatal	72 y/o male therapy-resistant NHL, PMH of CMV-positive interstitial pneumonia 3 months earlier, which recurred	100 mg Pulmonary mycosis 2 weeks	<u>Pre-mycamine:</u> N/A <u>Maximum Levels:</u> T.bili 11 and up (while on mica) Echo showed hepatomegaly.	Ca ge
Hepatic damage and jaundice appeared 11 days after initiation of mycamine. Hepatic damage was aggravated about 1 week One week later MOF progressed. Two days later, pt died of malignant lymphoma and pneumonia. Confounding factors: intracranial or CMV infection, MOF, and use of cephalosporin. Unlikely causal relationship.					
2003JP006590	Hepatocellular damage Fatal	54 y/o female rheumatoid arthritis, amyloidosis, on a ventilator	150 mg Fungal pneumonia 11 days	<u>Pre-mycamine:</u> N/A <u>Maximum Levels:</u> ALT 267 (while on mica) AST 313, AST 147 three days later (while on mica)	Fa ce fu

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

**APPEARS THIS WAY
 ON ORIGINAL**

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	C
Six days after initiation of micafungin, moderate liver damage identified on biochemistry panel. Micafungin was continued after Hepatic event unlikely related to micafungin, as LFTs were improving slightly until patient succumbed to multiple organ failure on cephalosporin and famotidine. Unlikely causal relationship					
LIVER DISORDER (n=2)					
2003JP007054	Liver Disorder Life-threatening	70 y/o female Fungal pneumonia, esophageal carcinoma, bone marrow depression (s/p chemotx and radiation tx)	50-100 mg Fungemia 2 days	<u>Pre-micafungin:</u> AST 46, ALT 57, LDH 282, GGT "slightly high" <u>Maximum Levels:</u> ALT 1654, AST 3900 (mica d/c that day)	M
Ten days after micafungin d/c, LFTs decreased to approx 2x baseline levels. Confounding factors: use of meropenem, neoplasia. Possible causal relationship					
2003JP007474	Liver Disorder Life-threatening	87 y/o female atrial fibrillation, asthma, hypertension,	50-150 mg UNK UNK	<u>Pre-micafungin:</u> N/A <u>Maximum Levels:</u> AST 400 (w/ mica 150 mg/d)	N
Liver disorder noted when micafungin dose increased from 50 to 150 mg daily. The dose of micafungin was reduced and stopped. Possible causal relationship					
HYPERBILIRUBINEMIA (n=5)					
2004JP001016	Hyperbilirubinemia Life-threatening	63 y/o male small cell lung cancer, post- op pyothorax with multiple marsupialization procedures	50-75 mg Aspergillosis 6 weeks	<u>Pre-micafungin:</u> T.bili 0.4 <u>Maximum Levels:</u> T.bili 7.3 (mica d/c that day)	im
Massive bleeding due to pyothorax w/ administration of packed red blood cells. Hyperbilirubinemia noted for the first time. Confounding factors: use of famotidine, possible transfusion reaction, neoplastic disease. Possible causal relationship.					
2004JP000850	Hyperbilirubinemia Fatal	69 y/o female Parkinson's disease, aspiration pneumonia	300 mg Fungemia 3 days	<u>Pre-micafungin:</u> T.bili 1.42, D.bili 2.07 <u>Maximum Levels:</u> T.bili 31.32, D.bili 32.18 (1 week after mica d/c)	Di pi (g zi
Three days after initiation of micafungin, progressive hyperbilirubinemia noted. Pt had previously received isoxicam without effect. Plasma exchange conducted over 3 days, about 1 week after micafungin d/c. Pt also given transfusion of packed red blood cells, change of antibiotics, gamma globulin treatment and PRBC transfusion, pt died from event. Confounding factors: ranitidine, neoplasia. Possible causal relationship					
2003JP007337	Hyperbilirubinemia Life-threatening	75 y/o male Septic shock, paralytic ileus, colonic perforation, diffuse peritonitis	150 mg Candida pneumonia 6 days	<u>Pre-micafungin:</u> T.bili 4.3 (increasing at the time) <u>Maximum Levels:</u> T.bili 12.2 (mica d/c that	Pa cli ve

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

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	C
				day)	
T.bili increased while on micafungin for 6 days. Micafungin d/c and the pt recovered from the event. However, patient exper days later, believed to be related to primary disease. Confounding factors: fluconazole, ciprofloxacin, clindamycin. Unlikely c					
2003JP006270	Hyperbilirubinemia Fatal	74 y/o male peritonitis due to perforation of duodenal ulcer, chronic renal failure	50 mg Systemic candida 7 days	<u>Pre-micafungin:</u> T.bili 4.8 <u>Maximum Levels:</u> T.bili 11 (mica d/c that day)	O ge ar
Pt was experiencing intraabdominal bile leak, endotoxemia, and MOF at the time of the event. T.bili peaked on day 7 of mic and T.bili decreased to 6.5 at the time of last report. One week later, pt died of hemorrhagic shock. Confounding factors: intr endotoxemia, MOF, omeprazole, cephalosporin use, ranitidine, ampicillin/sulbactam. Unlikely causal relationship.					
2003JP006683	Hyperbilirubinemia Fatal	55 y/o female AML, s/p allogenic BSCT 3 weeks earlier	150 mg Pneumonia 12 days	<u>Pre-micafungin:</u> T.bili 1.0 <u>Maximum Levels:</u> T.bili 46.7 (6 days after mica d/c)	Cy va ac fl
T.bili was normal prior to micafungin and began to increase 1 day after initiation of micafungin. Five days later, pt began to c including diarrhea, progressing to melena, skin eruption with decreased blood pressure and urine volume. Pt died of multi-or micafungin d/c. Confounding factors: GVHD, cyclosporine, famotidine, fluconazole, acyclovir, furosemide. Unlikely causal r					
HEPATIC FUNCTION ABNORMAL (n=10)					
2003JP006719	Hepatic function abnormal Fatal	72 y/o male Sepsis, chronic cardiac failure,	100 mg Sepsis 1 day	<u>Pre-micafungin:</u> N/A <u>Maximum Levels:</u> AST 6703, ALT 3800, LDH 3760 (mica d/c that day)	Q
Post-transfusion hepatitis suspected and lamivudine initiated. However, test results did not indicate viral hepatitis. Pt died 2 cause of death was MOF with aggravation of chronic heart failure due to fulminant hepatitis due to micafungin. Possible cau					
2004JP001237	Hepatic function abnormal, multi- organ failure , renal impairment, gastric mucosal lesion Fatal	84 y/o male angina, TIA, multiple cerebral infarction, pneumonia	300 mg Bronchopulmonary aspergillosis 6 days	<u>Pre-micafungin:</u> AST 20, ALT 23 <u>Maximum Levels:</u> AST 1004, ALT 755	O; ck
Pneumonia continually worsened. Pt developed hepatic dysfunction and renal impairment 6 days after initiation of micafungi Four days later, pt had tarry stools with anemia. Three days later, acute gastric mucosal lesion was diagnosed. The pt went consciousness with high levels of fibrinogen degradation products. Pt ultimately died of MOF 10 days after micafungin d/c. clarithromycin, cerebral infarction. Possible causal relationship.					
2003JP007341	Hepatic function abnormal Life-threatening	41 y/o male Myelodysplastic syndrome, atrial fibrillation, acute on chronic heart failure,	300 mg Bronchopulmonary aspergillosis 5 days	<u>Pre-micafungin:</u> AST 25, ALT 24, LDH 1548, T.bili 0.88 <u>Maximum Levels:</u>	ltr isc (v dc

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

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	Cr
		pneumonia, diabetes mellitus, hemochromatosis		AST 2292, ALT 1240, LDH 6886, T.bili 3.84 (mica d/c that day) Two weeks after mica d/c: AST 36, ALT 47, LDH 302	be
<p>Four days after initiation of micafungin, rifampin and isoniazid initiated for tuberculosis and pt transiently fell into a shock state next day and micafungin, itraconazole, rifampin, and isoniazid were discontinued that day. A week later, he was recovering from shock state. Confounding factors: shock state, hemochromatosis, heart failure, itraconazole, ranitidine, furosemide, meropenem, isoniazid relationship.</p>					
2003JP005464	Hepatic function abnormal Life-threatening	75 y/o female Hepatic cirrhosis, emphysema, pulmonary hypertension, deep mycosis, h/o pulmonary tuberculosis	100 mg Fungal infection 7 days	<u>Pre-micafungin:</u> AST 17, ALT 9, Alk Phos 214, LDH 197, GGT 25, T.bili 0.7 <u>Maximum Levels:</u> AST 429, ALT 398, LDH 986, Alk Phos 185, GGT 33, T.bili 1.5 (about 8 days after mica initiation) Two weeks after mica d/c: AST 36, ALT 47, LDH 302	Is ce
<p>Hepatic function worsened after initiation of micafungin. General condition worsened at this time, with hypotension. Hepatic micafungin discontinuation, at this time blood pressure also began to improve. Confounding factors: hepatic cirrhosis, hypotension, teicoplanin. Unlikely causal relationship.</p>					
2003JP000021	Hepatic function abnormal Life-threatening	82 y/o male tuberculosis, pneumonia	150 mg Bronchopulmonary aspergillosis 2 days	<u>Pre-micafungin:</u> AST 47, ALT 23, T.bili 1.2 <u>Maximum Levels:</u> AST 1270, ALT 1253, T.bili 2.4	Cr ro
<p>LFTs rose about two days after initiation of micafungin. Micafungin and cefozopran were d/c that day and events resolved at that time. Confounding factors: use of cephalosporin, itraconazole. Possible causal relationship.</p>					
2003JP007507	Hepatic function abnormal, pneumonia, anemia Fatal	54 y/o female Diabetes mellitus, atypical pulmonary mycobacteriosis, chronic cardiac failure, mitral valve replacement	100 mg Pulmonary mycosis 8 days	<u>Pre-micafungin:</u> AST 36, ALT 22 <u>Micafungin D/C:</u> AST 21, ALT 16 <u>Maximum Levels:</u> AST 1709, ALT 603 (6 days after micafungin d/c)	Cr si fa ir
<p>Micafungin discontinued before pt experienced increased LFTs. Six days after micafungin d/c, pt developed hepatic dysfunction (two weeks after discontinuation of micafungin), the pt was recovering from hepatic dysfunction when she died of respiratory failure. Confounding factors: chronic cardiac failure, clarithromycin, famotidine, aztreonam, amikacin. Unlikely causal relationship.</p>					
2003JP006638	Hepatic function abnormal	20 y/o male	150-300 mg	<u>Pre-micafungin:</u>	M

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

APPEARS THIS WAY
 ON ORIGINAL

MCN	Events & Outcome (1° event in bold)	Age, Gender & PMH	Micafungin Daily Dose, Indication & Duration	Laboratory Results	C
	abnormal Fatal	ALL, s/p BMT 1 month prior	Fungal infection 1 month	ALT 278, T.bili 2.99 <u>Maximum Levels:</u> AST 219 (10 days before death), ALT 278 (on same day mica initiated), T.bili 24.38 (day before pt died).	pr le
After dose of micafungin increased from 150 to 300 mg daily, hepatic function parameters suddenly increased. On the same massive hemorrhage and received multiple transfusions. Three days later, CMV antigen was positive and CMV colitis diagnosed lower GIT. About 10 days later, pt died of hemorrhagic shock. Micafungin was ongoing at death. Confounding factors: CMV causal relationship.					
2003JP005221	Hepatic function abnormal Fatal	UNK y/o male Pulmonary tuberculosis, hepatitis C infection, hepatic failure, renal failure, cerebral infarction	50 mg UNK UNK	UNK	No
Nine days after initiation of micafungin, pt developed hepatic function disorder due to hepatitis C and had increased SGOT, 5 later, pt died of aggravation of primary disease. Confounding factors: hepatitis C infection, hepatic failure, renal failure, cerebral relationship.					
2004JP000088	Hepatic function abnormal, bronchopulmonary aspergillosis Fatal	77 y/o female stomatitis, sepsis d/t pseudomonas aeruginosa, aplastic anemia, herpes simplex virus	150 mg bronchopulmonary aspergillosis 2 weeks	<u>Pre-micafungin:</u> AST 33, ALT 53 <u>Maximum Levels:</u> AST 148, ALT 223	Cl flu tri fil
Pt developed hepatic dysfunction 2 days after initiating micafungin. AST & ALT improved while receiving micafungin and the died the next day of invasive bronchopulmonary aspergillosis. Confounding factors: sepsis, herpes simplex infection, cephal trimethoprim/sulfamethoxazole, fluconazole. Unlikely causal relationship.					
2004JP001563	Hepatic function abnormal Life-threatening	77 y/o male MRSA infection, cardiac failure, vegetative state	100 mg Candidiasis 3 days	AST increased to 1000	Te
Pt developed hepatic disorder with AST increased 3 days after initiation of micafungin. No other information available. Conf teicoplanin. Not enough information for causal assessment.					

* Causal relationship between micafungin and the reported event(s) assessed by the author

Clinical Review

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

Micafungin sodium for Esophageal Candidiasis

Mycamine (Micafungin sodium)

REFERENCES

Pappas, PG, JH Rex, JD Sobel, SG Filler, WE Dismukes, TJ Walsh, and JE Edwards, 2004, Guidelines for treatment of candidiasis. *Clin. Infect. Dis.* 38:161-189.

Villanueva A, E Gotuzzo, A Arathoon, et al., 2002, A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am. J. Med.* 113:294-299.

Krause, DS, AE Simjee, C van Rensburg, J Viljoen, TJ Walsk, BP Goldstein, M Wible, and T Henkel, 2004, A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clin. Infect. Dis.* 39:770-775.

Viscoli, C, M Paesmans, M Sanz, E Castagnola, J Klastersky, P Martino, and M Glauser, 2001, Association between antifungal prophylaxis and rate of documented bacteremia in febrile neutropenic cancer patients. *Clin. Infect. Dis.* 32:1532-1537.

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

/s/

Mary Singer
3/14/05 01:42:09 PM
MEDICAL OFFICER

Eileen Navarro
3/14/05 01:48:56 PM
MEDICAL OFFICER