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

Table 63. Most Common Drug-Related Adverse Events* by Dose and Duration of Micafungin (adapted from applicant's appendix 3.2.2, Clinical Summary of Safety, Update, July, 2004)

Adverse Event COSTART Body System and Term	Micafungin ≥ 150 mg/day for ≥ 10 days or > 3mg/kg/day for weight < 40 kg N= 606	Micafungin < 150 mg/day for <10 days or < 3mg/kg/day for weight < 40 kg N= 1796
Metabolic and nutritional disorders:		
ALT increased	26 (4.3)	37 (2.1)
AST increased	23 (3.8)	41 (2.3)
Alkaline phosphatase increased	12 (2.0)	37 (2.1)
Hyperlipemia	9 (1.5)	1 (0.1)
Hypokalemia	9 (1.5)	21 (1.2)
Bilirubinemia	4 (0.7)	32 (1.8)
Hypocalcemia	1 (0.2)	28 (1.6)
Hypomagnesemia	1 (0.2)	31 (1.7)
Digestive System:		
Nausea	22 (3.6)	47 (2.6)
Liver function tests abnormal	16 (2.6)	30 (1.7)
Diarrhea	13 (2.1)	35 (1.9)
Vomiting	11 (1.8)	47 (2.6)
Body as a whole:		
Procedural complication	24 (4.0)	5 (0.3)
Abdominal pain	12 (2.0)	30 (1.7)
Chills	8 (1.3)	18 (1.0)
Fever	8 (1.3)	34 (1.9)
Cardiovascular system:		
Phlebitis	22 (3.6)	15 (0.8)
Nervous system:		
Headache	20 (3.3)	36 (2.0)
Skin and appendages:		
Rash	17 (2.8)	39 (2.2)
Pruritis	10 (1.7)	14 (0.8)
Maculopapular rash	9 (1.5)	8 (0.4)
Hemic and Lymphatic system:		
Leukopenia	16 (2.6)	43 (2.4)
Anemia	7 (1.2)	22 (1.2)

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Thrombocytopenia	5 (0.8)	18 (1.0)
Injection site reaction:		
Injection site inflammation	6 (1.0)	15 (0.8)

* Adverse events which occurred in $\geq 1.0\%$ in either group

***Medical Officer Comment:** For drug-related adverse events, there appears to be dose relationship with micafungin; while the incidence of all adverse events, regardless of relationship to study drug was similar in subjects who received ≥ 150 mg/day micafungin for a minimum of 10 days, 83.3% (505/606), and in those who received a lower dose or shorter duration of micafungin, 84.8% (1523/1796). The difference in incidence of drug-related adverse events between higher and lower doses and duration of micafungin, shown in this table could be related to the different patient populations who received different dose formulations, and differences in attribution of causality to study drug by the investigator.*

Drug-Related Adverse Events by Age, Race, and Underlying Condition

When analyzed by underlying disease, subjects with HIV had the highest incidence of drug-related adverse events, 40.7% (273/670), in comparison to those with a hematological malignancy or HSCT, 23.2% (219/946), or other underlying condition, 27.2% (99/364). The highest incidence of drug-related adverse events occurred in subjects between the ages of 16 and 65 years old, 31.0% (612/1972), in comparison to subjects younger than 16 years of age, 24.6% (60/244), and those 65 years of age and older, 24.2% (45/186). No significant differences were noted in the incidence of drug-related adverse events between different racial groups. In Caucasians, drug-related adverse events were reported in 458/1519 (30.2%) subjects, in blacks 145/531 (27.3%), and in other racial/ethnic groups 114/352 (32.4%).

***Medical Officer Comment:** The relationship of an adverse event to study drug as assessed by an investigator is highly subjective. For example, investigators may be less likely to attribute an adverse event to a study drug if the patient has multiple other medical problems and is on multiple concomitant medications.*

7.1.6 Less Common Adverse Events

Adverse Events with an incidence of 1.0 to $< 2.0\%$ in all micafungin-treated subjects and patients is shown in the table below. Those events that occurred in more subjects than volunteers were those that occurred in volunteers, and are highlighted in bold font in the table below.

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Table 64. Less Common Adverse Events* in Subjects and Patients who received Micafungin (adapted from Applicant's Appendix 2.74.3.1, 120-day Safety Update)

Adverse Event (COSTART Body System and Term)	Micafungin-treated Subjects N=2402 n (%)	Micafungin-Treated Patients N=1980 n (%)
Body as a Whole:		
Cachexia	36 (1.5)	36 (1.8)
Lab test abnormal	36 (1.5)	36 (1.8)
Accidental injury	33 (1.4)	33 (1.7)
Cellulitis	32 (1.3)	31 (1.6)
Ascites	31 (1.3)	31 (1.6)
Neck pain	31 (1.3)	30 (1.5)
Malaise	27 (1.1)	25 (1.3)
Abscess	19 (0.8)	19 (1.0)
Digestive System:		
Gastroenteritis	44 (1.8)	44 (2.2)
Melena	44 (1.8)	44 (2.2)
Ileus	42 (1.7)	42 (2.1)
Gastritis	41 (1.7)	41 (2.1)
Gastrointestinal disorder	40 (1.7)	40 (2.0)
Hematemesis	38 (1.6)	38 (1.9)
Flatulence	36 (1.5)	34 (1.7)
Rectal hemorrhage	36 (1.5)	36 (1.8)
Esophagitis	34 (1.4)	33 (1.7)
Gum/oral hemorrhage	33 (1.4)	33 (1.7)
Hepatomegaly	32 (1.3)	32 (1.6)
Mouth ulceration	30 (1.2)	27 (1.4)
Fecal incontinence	29 (1.2)	29 (1.5)
Colitis	28 (1.2)	28 (1.4)
Venoocclusive liver disease	22 (0.9)	22 (1.1)
Tooth disorder	22 (0.9)	21 (1.1)
Eructation	19 (0.8)	19 (1.0)
Metabolic and Nutritional Disorders:		
Lactate dehydrogenase increased	44 (1.8)	44 (2.2)
Hypoglycemia	41 (1.7)	41 (2.1)
Hyperchloremia	39 (1.6)	39 (2.0)
Hypermagnesemia	37 (1.5)	37 (1.9)
Weight loss	36 (1.5)	36 (1.8)
Hyperphosphatemia	34 (1.4)	34 (1.7)
Respiratory alkalosis	31 (1.3)	31 (1.6)

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Hyperlipemia	27 (1.1)	9 (0.5)
Hypochloremia	23 (1.0)	23 (1.2)
Respiratory acidosis	23 (1.0)	23 (1.2)
Alkalosis	20 (0.8)	20 (1.0)
Weight gain	19 (0.8)	19 (1.0)
Nervous System:		
Convulsion	30 (1.2)	30 (1.5)
Thinking abnormal	30 (1.2)	29 (1.5)
Hallucinations	25 (1.0)	25 (1.3)
Neuropathy	19 (0.8)	19 (1.0)
Respiratory System:		
Lung edema	40 (1.7)	40 (2.0)
Respiratory disorder	34 (1.4)	34 (1.7)
Bronchitis	23 (1.0)	23 (1.2)
Pleural disorder	22 (0.9)	22 (1.1)
Atelectasis	21 (0.9)	21 (1.1)
Hemic and Lymphatic System:		
WBC abnormal	41 (1.7)	41 (2.1)
Coagulation disorder	37 (1.5)	37 (1.9)
Lymphadenopathy	27 (1.1)	27 (1.4)
Prothrombin decreased	23 (1.0)	23 (1.2)
Splenomegaly	21 (0.9)	21 (1.1)
Eosinophilia	20 (0.8)	20 (1.0)
Cardiovascular System:		
Arrhythmia	36 (1.5)	36 (1.8)
Atrial fibrillation	36 (1.5)	36 (1.8)
Hemorrhage	33 (1.4)	33 (1.7)
Postural hypotension	28 (1.2)	27 (1.4)
Thrombophlebitis	28 (1.2)	25 (1.3)
Valvular heart disease	28 (1.2)	28 (1.4)
Deep thrombophlebitis	24 (1.0)	24 (1.2)
Pericardial effusion	24 (1.0)	24 (1.2)
Syncope	23 (1.0)	22 (1.1)
Skin and appendages:		
Skin ulcer	45 (1.9)	45 (2.3)
Urticaria	43 (1.8)	43 (2.2)
Folliculitis	37 (1.5)	37 (1.9)
Skin discoloration	29 (1.2)	28 (1.4)

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Vesiculobullous rash	25 (1.0)	24 (1.2)
Urogenital System:		
Urinary incontinence	46 (1.9)	46 (2.3)
Kidney function abnormal	42 (1.7)	42 (2.1)
Vaginal hemorrhage	31 (1.3)	31 (1.6)
Cystitis	29 (1.2)	29 (1.5)
Urine abnormality	23 (1.0)	19 (1.0)
Acute kidney failure	22 (0.9)	22 (1.1)
Urinary frequency	22 (0.9)	21 (1.1)
Musculoskeletal System:		
Cramps	35 (1.5)	34 (1.7)
Myasthenia	31 (1.3)	31 (1.6)
Special Senses:		
Abnormal vision	42 (1.7)	42 (2.1)
Dry eyes	40 (1.7)	40 (2.0)
Ear pain	40 (1.7)	39 (2.0)
Eye hemorrhage	36 (1.5)	36 (1.8)
Conjunctivitis	32 (1.3)	31 (1.6)
Eye pain	30 (1.2)	29 (1.5)
Taste perversion	29 (1.2)	23 (1.2)
Injection Site Reaction:		
Injection site inflammation	30 (1.2)	17 (0.9)

Medical Officer Comments: Those events that occurred in volunteers included cellulitis, neck pain, malaise, flatulence, esophagitis, mouth ulceration, tooth disorder, hyperlipemia, abnormal thinking, postural hypotension, thrombophlebitis, syncope, skin discoloration, vesiculobullous rash, urine abnormality, urinary frequency, cramps, ear pain, conjunctivitis, eye pain, taste perversion, and injection site inflammation. Some of these would be unexpected in a healthy volunteer.

Adverse events that occurred in the 2402 micafungin-treated subjects at an incidence of $\leq 1\%$ included the following, classified by COSTART Body System and Term in order of decreasing frequency (adapted from Applicant's Appendix 2.7.4.3.1, 120 day Safety Update):

Body as a Whole: tuberculosis, aggravated, pelvic pain, AIDS, hypothermia, peritonitis, tuberculosis, reactivated, relapse of primary malignancy, neck rigidity, graft rejection, hernia, sarcoma, drug level increased, anaphylactoid reaction, mucous membrane disorder, neoplasm benign, overdose, moniliasis, carcinoma, chills and fever, drug level decreased, immune system disorder, immunoglobulins decreased, infection superimposed, necrosis, photosensitivity reaction, primary graft dysfunction, surgical treatment

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Digestive System: esophageal ulcer, gingivitis, glossitis, leukoplakia of mouth, enteritis, tongue disorder, hepatic failure, hepatosplenomegaly, cholelithiasis, sialadenitis, cholecystitis, enterocolitis, duodenitis, pancreatitis, aphthous stomatitis, cholestatic jaundice, intestinal obstruction, liver damage, pancreas disorder, stomach ulcer, bile duct disorder, bloody diarrhea, duodenal ulcer, hepatitis, stomach atony, tongue edema, viral hepatitis nonspecific, cirrhosis of liver, fecal impaction, gastrointestinal carcinoma, hemorrhagic gastritis, oral moniliasis, parotid gland enlargement, peptic ulcer, tooth caries, abnormal stools, cheilitis, cholangitis, esophageal hemorrhage, gastrointestinal anomaly, hepatitis, intestinal perforation, liver fatty deposit, peptic ulcer hemorrhage, periodontal abscess, stomach ulcer hemorrhage, tenesmus, tongue discoloration, ulcerative stomatitis

Metabolic and Nutritional Disorders: gamma glutamyl transpeptidase increased, hypercalcemia, decreased bicarbonate, healing abnormal, hypovolemia, electrolyte abnormality, glycosuria, hypercholesterolemia, amylase increased, hyperuricemia, thirst, enzymatic abnormality, ketosis, creatinine clearance decreased, hyperammonemia, gout, avitaminosis, calcium disorder, creatine phosphokinase increased, globulin increased, hypocholestermia, uremia

Nervous System: delirium, hypertonia, abnormal dreams, coma, encephalopathy, stupor, abnormal gait, emotional lability, increased salivation, speech disorder, amnesia, extrapyramidal syndrome, intracranial hemorrhage, meningitis, hostility, cerebral hemorrhage, dystonia, hemiplegia, neuralgia, aphasia, cerebrovascular accident, foot drop, reflexes decreased, vertigo, withdrawal syndrome, apathy, brain edema, movement disorder, neuritis, nystagmus, vocal chord paralysis, ataxia, cerebrospinal fluid abnormal, dementia, encephalitis, facial paralysis, grand mal convulsion, psychosis, acute brain syndrome, brain abscess, CNS depression, CNS neoplasia, benign, cogwheel rigidity, flaccid paralysis, hyperesthesia, hyperkinesia, intracranial hypertension, myelitis, myoclonus, paranoid reaction, personality disorder, sleep disorder, subarachnoid hemorrhage

Respiratory System: lung hemorrhage, pneumothorax, respiratory distress syndrome, apnea, pulmonary embolus, pulmonary tuberculosis reactivated, voice alteration, emphysema, stridor, laryngitis, lung fibrosis, pulmonary hypertension, aspiration pneumonia, interstitial pneumonia, sputum increased, laryngismus, nasal septum disorder, pulmonary mycosis

Hemic and Lymphatic System: pancytopenia, thrombocythemia, cyanosis, thromboplastin decreased, acute myeloblastic leukemia, purpura, hypochromic anemia, spleen disorder, bleeding time increased, hemolytic anemia, leukemia, basophilia, erythrocytes abnormal, hemolysis, lymphocytosis, lymphoma, monocytosis, sedimentation rate increased, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, fibrinogen decreased, fibrinogen increased, lymphedema, marrow depression, normocytic anemia, reticuloendothelial hyperplasia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura

Cardiovascular System: cardiomegaly, peripheral vascular disorder, cardiovascular disorder, congestive heart failure, heart arrest, atrial flutter, pallor, palpitation, heart failure, ventricular

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extrasystoles, ventricular tachycardia, electrocardiogram abnormal, pericarditis, sinus bradycardia, supraventricular tachycardia, cardiomyopathy, subdural hematoma, endocarditis, extrasystoles, migraine, thrombosis, ventricular arrhythmia, arterial anomaly, arterial thrombosis, increased capillary fragility, myocardial ischemia, occlusion, angina pectoris, arteriosclerosis, AV block complete, coronary artery disorder, mesenteric occlusion, myocardial infarct, spider angioma, vascular anomaly, vascular disorder, vascular headache, vasculitis

Skin and Appendages: *Herpes* zoster, exfoliative dermatitis, acne, petechial rash, eczema, pustular rash, breast pain, furunculosis, skin neoplasm benign, skin nodule, contact dermatitis, nail disorder, subcutaneous nodule, skin erythema, angioedema, seborrhea, skin infection, sunburn, breast neoplasm benign, gynecomastia, leukoderma, psoriasis, skin carcinoma, skin hypertrophy, skin necrosis

Urogenital System: hemorrhagic cystitis, vaginitis, albuminuria, penis disorder, scrotal edema, urinary retention, polyuria, anuria, urinary urgency, testis disorder, urination impaired, leucorrhea, kidney pain, menorrhagia, urethral pain, vulvovaginal disorder, bladder stneosis, dysmenorrhea, genital edema, kidney tubular disorder, kidney tubular necrosis, metrorrhagia, nocturia, prostatic disorder, pyelonephritis, urinary tract disorder, urogenital disorder, abnormal ejaculation, balanitis, carcinoma, renal, hydronephrosis, impotence, menstrual disorder, nephritis, ovarian disorder, uterine hemorrhage, vaginal moniliasis

Musculoskeletal System: arthrosis, joint disorder, twitching, bone disorder, tendon disorder, arthritis, generalized spasm, muscle atrophy, myopathy, pathological fracture, pyogenic arthritis, synovitis, tendinous contracture

Special Senses: ear disorder, otitis media, conjunctival edema, impaired hearing, lacrimation disorder, deafness, photophobia, tinnitus, retinal disorder, taste loss, eye disorder, miosis, otitis externa, anisocoria, retinitis, blepharitis, diplopia, keratitis, retinal hemorrhage, scleritis, blindness, corneal lesion, papilledema, corneal ulcer, exophthalmos, parosmia, strabismus, uveitis, vestibular disorder

Injection Site Reaction: injection site pain, injection site edema, injection site reaction, injection site hemorrhage

Endocrine System: hypothyroidism, adrenal cortex insufficiency, ADH inappropriate, addisonian crisis, Cushing's syndrome, diabetes insipidus, diabetes mellitus

Medical Officer Comment: Notably, hepatic failure was an uncommon adverse event in the safety database, occurring in 0.5% (10/1980) patients. Other uncommon adverse of interest included hepatitis (nonspecific), reported in 0.2% (3/1980) patients, liver damage in 0.2% (4/1980) patients, cholestatic jaundice in 0.3% (5/1980), hemolytic anemia or hemolysis in 0.3% (5/1980), pancytopenia in 0.9% (17/1980), and anaphylactoid reaction in 0.2% (3/1980) patients.

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7.1.7 Laboratory Findings

Hepatic, renal and hematologic laboratory findings were discussed above with their respective safety sections. Additionally, there was no significant difference in the mean or median values for calcium, potassium, magnesium, or sodium measured at baseline and end-of-therapy, for all subjects. Overall, except for liver function tests, described in the hepatic safety section, below, clinically significant effects on serum chemistry or hematological parameters were not observed in the population of patients with micafungin exposure.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were collected in all the clinical studies, but not analyzed in this review for the overall safety database. In study 03-7-005, one of the pivotal studies submitted for this NDA, in which patients received 150 mg/day micafungin, the proposed dose for treatment of esophageal candidiasis, no clinically significant changes from baseline to end-of-therapy were observed for systolic or diastolic blood pressure, heart rate, or temperature.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were not obtained routinely in the clinical studies; however, electrocardiograms were obtained in a number of drug-interaction studies in healthy volunteers, intervals in healthy volunteers, and no significant effects on the QT interval were observed. No significant effects on QT interval with micafungin were observed.

7.1.10 Immunogenicity

No clinical studies to evaluate immunogenicity were performed. In preclinical studies in rodents and guinea pigs, micafungin did not induce delayed or immediate hypersensitivity in skin tests, active system anaphylaxis, or passive cutaneous anaphylaxis. Additionally, a micafungin-guinea pig plasma protein complex did not induce a type I immunological reaction. Theoretically, because micafungin is highly protein bound in serum, it could act as a hapten and induce an immunologic reaction.

In the clinical studies, several patients experience anaphylactoid reactions; and in the postmarketing experience in Japan, there were reports of anaphylaxis and anaphylactic shock possibly related to micafungin. We have proposed a WARNING statement regarding anaphylaxis and anaphylactoid reactions in the micafungin label.

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In secondary pharmacodynamic studies in rats, the micafungin dose required for histamine release or heart rate and blood pressure effects was 3 times that of caspofungin (i.e. 32 mg/kg micafungin required in rats for histamine release in comparison to 10 mg/kg caspofungin). For blood pressure effects in unanesthetized rats, 32 mg/kg micafungin was required in comparison to 1 mg/kg caspofungin.

Medical Officer Comments: A potential for histamine-release and associated effects at high doses of micafungin is suggested based on these preclinical studies. The doses at which histamine release was observed in animals were considerably higher than the proposed dose of micafungin for treatment of esophageal candidiasis. The applicant suggested that histamine-release can be minimized by avoiding rapid infusion or bolus injection of micafungin.

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

Medical Officer Comments: Negative tests for hypersensitivity in animals do not preclude a potential for hypersensitivity reactions in humans.

Healthy Volunteers

Adverse events included by the applicant under this heading included the COSTART terms rash, maculopapular rash, vesiculobullous rash, pruritus, vasodilatation, urticaria, eosinophilia, anaphylactoid reaction and allergic reaction. The terms, facial edema, angioedema, and skin erythema were included in these analyses, because they could also be indicative of an allergic reaction. The terms, hypotension, tachycardia, cyanosis, hypertension, dyspnea and stridor were not included in this category, although any of these events could also signify an allergic or histamine-mediated reaction. A number of allergic/histamine-type reactions were reported in healthy volunteers who received micafungin in single-dose and repeat-dose micafungin studies, as shown in Tables 65 and 66 below.

Table 65. Allergic and Histamine-type Reactions in Healthy Volunteers who received Micafungin in Single-Dose studies* (adapted from Applicant's Appendix 3.3, ISS)

Adverse Event Body System and (COSTART Term)	Healthy Volunteers N=198
Face edema	1 (0.5)
Rash	7 (3.5)
Skin erythema	2 (1.0)
Maculopapular rash	1 (0.5)
Pruritus	1 (0.5)
Vesiculobullous rash	1 (0.5)
Vasodilatation	4 (2.0)

*studies included 97-0-040, FJ00001, FJ0004, FJ0005, FG-21-04, FG-21-06, FG-21-15, FG-21-16

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Table 66. Allergic and Histamine-type Reactions in Healthy Volunteers who received Micafungin in Repeat-Dose Studies* (adapted from Appendix 2.3, ISS)

Adverse Event Body System and (COSTART Term)	Healthy Volunteers N=184
Rash	8 (4.3)
Pruritis	4 (2.2)
Maculopapular rash	3 (1.6)
Vasodilatation	13 (7.1)

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

Medical Officer Comments: Rash was the most common adverse event in both single-dose and repeat-dose micafungin studies in healthy subjects; while vasodilatation was seen more frequently in the repeat-dose studies. When analyzed by dose, vasodilatation occurred in 12 subjects who received 100 mg/day and 1 subject who received 150 mg/day micafungin. When analyzed by treatment duration, 11 subjects who experienced vasodilatation received < 9 days micafungin; while only 2 received micafungin for ≥ 10 days. Definitive conclusions regarding a dose relationship of micafungin to the occurrence of vasodilatation cannot be drawn from these data, because of the small number of subjects.

Allergic and Histamine-type Reactions in Patients

Overall, 674 of 2402 (28.1%) subjects experienced an adverse event in this category. In patients, 652/1980 (32.9%) experienced an allergic or histamine-mediated adverse event, in 107 of 1980 (5.4%), the event was considered at least possibly drug-related, as summarized in the table below. The most common adverse event in this category in patients was rash.

Table 67. All allergic and Histamine-type Reactions in Patients who received Micafungin (adapted from Appendix 11.2.1.1, and 4.2.2, safety update)

Adverse Event COSTART Body System and Term	Micafungin-treated Patients N=1980	Related adverse events in Micafunin- treated Patients N=1980
Any adverse event	652 (32.9)	107 (5.4)
Rash	381 (19.2)	49 (2.5)
Pruritus	176 (8.9)	20 (1.0)
Allergic reaction	106 (5.4)	6 (0.3)
Vasodilatation	97 (4.9)	15 (0.8)
Maculopapular rash	62 (3.1)	15 (0.8)
Vesiculobullous rash	24 (1.2)	0
Urticaria	43 (2.2)	9 (0.5)
Eosinophilia	20 (1.0)	5 (0.3)
Anaphylactoid reaction	3 (0.2)	2 (0.1)

Medical Officer Comment: The most common adverse event in patients was rash, including maculopapular and vesiculobullous rash. This was also the most common

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drug-related adverse event in this category. In addition to those events listed above, facial edema was reported in 72 (3.6%) patients, angioedema in 2 (0.1%) patients, exfoliative dermatitis in 2 (0.1%) patients, and were considered drug-related in 2 (0.1%), and 0 %2 (0.1%) patients, and respectively.

Serious Allergic and Histamine-type reactions

No serious allergic or histamine-type reactions were reported in micafungin-treated healthy volunteers. Those reported in patients are shown in the table below.

Table 68. Serious Allergic and Histamine Reactions in Micafungin-treated Patients (adapted from Applicant's Appendix 11.2.1.2)

Serious Adverse Event COSTART Term	All Serious Adverse Events Micafungin-treated Patients N=1980	Serious Drug-Related Adverse Events Micafungin-treated patients N=1980
Any serious adverse event	14 (0.7)	10 (0.5)
Rash	4 (0.2)	4 (0.2)
Allergic reaction	5 (0.3)	3 (0.2)
Anaphylactoid reaction	2 (0.1)	1 (0.1)
Urticaria	1 (0.1)	1 (0.1)
Vasodilatation	1 (0.1)	1 (0.1)
Maculopapular rash	1 (0.1)	0

Medical Officer Comments: Rash and allergic reactions were the most common serious adverse events in patients.

Allergic and Histamine-type Reactions in Fluconazole-Controlled Studies

In fluconazole-controlled studies, allergic and histamine-type reactions occurred in 369/932 (39.6%) patients treated with micafungin, and in 331/787 (42.1%) of those who received fluconazole, as summarized in the Table below. Drug-related adverse events included rash in 25 of 932 (2.7%), pruritus in 12 (1.3%), urticaria in 6 (0.6%), allergic reaction in 2 (0.2%), and anaphylactoid reaction in 2 (0.2%) of micafungin-treated patients.

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Table 69. Allergic and Histamine-Type Reactions in Fluconazole-Controlled Studies† (adapted from Applicant's Appendices 2.7.4.3.3 and 6.1.3, ISS, July, 2004)

Adverse Event* COSTART Term	Micafungin N=932	Fluconazole N=787
Any adverse event	369 (39.6)	331 (42.1)
Rash	229 (24.6)	198 (25.2)
Pruritus	104 (11.2)	105 (13.3)
Allergic Reaction	67 (7.2)	53 (6.7)
Vasodilatation	61 (6.5)	73 (9.3)
Maculopapular rash	41 (4.4)	17 (2.2)
Urticaria	27 (2.9)	13 (1.7)
Vesiculobullous rash	8 (0.9)	10 (1.3)
Anaphylactoid reaction	3 (0.3)	0
Skin erythema	0	1 (0.1)

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

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

Medical Officer Comments: The overall incidence of these reactions was similar in the micafungin and fluconazole groups. If the terms, rash, maculopapular rash, and vesiculobullous rash are combined, a total of 278/932(29.8%) micafungin-treated and 225/787 (28.5%) of fluconazole-treated patients developed some type of rash.

Serious allergic or histamine-type reactions reported in fluconazole-controlled studies are shown in the following table.

Table 70. Serious Allergic or Histamine-type reactions in Fluconazole-controlled studies (adapted from appendices 11.2.2.2, safety update and R9 1.2 (November 1, 2004))

Serious Adverse Event COSTART Body System and Term	Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787
Any serious adverse event	8 (0.9%)	2 (0.3)
Vasodilatation	0 (0)	1 (0.1)
Allergic reaction	2 (0.2)	0 (0)
Anaphylactoid reaction	2 (0.2)	0 (0)
Maculopapular rash	1 (0.1)	0 (0)
Rash	3 (0.3)	1 (0.1)

Medical Officer Comments: Although the number of patients with serious adverse reactions of this type was small, more serious events were reported in micafungin-treated patients than in those who received fluconazole, with the exception of vasodilatation. See individual study reports, FG463-21-09 and 03-7-005 and 97-7-003 for patient narratives for rash and anaphylactoid reaction in the esophageal candidiasis studies. Notably in

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study 97-7-003, one patient developed erythema multiforme (coded in the database as rash) considered probably related to micafungin.

Discontinuation of Micafungin due to Allergic or Histamine-type reactions

Adverse events which resulted in micafungin discontinuation included allergic reaction in 7 of 2402 (0.3%) subjects, anaphylactoid reaction in 2 (0.1%), rash in 12 (0.5%), and urticaria in 2 (0.1%) of subjects, overall. Those considered related to micafungin included rash in 12 (0.5%), allergic reaction in 7 (0.3%), and anaphylactoid reaction in 2 (0.1%).

Dose-Relationship of Allergic or Histamine-type Adverse Events to Micafungin

There was no obvious dose-relationship between micafungin and serious allergic or histamine-type adverse events. The sponsor analyzed adverse events in patients who received at least 150mg/day micafungin for at least 10 days and in those who did not received that dose or duration, as shown in the table below.

Table 71. Incidence of Allergic and Histamine-Type Reactions by Dose of Micafungin in all Subjects (adapted from Applicant's Appendix 11.2.4.1, ISS, July, 2004)

Adverse Event* COSTART Term	Micafungin ≥ 150 mg/day for ≥ 10 days N=606	Micafungin ≤ 150 mg/day or ≤ 10 days N=1796
Any adverse event	146 (24.1)	528 (29.4)
Rash	72 (11.9)	321 (17.9)
Vasodilatation	10 (1.7)	93 (5.2)
Pruritus	41 (6.8)	140 (7.8)
Maculopapular rash	23 (3.8)	43 (2.4)
Allergic reaction	17 (2.8)	89 (5.0)
Urticaria	13 (2.1)	30 (1.7)
Eosinophilia	10 (1.7)	10 (0.6)
Anaphylactoid reaction	0	3 (0.2)
Vesiculobullous rash	6 (1.0)	19 (1.1)

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

Medical Officer Comments: These data do not suggest any dose relationship between micafungin and allergic or histamine-mediated reactions. However, the patient populations differ demographically. Most patients who received 150 mg or more of micafungin daily were those with HIV and esophageal candidiasis or patients with invasive aspergillosis.

Postmarketing Reports of Allergic Reactions and Histamine-type Reactions

Postmarketing adverse events in Japan from April, 2003 to April 2004, were reviewed by Dr. Adrienne Rothstein, in the ODS. Serious adverse events identified in this time frame included allergic reaction (7 cases), serious skin reactions (5 cases), and vascular reactions (5 cases).

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Serious allergic reactions included 3 cases of anaphylactoid reactions, all of which were possibly or probably related to micafungin, 2 events of anaphylactic shock, both of which were possibly related to micafungin, and 2 infusion-related reactions, 1 of which was possibly related to micafungin.

Serious skin reactions included 2 cases of toxic epidermal necrolysis, both of which were possibly micafungin-related; 2 cases of dermatitis medicamentosa, neither of which there was enough information to make a determination regarding causality; and 1 case of rash, for which there was insufficient information to assess causality. An additional report of toxic epidermal necrolysis was identified in a previous periodic safety update.

Shock was identified as a serious adverse event in 5 reports, and of these cases, causal role of micafungin was unlikely in 2 cases, and no assessment could be made in the other 3 cases. The ODS recommended adding a WARNING about the possibility of anaphylactoid or anaphylactic reactions during micafungin infusion, and to monitor for serious skin reactions post-approval of micafungin in the U.S.

Conclusions Regarding Allergic Reactions and Histamine-type Reactions

A safety signal was identified for histamine-mediated reactions in the preclinical studies. In rats, histamine release was manifested as cardiovascular effects, particularly increased heart rate and decreased blood pressure, and was associated with high doses of micafungin. Although histamine release was measured in dogs, no cardiovascular effects were observed.

In healthy volunteers, rash and vasodilatation were the most common allergic or histamine-type reactions. In patients, the most common adverse event in this category was rash. The incidence of these reactions was similar in patients who received either micafungin or fluconazole in the fluconazole-controlled studies. Most adverse events in this category were considered mild.

Serious adverse reactions in the clinical studies, some of which were attributed to micafungin, included rash, allergic reactions, and anaphylactoid reactions. Anaphylaxis was not reported in the clinical studies; while one case of erythema multiforme was observed. Rash was the most common allergic or histamine-mediated adverse event, which resulted in micafungin discontinuation.

It should be noted that infusion-related reactions in the overall safety database were not evaluated, although data regarding these events was collected prospectively in study FG463-21-09. Events in this category would include fever, chills/rigors, hypotension, hypertension, facial flushing, vasodilatation, vomiting, chest pain, tachycardia, cyanosis, skin erythema, rash, or other reactions. Some of these reactions are histamine-mediated (rash, vasodilatation, facial flushing). However, most of these adverse reactions are non-specific, and unless they were observed during micafungin infusion, would not necessarily indicate an infusion-related reaction. In study FG463-21-09, infusion related reactions occurred in 53 of 185 (28.6%) patients who received micafungin and in 17 of 60 (28.3%) patients who received fluconazole.

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A number of serious allergic and serious skin reactions, at least possibly related to micafungin have been reported with micafungin use in the postmarketing period in Japan.

We propose to add a WARNING in the micafungin label regarding the potential of micafungin for serious anaphylaxis, including shock, and for anaphylactoid reactions. Postmarketing surveillance in the U.S. should include monitoring for serious skin reactions, as well as anaphylaxis, and anaphylactoid reactions.

7.1.12.2 Respiratory System

Respiratory system adverse events were reported in 1005/2402 (41.8%) subjects; while drug-related adverse events occurred in 33/2402 (1.4%) subjects. The most common adverse events considered at least possibly related to micafungin included cough in 7 (0.3%), dyspnea in 7 (0.3%), pharyngitis in 7 (0.3%) subjects. The incidence of serious respiratory adverse events was 9.0% (217/1980 patients); while drug-related serious adverse events occurred in 9/1980 (0.5%) patients. These latter events included dyspnea in 4 (0.2%), hypoxia in 3 (0.2%), and pulmonary embolus in 2 (0.1%) patients. No serious respiratory system adverse events occurred in healthy volunteers. The incidence of respiratory system adverse events was similar in patients treated with micafungin, 48.1% (448/932) or fluconazole, 52.6% (414/787) in the studies which used fluconazole as a comparator. Micafungin was discontinued in 3.1% (61/1980) patients, due to respiratory adverse events, most commonly respiratory failure or pneumonia. The rate of drug discontinuation due to respiratory adverse events was similar in micafungin-treated (1.0%) and fluconazole-treated (1.0%) patients in fluconazole-controlled studies. A total of 129/1980 (6.5%) patients died due to respiratory adverse events; however, none of the deaths was attributable to micafungin.

In the postmarketing experience in Japan, 35 serious adverse events, at least possibly related to micafungin, were reported in the time period from 1 January, 1998 to 8 April, 2004. The most common of these was respiratory failure (6 cases), followed by hemoptysis (4 cases). Notably, pulmonary embolism was reported only once in this time frame.

Overall, respiratory events in the clinical studies reflected the underlying disease states of the patients enrolled in the studies, and most of the adverse events were not related to micafungin. We have proposed that the following adverse events, dyspnea, hypoxia, apnea and pulmonary embolism, be included in the micafungin label under clinically significant adverse events. Pulmonary embolus is of some concern, given the potential for micafungin to cause phlebitis or thrombophlebitis, and we plan to carefully monitor for this event in the postmarketing period.

7.1.12.3 Cardiovascular System

A number of cardiovascular adverse events of interest were associated with micafungin in the clinical studies, including hypotension, hypertension, tachycardia, vasodilation, phlebitis and thrombophlebitis. These are discussed in more detail below. Additionally, serious adverse events of cardiac arrest and arrhythmia were reported in micafungin-treated patients. Although there is no

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convincing evidence that these events were related to micafungin, there is some theoretical concern that micafungin could have some role in these events, as discussed further below.

Preclinical Studies

(1) Microelectrode Assessment of Action Potential

This study, conducted in Japan by _____ n
August 2003 in guinea pig papillary muscle, concludes that micafungin did not effect change in the action potential duration (APD) at 90% repolarization, resting membrane potential, action potential amplitude (APA) or maximum rate of depolarization when tested at concentrations of 1×10^{-7} to 1×10^{-6} . Shortening of the action potential was however noted at greater concentrations (1×10^{-5} , shortening of APD 90 by 9.5 ± 0.9 msec). This was considered to be slight compared to the positive control sotalol that induced a 43.0 ± 2.9 msec APD 90 prolongation and a significantly decreased APA of 2.4 ± 0.2 mV. These findings are summarized in the following Figure.

Figure 1. Effect of Micafungin (FR179463) on Action Potential in Guinea Pig Papillary Muscle

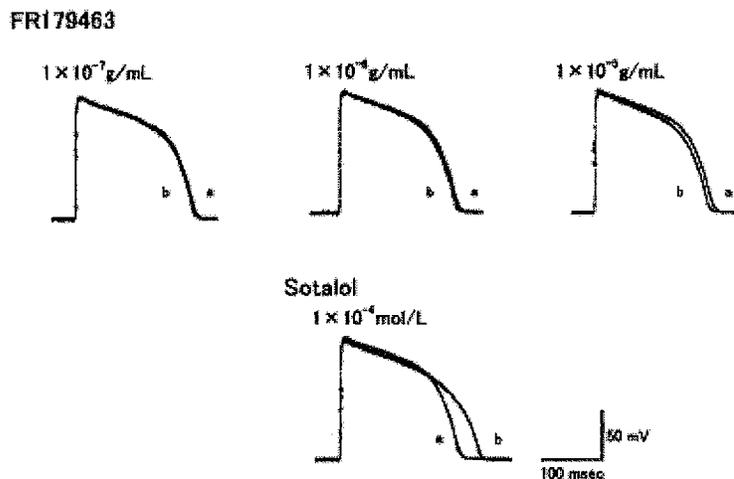


Fig.1 Representative tracings of the effects of FR179463 and sotalol. Pre (a) and post (b) treatment, preparation No.2-1.

2) hERG Channel Assay:

The human ether a-go-go related gene transfected human embryonic kidney cells (hERG-transfected cells) were exposed to similar concentrations of micafungin (1×10^{-7} , 1×10^{-6} , and 1×10^{-5}) and positive control identified only as E-4031, tested at one concentrations (1×10^{-7}). hERG currents passing through the cell membrane were recorded under voltage-gated conditions using the whole cell patch clamp technique. The effects of the drugs exposure was determined by changes in the peak amplitude of the tail current induced by a repolarizing then a depolarizing pulse. Percentage of current suppression in each drug

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treatment is shown in the histogram, as mean + S.D (n=5), with comparison to vehicle control (water for injection, WFI), as shown in the figure below.

Figure 2. Effect of Micafungin (FR179463) on hERG-transfected human cells

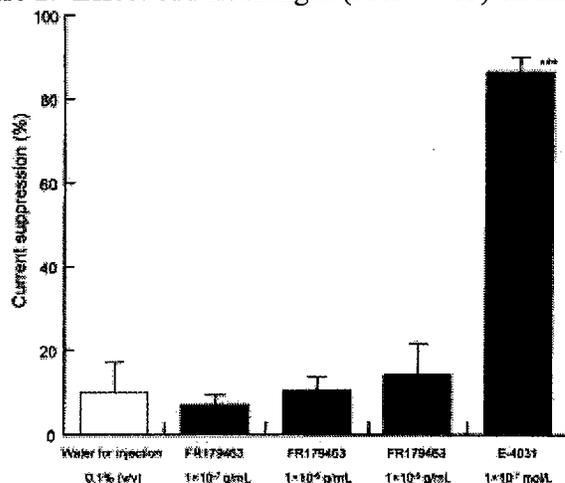


Fig. 1. Suppressive effects of FR179463 on the hERG potassium channel expressed in HEK293 cells

*** indicates significant difference from control at $p < 0.01$ by T test.

The authors conclude that the suppressive rates of micafungin on the hERG current was no different from vehicle control (highest suppression 14.1% at 1×10^{-5} , approximately 7.7 μM or 10 - 20 fold the therapeutic blood level of micafungin for candidiasis (0.5 to 1 $\mu\text{g/mL}$).

In rats, cardiovascular effects (increased heart rate and decreased blood pressure) noted at 100 mg/kg micafungin were attributed to plasma histamine release at that dose. No such effects were noted in dogs at the same dose, although slight increases in plasma histamine were reported. In the 4-, 13-, and 39- week dog studies, electrocardiograms (ECGs) were obtained, and no increase in QT interval was observed.

Cardiovascular Adverse Events in Healthy Volunteers

In single-dose micafungin studies in healthy volunteers, cardiovascular adverse events were reported in 7/198 (3.5%) subjects. These events included vasodilatation in 4 subjects, and chest pain, pallor, and thrombosis, each in 1 subject. Vasodilatation is discussed in more detail in this review in the section on allergic and histamine-mediated reactions.

In repeat-dose micafungin studies, 40 of 184 subjects had at least one cardiovascular adverse event, as listed in Table - below. No cardiovascular adverse event occurred in subjects who received repeat doses of less than 100 mg micafungin. Most of these events occurred in subjects who received repeated doses of 150 mg micafungin; however, 12 of the 13 cases of vasodilatation occurred in subjects who received repeated doses of 100 mg micafungin; and all of the cases of phlebitis and thrombophlebitis occurred in those who received the 150 mg dose.

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Table 72. Cardiovascular Adverse Events in Healthy Volunteers in Repeat-dose Studies (adapted from applicant's Appendix 1.5 ISS)

Cardiovascular Adverse Events (COSTART Term)	Micafungin-treated subjects* N=184	Subjects who received 100 mg† micafungin N=53	Subjects who received 150 mg† micafungin N=119
Any adverse event	40 (21.7)	14 (26.4)	26 (21.8)
Phlebitis	17 (9.2)	0 (0)	17 (9.2)
Vasodilatation	13 (7.1)	12 (22.6)	1 (0.8)
Chest pain	4 (2.2)	2 (3.8)	2 (1.7)
Thrombophlebitis	3 (1.6)	0 (0)	3 (2.5)
Tachycardia	2 (1.1)	0 (0)	2 (1.7)
Palpitation	1 (0.5)	0 (0)	1 (0.8)
Postural hypotension	1 (0.5)	0 (0)	1 (0.8)
Sinus bradycardia	1 (0.5)	0 (0)	1 (0.8)
Syncope	1 (0.5)	0 (0)	1 (0.8)

* mean daily dose in studies 01-0-104, 01-0-105, 03-0-175, 03-0-176, 03-0-177, and 03-0-178, FJ0002, and FJ0005

† 100 mg = (> 87.5 mg to ≤ 125 mg); 150 mg = (>125 mg to ≤ 175 mg)

Medical Officer Comments: None of these events in healthy volunteers were considered serious. Phlebitis and thrombophlebitis will be discussed in the section on injection site reactions. Vasodilatation, tachycardia, and hypotension are associated with histamine-type reactions, and were also observed in animal studies.

Cardiovascular Safety in Normal Volunteers (Study 03-0-176)

Electrocardiographic studies were obtained in several drug interaction studies; including Study 03-0-176. This phase 1 open-label drug interaction and pharmacokinetic study consisted of 30 healthy adult male and female volunteers (subjects) who sequentially received a single oral dose of mycophenolate mofetil (MMF) (1500 mg as three 500 mg tablets) on day 1, followed by a 1-week washout period. Micafungin (150 mg/day) was subsequently administered for 15 successive days (days 8 through 22). On day 22 a second single oral dose of MMF (1500 mg as three 500 mg tablets) was administered concomitantly with micafungin.

A 12 lead resting electrocardiogram (ECG) was obtained at baseline, on days 21 and 25, as well as when clinically indicated. Vital signs monitoring and pharmacokinetic studies were periodically evaluated throughout the study as per protocol design. No cardiovascular events occurred in the 25 day study period, other than 2 events of phlebitis that occurred in subjects receiving micafungin alone. The applicant reported no clinically or electrographically significant waveform and ECG segment changes, as summarized in the following table.

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Table 73. Summary of ECG Results in Healthy Volunteers in Study 03-0-176

SUMMARY OF ECG RESULTS SAFETY ANALYSIS SET

PARAMETER	CLASS	SCHEDULED VISIT		
		SCREEN (N=30)	DAY 21 (N=30)	FINAL VISIT (1) (N=30)
RESULT	NORMAL	20 (66.7%)	23 (76.7%)	27 (90.0%)
	ABNORMAL, NOT CLINICALLY SIGNIFICANT	10 (33.3%)	7 (23.3%)	3 (10.0%)
	ABNORMAL, CLINICALLY SIGNIFICANT	0 (0.0%)	0 (0.0%)	0 (0.0%)

The individual post-baseline events are summarized below (obtained from the Appendix 12.3.8.2 to the applicant's Study Report of Study 176):

Subject	Day	Electrocardiogram result
10110105	21	NON-SPECIFIC ST-T WAVE CHANGES
10110108	-11	SINUS BRADYCARDIA
	21	INCOMPLETE RIGHT BUNDLE BRANCH BLOCK
10110109	-11	SINUS BRADYCARDIA
	21	NON-SPECIFIC ST-T WAVE CHANGES
10110117	21	SINUS BRADYCARDIA
10110119	25	SINUS BRADYCARDIA
10110123	21	INCOMPLETE RIGHT BUNDLE BRANCH BLOCK
10110126	21	NON-SPECIFIC ST-T WAVE CHANGES
10110126	25	NON-SPECIFIC ST-T WAVE CHANGES
10110127	-11	SINUS BRADYCARDIA
	25	SINUS BRADYCARDIA
10110130	21	SINUS BRADYCARDIA

None of these changes were considered clinically significant by the usual electrocardiographic criteria. No clinical events accompanied these electrocardiographic changes.

Medical Officers Comment: Three subjects had baseline sinus bradycardia. This is not unexpected, considering that these resting electrocardiograms were obtained in healthy young normal volunteers.

Cardiovascular Safety in Normal Volunteers Study FG-463-21-15

This study was reviewed with regards to ECG changes by Dr. Joette Meyer for the NDA 21-506 submission. Study FG463-21-15 was a drug interaction study between micafungin and ritonavir. Twenty five subjects received a single intravenous dose of micafungin on study day 1, followed by a washout period of 5 days. Subjects then received ritonavir 300 mg orally twice daily on days 6 to 17, with a second intravenous dose of micafungin (200 mg) co-administered with the AM dose of ritonavir on day 10. ECGs were performed and serum samples were obtained for measurement of micafungin concentration pre-dose, and 1,4, and 12 hours post-dose on days 1,9,and 10. The systemic exposures of micafungin (AUC and C_{max}) were similar when micafungin was given alone or with ritonavir. Two subjects had QT_c intervals higher than the upper limit of the reference range (≥ 441 msec) at isolated time points; but no subject had a QT_c interval above 500 msec. One subject had a QT_c value of 454 msec at 4 hours after receiving micafungin on day 1; however, the two other ECGs recorded at this time point showed QT_c .

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intervals within normal range (411 and 419 msec). The second subject had a QT_c interval of 449 msec 1 hour after receiving micafungin and ritonavir on day 10; however the two other ECGs recorded at this time point showed QT_c values within normal range (374 and 388 msec). No subjects had a maximum change in QT_c interval of ≥ 60 msec. It was concluded from this study that no apparent effects on the QT/QT_c interval were observed with micafungin with or without ritonavir.

Medical Officer Comment: There were no apparent clinically significant effects observed on the QT/QT_c interval in this study in healthy volunteers.

The applicant summarized the QT data from healthy volunteer studies as follows: "QT intervals were measured in the healthy volunteer drug interaction studies, FG-463-21-04 (tacrolimus), FG-463-21-05 (cyclosporine), FG-463-21-06 (prednisolone), FG-463-21-15 (ritonavir) and FG-463-21-16 (rifampin), where micafungin was administered at a dose of 200 mg. There was no evidence of QT_c interval prolongation following micafungin administration, as summarized in the table below.

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Table.74. Summary of QT data in Studies FG463-21-06 and FG463-21-16

Summary of Global Mean 12-Lead ECG QT/QTc Intervals

		QT (ms)			
	Pre-dose	2hr	Pre-dose ¹	24hr ¹	
Mean	400	406	389	396	
SD	27.8	25.4	24.5	20.6	
Median	398	405	388	397	
Min	345	349	345	338	
Max	491	481	447	443	
N	96	96	48	48	
		QTc (ms)			
	Pre-dose	2hr	Pre-dose ¹	24hr ¹	
Mean	394	392	392	383	
SD	17.4	19.8	17.1	19.8	
Median	396	395	393	384	
Min	345	342	345	341	
Max	430	433	430	424	
N	96	96	48	48	

¹: Studies FG-463-21-06 and FG-463-21-16 only

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Cardiovascular Adverse Events in Patients

Cardiovascular adverse events were reported in 918 of 2402 (38.2%) subjects, and in 871 of 1980 (44.0%) patients in the safety database. The table below shows the most common cardiovascular events, and those considered related to micafungin observed in patients. The most common adverse events were hypotension, hypertension and tachycardia. The most common drug-related adverse events were phlebitis, hypertension, vasodilation, and hypotension.

Table 75. Common* Cardiovascular Adverse Events in Micafungin-treated and Patients (adapted from applicant's Appendix 2.7.4.3.1)

Adverse Events ** Cardiovascular System (COSTART Term)	All Adverse Events Micafungin-treated Patients N=1980	Drug-Related Adverse Events Micafungin-treated Patients N=1980
Any adverse event	871 (44.0)	95 (4.8)
Hypotension	239 (12.1)	10 (0.5)
Tachycardia	223 (11.3)	9 (0.5)
Hypertension	200 (10.1)	16 (0.8)
Chest pain	150 (7.6)	6 (0.3)
Vasodilatation	97 (4.9)	15 (0.8)
Phlebitis	80 (4.0)	26 (1.3)
Shock	53 (2.7)	0
Bradycardia	52 (2.6)	1 (0.1)
Arrhythmia	36 (1.8)	1 (0.1)
Atrial fibrillation	36 (1.8)	3 (0.2)
Hemorrhage	33 (1.7)	0
Valvular heart disease	28 (1.4)	0
Postural hypotension	27 (1.4)	1 (0.1)
Thrombophlebitis	25 (1.3)	4 (0.2)
Deep thrombophlebitis	24 (1.2)	0
Pericardial effusion	24 (1.2)	0
Syncope	22 (1.1)	1 (0.1)

*occurring in ≥ 1 % subjects or patients

** Patients could experience more than one adverse event within a Body System

Additional drug-related adverse events not shown in this Table included chest pain in 6 (0.3%) patients, palpitation, 5 (0.3%), cardiomyopathy in 1 (0.1%), congestive heart failure in 1 (0.1%), heart arrest in 1 (0.1%), pallor in 1 (0.1%), peripheral vascular disorder in 1 (0.1%), vascular headache in 1 (0.1%), ventricular extrasystoles in 1 (0.1%), and ventricular tachycardia each in 1 (0.1%) patient.

Medical Officer Comments: Because this patient population included a significant proportion of patients who were seriously ill and had multiple underlying medical conditions, including diabetes, hypertension, cardiovascular disease, and sepsis, establishing a relationship between micafungin and some of the common cardiovascular

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events in these studies is difficult. However, as discussed further below, phlebitis and thrombophlebitis are clearly associated with micafungin treatment. Additionally, events such as hypotension, hypertension, tachycardia, and vasodilation may be associated with histamine-type reactions which were also observed in animal studies and healthy volunteers.

Cardiovascular Adverse Events in Fluconazole-controlled Studies

The incidence of cardiovascular system adverse events was generally similar in patients treated with either micafungin or fluconazole. However, phlebitis and thrombophlebitis occurred more frequently in patients treated with micafungin. Additionally, arrhythmia was reported more often in micafungin-treated patients. The most common cardiovascular events in these studies are listed in the table below. Adverse events considered drug-related were reported in 34/932 (3.6%) micafungin-treated, and in 21/787 (21%) fluconazole-treated patients. The most common adverse experience considered related to micafungin was phlebitis, which occurred in 12/932 (1.3%) patients; while phlebitis was attributed to fluconazole in 0.8% patients.

Table 76. Common Cardiovascular Adverse Events* in Patients in Fluconazole-Controlled Studies† (adapted from applicant's Appendix 2.7.4.3.3)

Cardiovascular System Adverse Events ** (COSTART Term)	Micafungin N=932	Fluconazole N=787
Any cardiovascular adverse event	397 (42.6)	366 (46.5)
Hypertension	103 (11.1)	120 (15.2)
Tachycardia	121 (13.0)	114 (14.5)
Hypotension	95 (10.2)	94 (11.9)
Vasodilatation	61 (6.5)	73 (9.3)
Chest pain	69 (7.4)	70 (8.9)
Bradycardia	13 (1.4)	19 (2.4)
Postural hypotension	15 (1.6)	18 (2.3)
Phlebitis	50 (5.4)	14 (1.8)
Atrial fibrillation	12 (1.3)	12 (1.5)
Hemorrhage	9 (1.0)	12 (1.5)
Syncope	12 (1.3)	11 (1.4)
Arrhythmia	16 (1.7)	10 (1.3)
Congestive heart failure	3 (0.3)	10 (1.3)
Cardiomegaly	7 (0.8)	8 (1.0)
Thrombophlebitis	16 (1.7)	6 (0.8)

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

*adverse events that occurred in $\geq 1\%$ in patients treated with either micafungin or fluconazole

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

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Medical Officer Comments: While the cardiovascular adverse event profile was generally similar in these studies, phlebitis, thrombophlebitis, and arrhythmia were noted to occur more frequently in patients treated with micafungin. These events are discussed further below.

Serious Cardiovascular Events

No serious cardiovascular event was reported in healthy volunteers. Serious cardiovascular events occurred in 154/1980 (7.8%) of patients who received micafungin. Twelve patients (0.6%) experienced a serious cardiovascular event determined by the investigator to be related to micafungin. All serious cardiovascular events and those considered by the investigator to be related to micafungin are shown in Table __ below.

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Table 77. Serious Cardiovascular Adverse Events in Micafungin-treated Patients (adapted from Applicant's Appendices 8.1.2 and 8.8 Safety update)

Serious Adverse Events* Cardiovascular System (COSTART Term)	All adverse events in Micafungin-treated patients N=1980	Related adverse events in Micafungin-treated Patients N=1980
Any serious cardiovascular adverse event	154 (7.8)	12 (0.6)
Shock	48 (2.4)	0 (0)
Hypotension	39 (2.0)	3 (0.2)
Atrial fibrillation	14 (0.7)	3 (0.2)
Heart arrest	13 (0.7)	1 (0.1)
Deep thrombophlebitis	7 (0.4)	0 (0)
Hypertension	7 (0.4)	2 (0.1)
Pericardial effusion	7 (0.4)	0 (0)
Congestive heart failure	6 (0.3)	0 (0)
Tachycardia	6 (0.3)	0 (0)
Chest pain	5 (0.3)	0 (0)
Heart failure	5 (0.3)	0 (0)
Hemorrhage	4 (0.2)	0 (0)
Arrhythmia	4 (0.2)	0 (0)
Bradycardia	3 (0.2)	0 (0)
Peripheral vascular disorder	3 (0.2)	1 (0.1)
Subdural hematoma	2 (0.1)	0 (0)
Atrial flutter	2 (0.1)	0 (0)
Cardiomyopathy	2 (0.1)	0 (0)
Electrocardiogram abnormal	2 (0.1)	0 (0)
Pericarditis	2 (0.1)	0 (0)
Ventricular tachycardia	2 (0.1)	0 (0)
Arterial anomaly	1 (0.1)	0 (0)
Endocarditis	1 (0.1)	0 (0)
Increased capillary fragility	1 (0.1)	0 (0)
Mesenteric occlusion	1 (0.1)	0 (0)
Myocardial infarct	1 (0.1)	0 (0)
Palpitation	1 (0.1)	1 (0.1)
Postural hypotension	1 (0.1)	0 (0)
Syncope	1 (0.1)	0 (0)
Thrombophlebitis	1 (0.1)	1 (0.1)
Thrombosis	1 (0.10)	0 (0)
Vasodilatation	1 (0.1)	1 (0.1)

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

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***Medical Officer Comments:** The most common serious cardiovascular adverse events were shock, hypotension, atrial fibrillation, and heart arrest. Hypotension and atrial fibrillation were also the most common events considered related to micafungin. As noted previously, in these seriously ill patients with multiple medical conditions, and receiving multiple medications, attribution of adverse events to micafungin is difficult. However, micafungin was shown to cause significant vascular irritation in rats, and phlebitis and thrombophlebitis were observed commonly in patients who received micafungin, and in many cases were considered related to micafungin. As shown below (Table __), there did not appear to be an excess of serious cardiovascular events in the micafungin treatment group in comparison to the fluconazole group.*

Narrative Summary for Patient with Serious Adverse Event “Heart Arrest” Possibly Related to Micafungin

Patient 020783 was a 46 year-old Caucasian male with leukemia who underwent allogeneic HSCT. He was enrolled in study 98-0-046 for treatment of invasive pulmonary aspergillosis. A narrative summary for this patient was not provided. Information was obtained from the patient profile provided by the Applicant. Baseline conditions included chills, confusion, leukopenia, anxiety, anorexia, bilirubinemia, maculopapular rash, sepsis, thrombocytopenia, abdominal pain, diarrhea, hemoptysis, hyperglycemia, rectal hemorrhage, hemorrhagic cystitis, hypokalemia, hypomagnesemia, nausea, oliguria, mucositis, valvular heart disease, jaundice, anemia, agitation, delirium, and increased cough. The patient received micafungin 75 mg/day for 7 days, micafungin was then interrupted for 2 days due to an adverse event, and then restarted again for another 3 days, at which point micafungin was discontinued due to an adverse event. Serious adverse events in this patient included encephalopathy and heart arrest, both reported on study day 6. The investigator considered the heart arrest possibly related to micafungin. The patient recovered from the cardiac arrest, but died on study day 30 due to encephalopathy. The investigator considered this event possibly related to micafungin. Other (non-serious) adverse events reported during treatment included edema, epistaxis, pleural disorder, fever, hypertension, sepsis, ileus, lung disorder, graft versus host disease, acidosis, apnea, hyperventilation, hypotension, hypothermia, respiratory alkalosis, gastrointestinal disorder, rectal disorder, enlarged abdomen, and procedural complication. Concomitant medications during and post-micafungin treatment included Abelcet®, insulin, potassium, GM-CSF, haldol, mycophenolate mofetil, ativan, vancomycin, lomofil, fentanyl, versed, amiodarone, adenosine, gentamicin, carafate, phenylephrine, triamcinolone, viox, lasix, diltiazem, ursodiol, bicitra, methylprednisolone, sodium bicarbonate, and nystatin. Laboratory data was reviewed and significant laboratory abnormalities are shown in the following table. Electrocardiogram data was not available.

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Laboratory Values* for Patient 020783 (Baseline to Study Day 6)

Study Day	WBC	Hemoglobin	Platelet count	BUN	Creatinine	Sodium	Potassium
Baseline	0.2	10.3	34	78	2.4	142	4.0
Day 6	1.3	9.5	11	64	2.0	151	4.9
	Bicarbonate	Albumin	AST	ALT	Alkaline phosphatase	Total bilirubin mg/dL	Calcium mg/dL
Baseline	22	2.7	Not done	21	72	14	8.4
Day 6	13	2.8	Not done	20	84	8.6	8.2

* Normal laboratory values are found in the Appendix, section 10

Medical Officer Comments: Cardiac arrest occurred in a 46-year old male with no reported coronary artery disease at baseline, although valvular heart disease was noted as an underlying condition. On the day of the cardiac arrest, the patient was hypernatremic and hypocalcemic, but serum potassium was normal, and arrhythmia was not reported as an adverse event. Certainly, ongoing sepsis and presumed metabolic acidosis could have contributed to this adverse event. The clinical information provided was not sufficient to determine whether cardiac arrest in this patient was related to micafungin.

Serious Cardiovascular Adverse Events in Fluconazole-Controlled Studies

A total of 31/932 (3.3%) of patients who received micafungin and 26/787 (3.3%) patients who received fluconazole in these studies experienced a serious cardiovascular adverse event, as shown in the table below.

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Table 78. Serious cardiovascular Adverse Events in Fluconazole-Controlled Studies†

Serious Adverse Events* Cardiovascular System COSTART Term	Micafungin N=932	Fluconazole N=787
Any serious cardiovascular adverse event	31 (3.3)	26 (3.3)
Congestive heart failure	1 (0.1)	5 (0.6)
Shock	2 (0.2)	4 (0.5)
Heart arrest	1 (0.1)	3 (0.4)
Hypotension	14 (1.5)	3 (0.4)
Atrial fibrillation	9 (1.0)	2 (0.3)
Cardiomegaly	0	2 (0.3)
Cardiomyopathy	1 (0.1)	2 (0.3)
Chest pain	1 (0.1)	2 (0.3)
Postural hypotension	0	2 (0.3)
Subdural hematoma	0	2 (0.3)
Tachycardia	1 (0.1)	2 (0.3)
Bradycardia	0	(0.1%)
Heart failure	1 (0.1)	1 (0.1)
Hypertension	1 (0.1)	1 (0.1)
Pericardial effusion	1 (0.1)	1 (0.1)

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

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

Additional serious adverse events each reported in 1 patient who received micafungin, but in no patients who received fluconazole included vasodilatation, arrhythmia, atrial flutter, deep thrombophlebitis, abnormal electrocardiogram, hemorrhage, increased capillary fragility, and pericarditis.

***Medical Officer Comments:** Although the incidence of serious cardiovascular adverse events was similar in the two treatment groups, hypotension and atrial fibrillation were more common among patients who received micafungin than those who received fluconazole. Most patients with hypotension or atrial fibrillation reported as serious adverse events had been enrolled in study 98-0-050 (micafungin for Candida prophylaxis). These patients had underlying hematologic malignancies or had received a HSCT, and would be expected to multiple concomitant medical problems. However, 4 patients who received micafungin in study FG463-21-09 compared to no patients in the fluconazole arm in that study developed hypotension. Patients in this study had esophageal candidiasis and AIDS, and hypotension would be unexpected unless they had concomitant sepsis, hemorrhage or another opportunistic infection. In one patient with hypotension, the investigator considered this adverse event probably related to micafungin, and a narrative summary for this patient is provided below. Additionally, the patients with heart arrest and arrhythmia were enrolled in FG463-21-09 and 03-7-005,*

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respectively. Patients in these studies had HIV/AIDS and esophageal candidiasis and such events are generally unexpected in this population of mostly young adults.

Narrative Summaries for Selected Serious Cardiovascular Events

Cases of hypotension, heart arrest and arrhythmia which occurred in the esophageal candidiasis studies are summarized below.

Hypotension:

Patient 1105 was a 35 year-old black female with AIDS, and a CD4 count of 38 cell/mm³. The patient received micafungin 50 mg/day for 21 days for esophageal candidiasis. Immediately after micafungin infusion on study day 4, the patient developed rigors, hypotension, and vomiting which were reported as serious adverse events which resolved within 30 minutes. The investigator determined that a relationship to micafungin for these events was highly probable. The patient was also tachycardic during this episode (heart rate 120 bpm). Other adverse events reported during micafungin treatment were anemia and diarrhea. Blood pressures obtained during the episode of hypotension were not recorded on the case report form or in the narrative summary.

Medical Officer Comments: Because of the temporal relationship of these events (hypotension, rigors, and vomiting) to micafungin administration, and rapid resolution after the micafungin infusion was complete, these could be considered infusion-related events, possibly histamine-related. Similar reactions were described in animal toxicology studies. I would concur with the investigator that this symptom complex was probably related to micafungin.

Patient 1904 was a 33 year-old black male with AIDS and a CD4 count of 0 cells/mm³, enrolled in study FG463-21-09 for treatment of esophageal candidiasis. Baseline conditions included tuberculosis, anemia, cachexia, and lymphadenopathy. A narrative summary for this patient was included in the FG463-21-09 study report. The patient received micafungin 100 mg/day for 9 days for esophageal candidiasis, and was discontinued on day 9 due to pulmonary edema. Sepsis (bacteremia and early systemic inflammatory response syndrome) was reported as a serious adverse event on day 10, hypotension on day 11, shock on day 13, and the patient died on day 14 due to cardiac arrest. None of the serious adverse events or death in this patient was attributed to micafungin by the investigator.

Medical Officer Comments: This patient had gram-negative bacteremia, sepsis, and shock (presumably septic shock) which probably caused the hypotension in this patient. I would concur with the investigator that the hypotension was not related to micafungin.

Patient 2404 was a 29 year-old male with AIDS and a CD4 count of 12 cells/mm³, enrolled in study FG463-21-09 for treatment of esophageal candidiasis. Baseline conditions included tuberculosis, weight loss, anemia, asthenia and fever. The patient received micafungin 50 mg/day for 14 days for esophageal candidiasis. On study day 13, aggravated tuberculosis was reported as a serious adverse event. The following day, hypotension was reported as a serious adverse event

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from which the patient recovered. However, he developed hypoxemia and died on study day 16 due to respiratory failure. None of these adverse events was considered related to micafungin.

Medical Officer Comments: Insufficient information was provided to determine the etiology of hypotension in this case, certainly a new opportunistic infection such as bacterial pneumonia or sepsis, which were not reported, may have caused hypotension.

Heart Arrest:

Patient 1908 was a 27 year-old black female with AIDS enrolled in study FG463-21-09 for treatment of esophageal candidiasis, who died due to cardiac arrest on study day 3. Sepsis, hypotension, pulmonary edema and cardiomyopathy were reported as serious adverse events on the same day. See FG463-21-09 study report for full narrative summary for this patient. .

Medical Officer Comments: These events were not attributed to micafungin by the investigator, and I would concur with that assessment.

Arrhythmia:

Patient 10625002 was a 35 year-old black female with AIDS enrolled in study 03-7-005, for treatment of esophageal candidiasis, who died due to an arrhythmia (ventricular fibrillation). See individual study report for narrative summary.

Medical Officer Comments: This event was not considered to be related to micafungin, and I concur with that assessment.

Deaths due to Cardiovascular Events

Cardiovascular adverse events were listed as the primary cause of death in 79/1980 (4.0%) patients who received micafungin. No volunteers died as a result of cardiovascular adverse events. Cardiovascular events resulting in death are shown in the table below. None of these deaths in patients were attributed to micafungin.

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Table 79. Cardiovascular Events Resulting in Death in Micafungin-treated Patients (adapted from applicant's Appendix 2.7.4.9.3, safety update)

Cardiovascular Adverse Events/Primary cause of Death (COSTART Term)	Micafungin-treated Patients N=1980
Any adverse event	79 (4.0)
Shock	51 (2.6)
Heart arrest	7 (0.4)
Heart failure	7 (0.4)
Congestive heart failure	4 (0.2)
Endocarditis	4 (0.2)
Arrhythmia	1 (0.1)
Hemorrhage	1 (0.1)
Hypotension	1 (0.1)
Increased capillary fragility	1 (0.1)
Myocardial infarct	1 (0.1)
Peripheral vascular disorder	1 (0.1)

Medical officer Comments: Shock was the most common cardiovascular cause of death in micafungin-treated patients.

Deaths due to Cardiovascular Adverse Events in Fluconazole-Controlled Studies

In fluconazole-controlled studies, a cardiovascular adverse event was the primary cause of death in 12/932 (1.3%) micafungin-treated patients, and in 13 of 787 (1.7%) fluconazole-treated patients. The adverse event profile was similar in the two treatment arms, as shown in the table below.

Table 80. Cardiovascular Events Resulting in Death in Fluconazole-Controlled Studies

Cardiovascular Adverse Events/Primary cause of Death (COSTART Term)	Micafungin-treated Patients N=932	Fluconazole-treated Patients N=787
Any adverse event	12 (1.3)	13 (1.7)
Shock	3 (0.3)	7 (0.9)
Heart failure	2 (0.2)	3 (0.4)
Heart arrest	4 (0.4)	2 (0.3)
Subdural hematoma	0 (0)	1 (0.1)
Arrhythmia	1 (0.1)	0 (0)
Congestive heart failure	1 (0.1)	0 (0)
Increased capillary fragility	1 (0.1)	0 (0)

Medical Officer Comments: In these studies, the only cardiovascular cause of death which occurred in more micafungin- than fluconazole-treated patients was heart arrest, noted in 4 and 2 patients, respectively.

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Discontinuation of Micafungin due to Cardiovascular Events

Micafungin was discontinued in 46 of 1980 (2.3%) patients due to cardiovascular adverse events as shown in the table below. Additionally, micafungin dosing was discontinued in one healthy volunteer due to phlebitis.

Table 81. Cardiovascular Adverse Events leading to Micafungin Discontinuation

Cardiovascular System (COSTART Term)	Micafungin-treated patients N=1980
Any adverse event	46 (2.3)
Shock	26 (1.3)
Heart arrest	3 (0.2)
Atrial fibrillation	2 (0.1)
Heart failure	2 (0.1)
Hypotension	2 (0.1)
Peripheral vascular disorder	2 (0.1)
Subdural hematoma	2 (0.1)
Arrhythmia	1 (0.1)
Congestive heart failure	1 (0.1)
Deep thrombophlebitis	1 (0.1)
Electrocardiogram abnormal	1 (0.1)
Increased capillary fragility	1 (0.1)
Myocardial infarct	1 (0.1)
Palpitation	1 (0.1)

The applicant also analyzed adverse events that resulted in dose interruption or reduction of micafungin. Among 1980 patients, 8 required micafungin dose interruption or reduction due to cardiovascular adverse events. These events included arrhythmia (2 patients), bradycardia (1 patient), heart arrest (1 patient), hypertension (1 patient), hypotension (1 patient), palpitation (1 patient), phlebitis (1 patient), and vasodilatation (1 patient).

In fluconazole-controlled studies, micafungin was discontinued due to a cardiovascular event in 9/932 (1.0%) patients, and fluconazole in 10/787 (1.3%) patients. These data are shown in the following table.

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Table 82. Cardiovascular Adverse Events Resulting in Study Drug Discontinuation in Fluconazole-Controlled Studies† (adapted from Applicant's Table R10 1.2)

Cardiovascular Adverse Event* COSTART Term	Micafungin N=932	Fluconazole N=787
Any cardiovascular event	9 (1.0)	10 (1.3)
Shock	2 (0.2)	4 (0.5)
Subdural hematoma	0	2 (0.3)
Heart arrest	0	2 (0.3)
Hypotension	0	1 (0.1)
Tachycardia	0	1 (0.10)
Vasodilatation	0	1 (0.1)
Arrhythmia	1 (0.1)	0
Atrial fibrillation	2 (0.2)	0
Heart failure	1 (0.1)	0
Increased capillary fragility	1 (0.1)	0
Palpitation	1 (0.1)	0

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

*Patients could experience more than one adverse event within a Body System

Medical Officer Comments: Hypotension, tachycardia, and vasodilatation, all events potentially caused by histamine release, did not result in micafungin discontinuation in these studies. Events resulting in discontinuation of micafungin occurred only in 1 or 2 patients each, and meaningful comparison to the fluconazole treatment group is limited.

Post-marketing Cardiovascular Adverse Events in Japan

Nine serious cardiac adverse events were identified in the review of Japanese postmarketing adverse events in the time period from April 8, 2003 to April 8, 2004, by the ODS reviewers in their consultation to the DSPIDP. These events included 4 reports of arrhythmias. One case each of supraventricular tachycardia, and ventricular tachycardia were considered unlikely related to micafungin; and one case each of atrial fibrillation and ventricular tachycardia could not be assessed as to causality. The other four cases could not be assessed regarding causality due to insufficient information. Five reports of shock were reviewed, and 2 cases were judged to be unrelated to micafungin. Insufficient data was provided to assess causality in the other 3 cases of shock. Five cases of acute cardiac failure were reported, one case was considered possibly related to micafungin. In this case, the patient also developed prolongation of the QT interval, as described below.

Acute Cardiac Failure Medwatch Number MCN 2003JP006689.

Acute cardiac failure occurred in a patient who developed prolonged QTc (QTc 500 msec). Patient was a 54 year old male with fungal infection, AML, neutropenic fever and mild cardiac dysfunction. Four days after initiation of micafungin, patient developed acute heart failure with dyspnea. Testing revealed pulmonary congestion, prolonged QTc interval, hepatic and renal impairment. The patient was receiving amikacin, itraconazole, allopurinol, panipenem,

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demonstrated vascular hemorrhage and infiltration of perivascular tissue at micafungin doses of 10 and 32 mg/kg. These effects were not observed in dogs treated at a micafungin dose of 32 mg/kg; or in rabbits injected with micafungin at concentrations of 0.5 mg/mL, 1 mg/mL, and 2 mg/mL. We have proposed that phlebitis be reported as a drug-related adverse event in the Adverse Event portion of the micafungin label. Major vascular events, such as deep venous thrombosis, pulmonary embolism, myocardial ischemia or infarction, cerebral infarction or stroke did not occur at a higher incidence in patients who received micafungin than in those who received fluconazole in these clinical studies. However, postmarketing surveillance for these events in a larger population will be important.

Hypotension, hypertension, tachycardia, and vasodilatation were common cardiovascular adverse events identified in the clinical studies. None of these occurred more frequently in patient who received micafungin than in those who received fluconazole. However, some of these events occurred in healthy volunteers who received micafungin (vasodilatation, tachycardia, and postural hypotension). These events may be associated with histamine release, which was observed in the preclinical studies, and is also known to occur with the echinocandin, caspofungin. We have proposed to label these adverse events, in the Adverse Event section of the micafungin label.

Preclinical studies *in vitro* and in animals did not suggest any potential for QT prolongation. In healthy volunteers, no significant changes in QT/QT_c interval were observed with micafungin administration in two drug interaction studies. In the micafungin safety database there were no reports of QT prolongation or torsades de pointe; however, arrhythmia was reported as an adverse event in several patients who received micafungin. None of the cases of arrhythmia were attributed to micafungin. Most of the arrhythmias reported as adverse events were not further characterized, although ventricular tachycardia and ventricular fibrillation were reported. ECG monitoring was not included in the clinical studies involving patients, and ECG data was not submitted was not submitted with the study reports. Two cases of QT prolongation were reported with micafungin use in the post-marketing period, one of which was at least possibly related to micafungin. Serious cardiovascular adverse events including cardiac arrest, ventricular and atrial arrhythmias, and QT prolongation and should be monitored in the postmarketing period, as well as in ongoing and future clinical studies with micafungin.

7.1.12.4 Hepatic Safety

Hepatic safety concerns regarding micafungin were cited previously by Dr. Ekopimo Ibia in his review of micafungin safety for the following NDA submissions, 21-506. In Dr. Ibia's conclusions regarding safety, he noted that "there is a potential for hepatotoxicity... given the animal data". In this section, hepatic safety data from the preclinical studies, clinical studies in healthy volunteers, and in patients are summarized. As discussed below, the liver is a target organ for micafungin toxicity in animals. Additionally, significant elevations of hepatic transaminases, without clinically significant hepatic adverse events, were observed in a study of healthy volunteers who received both micafungin and mycophenolate mofetil. Likewise, abnormalities in liver enzymes were common in the clinical studies involving patients, and serious hepatic adverse events were observed, albeit uncommonly, in patients. Some of these

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events may have been caused by or worsened by micafungin. We have proposed a PRECAUTION for hepatic effects in the final micafungin labeling.

Background Information

Micafungin is an echinocandin antifungal agent. Its primary mechanism of action is inhibition of 1, 3- β -D-glucan (fungal cell wall component) synthesis. Currently, the only approved echinocandin antifungal agent is caspofungin (Cancidas®). Information regarding the potential hepatic toxicity from the product label for Cancidas® is summarized below. In addition, information regarding hepatotoxicity from the product labels for fluconazole and voriconazole are provided for comparison.

Selected portions of the Applicant's Japanese Micafungin Label

The most recent Japanese label for FUNGUARD (micafungin), published in February 2004, contains the following hepatic precautions:

PRECAUTIONS

1. Careful Administration (FUNGUARD should be administered with care in the following patients.)

- (1) Patients with a history of hypersensitivity to drugs
- (2) Patients with hepatic impairment (Administration of this product may aggravate hepatic impairment.)

2. Important Precautions

- (1) Hepatic function disorder or jaundice may develop in patients receiving this product. (See Clinically significant adverse reactions.) Additionally, hepatic lesions were noted in the high dose treatment group in animal studies. (See Other Precautions.) Patients should be carefully monitored by conducting liver function tests, etc.

Additionally, hepatic function disorder and jaundice are listed in the Adverse Reactions section under clinically significant adverse reactions, as follows:

- 3) Hepatic function disorder or jaundice:** Hepatic function disorder with increased AST (GOT), ALT (GPT), gamma GT or ALP, etc., or jaundice may occur (incidence unknown). Patients should be carefully monitored by periodic examination, etc. and appropriate measures such as discontinuation of treatment should be taken if such abnormalities are observed.

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Selected portions of the caspofungin (Cancidas®) label

Caspofungin is currently the only approved echinocandin antifungal agent, originally approved in 2001 for use in esophageal candidiasis, candidemia and other *Candida* infections, including intra-abdominal abscesses, peritonitis, and pleural space infections, invasive aspergillosis in patients refractory or intolerant to other therapies, and empiric therapy for presumed fungal infections in febrile, neutropenic patients.

The most recently approved label for caspofungin, on 29 September, 2004 contains a WARNING against concomitant use of cyclosporine and caspofungin due to elevations of hepatic transaminases in healthy subjects who received concomitant caspofungin and cyclosporine. The mechanism of transaminase elevation in subjects is not known; however, a pharmacokinetic interaction with caspofungin and cyclosporine results in increased drug exposure to cyclosporine (approximately 35% increase in caspofungin AUC). The WARNING from the caspofungin label is shown below:

WARNINGS

Concomitant use of CANCIDAS with cyclosporine is not recommended unless the potential benefit outweighs the potential risk to the patient. In one clinical study, 3 of 4 healthy subjects who received CANCIDAS 70 mg on Days 1 through 10, and also received two 3 mg/kg doses of cyclosporine 12 hours apart on Day 10, developed transient elevations of alanine transaminase (ALT) on Day 11 that were 2 to 3 times the upper limit of normal (ULN). In a separate panel of subjects in the same study, 2 of 8 who received CANCIDAS 35 mg daily for 3 days and cyclosporine (two 3 mg/kg doses administered 12 hours apart) on Day 1 had small increases in ALT (slightly above the ULN) on Day 2. In both groups, elevations in aspartate transaminase (AST) paralleled ALT elevations, but were of lesser magnitude (see ADVERSE REACTIONS). Hence, concomitant use of CANCIDAS with cyclosporine is not recommended until multiple-dose use in patients is studied.

Medical Officer Comments: As discussed further below, elevations of ALT were observed in healthy subjects who received micafungin concurrently with mycophenolate mofetil. However, there is no known pharmacokinetic interaction between these two drugs, unlike the cyclosporine- caspofungin interaction which results in increased caspofungin exposure.

Additionally, a PRECAUTION regarding hepatic effects of caspofungin is included in the most recent labeling, as shown below:

Hepatic Effects

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with CANCIDAS. In some patients with serious underlying conditions who were receiving multiple concomitant medications along with CANCIDAS, clinical hepatic abnormalities have also occurred. Isolated cases of significant hepatic dysfunction, hepatitis, or worsening hepatic failure have been reported in patients; a causal relationship to CANCIDAS has not been established. Patients who develop abnormal liver function tests during CANCIDAS therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing CANCIDAS therapy.

Medical Officer Comments: A similar hepatic precaution is proposed for the micafungin label due to similar hepatic laboratory abnormalities and clinical hepatic adverse events in the clinical studies submitted for this NDA.

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Selected portions of labels for Fluconazole

Fluconazole is a triazole antifungal agent, available in both oral and intravenous formulations, approved for use in vaginal candidiasis, oropharyngeal and esophageal candidiasis, other *Candida* infections, and cryptococcal meningitis, and prophylaxis of *Candida* infections in patients undergoing bone marrow transplantation. Fluconazole carries a WARNING regarding hepatotoxicity, as shown below from the most recent label, 7 October, 2004.

(1) Hepatic injury: DIFLUCAN has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of DIFLUCAN-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. DIFLUCAN hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during DIFLUCAN therapy should be monitored for the development of more severe hepatic injury. DIFLUCAN should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to DIFLUCAN.

Additionally, in the ADVERSE EFFECTS section of the label, hepatobiliary effects are prominently displayed, as follows:

Hepatobiliary: In combined clinical trials and marketing experience, there have been rare cases of serious hepatic reactions during treatment with DIFLUCAN. (See WARNINGS.) The spectrum of these hepatic reactions has ranged from mild transient elevations in transaminases to clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. Instances of fatal hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly AIDS or malignancy) and often while taking multiple concomitant medications. Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. In each of these cases, liver function returned to baseline on discontinuation of DIFLUCAN.

In two comparative trials evaluating the efficacy of DIFLUCAN for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other. The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials. These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking DIFLUCAN concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

Voriconazole is a triazole antifungal agent, available in intravenous and oral preparations, approved for use in invasive aspergillosis, esophageal candidiasis, candidemia in non-neutropenic patients, and certain disseminated *Candida* infections, as well as serious fungal infections caused by *Scedosporium apiospermum*, and *Fusarium* spp. in patients intolerant or refractory to other therapy. The most recent voriconazole label, published 20 December, 2004, includes a WARNING regarding hepatic toxicity, as follows:

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HEPATIC TOXICITY: In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with VFEND (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly hematological malignancy). Hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy (see PRECAUTIONS – Laboratory Tests and ADVERSE EVENTS – Clinical Laboratory Values)

Monitoring of hepatic function: Liver function tests should be evaluated at the start of and during the course of VFEND therapy. Patients who develop abnormal liver function tests during VFEND therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VFEND must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to VFEND (see PRECAUTIONS - Laboratory Tests, DOSAGE AND ADMINISTRATION - Dosage Adjustment, ADVERSE EVENTS - Clinical Laboratory Tests).

In the PRECAUTIONS section of the voriconazole label, recommendations for dosing in patients with mild-moderate hepatic insufficiency, and use in patients with severe hepatic insufficiency are included as follows:

Patients with Hepatic Insufficiency

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) receiving VFEND (see CLINICAL PHARMACOLOGY - Hepatic Insufficiency, DOSAGE and ADMINISTRATION - Hepatic Insufficiency).

VFEND has not been studied in patients with severe cirrhosis (Child-Pugh Class C). VFEND has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and should only be used in patients with severe hepatic insufficiency if the benefit outweighs the potential risk. Patients with hepatic insufficiency must be carefully monitored for drug toxicity.

The PRECAUTIONS also contains a section regarding monitoring of hepatic laboratory tests, as follows:

Patient management should include laboratory evaluation of renal (particularly serum creatinine) and hepatic function (particularly liver function tests and bilirubin).

Additionally, monitoring of liver function tests is recommended in the ADVERSE EVENTS section of the voriconazole label, as shown below.

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The overall incidence of clinically significant transaminase abnormalities in all therapeutic studies was 12.4% (206/1655) of patients treated with voriconazole. Increased incidence of liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

Voriconazole has been infrequently associated with cases of serious hepatic toxicity including cases of jaundice and rare cases of hepatitis and hepatic failure leading to death. Most of these patients had other serious underlying conditions.

Liver function tests should be evaluated at the start of and during the course of VFEND therapy.

Patients who develop abnormal liver function tests during VFEND therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VFEND must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to VFEND (see WARNINGS and PRECAUTIONS - Laboratory Tests).

Itraconazole, another triazole antifungal agent, approved for use as empiric therapy for febrile, neutropenic patients with suspected fungal infections, blastomycosis, histoplasmosis, and aspergillosis, the latter in patients who were intolerant or refractory to amphotericin B therapy. Itraconazole oral solution was approved for use in treatment of esophageal candidiasis. The itraconazole label also contains WARNINGS and PRECAUTIONS regarding serious hepatic effects.

Medical Officer Comments: All of the triazole antifungal agents carry warnings regarding potential hepatotoxicity. Amphotericin B, on the other hand, can cause significant renal dysfunction or renal failure. Caspofungin carries a warning only for concomitant use of cyclosporine because of potentially harmful elevations of hepatic transaminases and precautions against hepatic adverse effects. The incidence of nephrotoxicity was shown to be lower in patients treated with caspofungin than in those who received AmBisome in studies conducted for caspofungin approval (Cancidas® label). Micafungin, as discussed below, appears to have a similar hepatic safety profile to caspofungin. Renal safety of micafungin is discussed in section 7.1.12.5 below.

Preclinical Studies and Hepatic Effects

The liver is a target organ in animals. As summarized by Dr. Owen McMaster in the pharmacology/toxicology review for NDA 21-506, 29 April, 2002 "liver toxicity included enlarged, discolored livers with centrilobular hypertrophy, single cell necrosis, acidophilic bodies, nuclear hypertrophy, vacuolation, bile duct proliferation and mitosis. In rats and dogs, increased serum AST, ALT, alkaline phosphatase and bilirubin were noted. Additionally, at very high doses administered for prolonged periods, irreversible changes were noted in the liver in dogs and rats. In the 26-week rat study (micafungin dosed at 5 times clinical exposure), histopathological liver changes persisted after a 4- or 13-week recovery period. Similarly, in a 13 week dog study, histopathological hepatic changes persisted after a 13-week recovery period.

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Medical Officer Comment: See Dr. McMaster's review (NDA 21-506, 4/29/02) on the preclinical pharmacology and toxicology of micafungin for full details. Notably, at that time, Dr. McMasters recommended that the micafungin label should include

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Table 83. Summary of Preclinical Hepatic Findings (adapted from Dr. Owen McMaster's pharmacology/toxicology review, NDA 21-506, 29 April, 2002)

Study	Animal Dose with Hepatic Finding	Calculated HED* (mg/kg/day)	Approximate multiple of proposed human dose (150 mg/day)**	Liver-Related Findings
GLR970114 Single dose toxicity in dogs	200 mg/kg	108	54 x	Increased AST, LDH
GLR970115 4-week toxicity in rats	10 mg/kg	1.6	< 1 x	Increased total bilirubin, AST, ALT, LDH
GLR970115 4-week toxicity in rats	32 mg/kg	5.1	2.6 x	Increased acidophilic bodies, single cell necrosis, slight nuclear hypertrophy, hepatocellular vacuolation, mild round cell infiltration/accumulation in sinusoids (probably a reaction to necrosis)
GLR970291 13-week toxicity in rats	10 mg/kg	1.6	< 1 x	Increased total bilirubin
GLR010153 26-week toxicity in rats	10 mg/kg	1.6	< 1 x	Nuclear hypertrophy, vacuolation, and round cell infiltration/accumulation in liver sinusoid
GLR010153 26-week toxicity in rats	32 mg/kg	5.1	2.6 x	Increased AST, ALT, alkaline phosphatase, total bilirubin; increased liver weight at necropsy; nuclear hypertrophy, single cell necrosis, cytoplasmic acidophilic body in hepatocytes, mild round cell infiltration; accumulation in the sinusoid, vacuolation of hepatocytes, mitosis in hepatocytes, multinucleated hepatocytes

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Table 83. (continued) Summary of Preclinical Hepatic Findings (adapted from Dr. Owen McMaster's pharmacology/toxicology review, NDA 21-506, 29 April, 2002)

Study	Animal Dose with Hepatic Finding	Calculated HED* (mg/kg/day)	Approximate multiple of proposed human dose (150 mg/day)**	Liver-Related Findings
GLR970118 4-week toxicity in dogs	32 mg/kg	17	8.5 x	Liver enlargement, centrilobular hypertrophy, increased liver size and weight, liver discoloration
GLR970292 13-week toxicity in dogs with 4-week recovery	32 mg/kg	17	8.5 x	Increased liver weight, enlarged, discolored liver, and centrilobular hypertrophy (liver discoloration and centrilobular hypertrophy observed at 4-week recovery).
GLR000510 39-week toxicity in beagle dogs	3.2 mg/kg; 10 mg/kg	1.7; 5.4	< 1 x; 2.7 x	Increased liver weight and liver swelling
GLR000510 39-week toxicity in beagle dogs	32 mg/kg	17	8.5 x	Increased liver weight, swollen, discolored liver with centrilobular hypertrophy

*HED= human equivalent dose calculated based on body surface area

**The proposed dose of micafungin for esophageal candidiasis is 150 mg/day, or approximately 2 mg/kg in 70 kg person; while that for prophylaxis of Candida infections in hematopoietic stem cell transplant patients is 50 mg/kg/day, or approximately 0.7 mg/kg/day in a 70 kg person.

In addition to the animal studies tabulated above, an *in vitro* study of hepatotoxicity, GLR040501, was submitted with the micafungin safety update, August, 2004. In this study, treatment of rat hepatocytes revealed cytotoxicity with caspofungin, amphotericin B and ketoconazole, fluconazole, and micafungin using two separate assays.

Medical Officer Comments: Both animal and *in vitro* studies demonstrate a clear hepatic safety signal for micafungin.

Clinical Hepatic Safety

The total safety database for micafungin at the time of the 120-day safety update submitted in August, 2004, was 2402 subjects, including healthy volunteers and patients, from phase 1, 2 and 3 studies conducted by Fujisawa. The applicant pooled safety data from 32 studies, as listed in section 4.2 above.

Studies in Healthy Volunteers

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Single-Dose Micafungin Studies

In nine single-dose micafungin studies, 74/198 (37.4%) healthy volunteers experienced a treatment-emergent adverse event. The most common events were headache (6.6%), injection site inflammation (5.6%), dizziness (5.6%), injection site pain (4.0%), rash, (3.5%), back pain (4.0%), flu syndrome (3.5%), abdominal pain (3.0%), nausea (3.0%), diarrhea (2.5%), taste perversion (2.5%), and abnormal liver function tests in 5/198 (2.5%) subjects.

The five subjects with abnormal liver function tests reported as an adverse event participated in study FG-463-21-15, a drug interaction study of micafungin and ritonavir in healthy volunteers. This study is discussed in more detail below relative to hepatic safety in this section on drug-drug interaction studies.

Repeat-Dose Micafungin Studies

In 8 repeat-dose studies in healthy volunteers, the most common adverse events were procedural complications in 35/184 (19%), nausea in 21/184 (11.4%), and headache in 21/184 (11.4%). Hepatic-related adverse events in these studies included abnormal liver function tests, which occurred in 12/184 (6.5%) subjects, increased ALT in 15/184 (8.2%) subjects, increased AST in 11/184 (6.0%) subjects, and bilirubinemia in 1/184 (0.5%) subjects, as shown in the following table. No clinical hepatic adverse events were reported in these studies.

Table 84. Hepatic Adverse Events in Healthy Volunteers (Repeat-Dose Studies*) by Duration of Therapy with Micafungin (adapted from Appendix 2.3, eNDA 21-754)

Adverse Event COSTART Term	Treatment duration 1-9 days N=45	Treatment duration ≥ 10 days N=139	Micafungin Total N=184
	n (%)	n (%)	n (%)
Liver function tests abnormal	1 (2.2)	11 (7.9)	12 (6.5)
AST increased	0 (0)	15 (10.8)	15 (8.2)
ALT increased	0 (0)	11 (7.9)	11 (6.0)
Bilirubinemia	1 (2.2)	0 (0)	1 (0.5)

N= number of subjects in safety population

n (%) = number and percentage of subjects with adverse event. Subjects could experience more than one adverse event within a COSTART Body System.

*Repeat dose studies included FJ-463-005, 01-0-015, 01-0-104, 03-0-175, 03-0-176, 03-0-177, 03-0-178, FJ463-0002

All of the hepatic laboratory adverse events in these studies occurred at the highest dose of micafungin tested, 150 mg/day, and most occurred at longer durations of micafungin administration (≥ 10 days), as shown in the following table.

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Table 85. Hepatic Adverse Events in Healthy Volunteers (Repeat-Dose Studies*) by Dose of Micafungin (adapted from Appendix 1.5, eNDA 21-754)

Adverse Events COSTART Term	Micafungin 50 mg/day N=6	Micafungin 75 mg/day N=6	Micafungin 100 mg/day N=53	Micafungin 150 mg/day N=119	Micafungin Total N=184
	n (%)	n (%)	n (%)	n (%)	n (%)
Liver function tests abnormal	0 (0)	0 (0)	0 (0)	12 (10.1)	12 (6.5)
AST increased	0 (0)	0 (0)	0 (0)	15 (12.6)	15 (8.2)
ALT increased	0 (0)	0 (0)	0 (0)	11 (9.2)	11 (6.0)
Bilirubinemia	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.5)

N= number of subjects in safety population

n (%) = number and percentage of subjects with adverse event. Subjects could experience more than one adverse event within a COSTART Body System.

*Repeat dose studies included FJ-463-005, 01-0-015, 01-0-104, 03-0-175, 03-0-176, 03-0-177, 03-0-178, FJ463-0002

The twelve patients with abnormal liver function tests reported as adverse events above, participated in the drug-drug interaction studies, 03-0-176 (mycophenolate mofetil-micafungin interaction study) and 03-0-178 (nifedipine-micafungin interaction study). The incidence of transaminase elevation in these and other drug-drug interaction studies is discussed below. No serious adverse events or deaths occurred in the repeat dose studies.

Medical Officer Comments: Hepatic laboratory adverse events were primarily associated with the 150 mg/day dose and at least 10 days of treatment with micafungin in these subjects.

Drug-Drug Interaction Studies in Healthy Volunteers

Unexpected elevations in transaminases were observed in several of the drug-interaction studies performed to investigate pharmacokinetic interactions between steady state micafungin and several other drugs, as summarized in the table below.

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Table 86. Incidence of Transaminase Elevation $\geq 2x$ ULN in Drug-Drug Interaction Studies in Healthy Volunteers (adapted from Applicant's Table 18, eNDA 21-754)

Study	N	Drugs	AST/ALT $\geq 2x$ ULN	AST/ALT $\geq 5x$ ULN	Outcome
			n (%)	n (%)	
03-0-175	30	Sirolimus- micafungin	0	0	NA
03-0-176	30	Mycophenolate mofetil- micafungin	9 (30.0)	2 (6.7%)	Transient
03-0-177	30	Fluconazole- micafungin	8 (26.7)	1 (3.3%)	Transient
03-0-178	30	Nifedipine- micafungin	8 (26.7)	0	Transient
FG-21-04	24	Tacrolimus- micafungin	5 (20.8)	0	Transient
FG-21-05	24	Cyclosporine- micafungin	2 (8.0)	0	Transient
FG-21-15	25	Ritonavir- micafungin	7 (28.0)	1 (4.0)	Transient
FG-21-06	24	Prednisolone- micafungin	0	0	NA
FG-21-16	24	Rifampin- micafungin	0	0	NA

N= number of subjects enrolled

n =number of patients with elevated AST and/or ALT $\geq 2X$ ULN or $\geq 5x$ ULN

NA= not applicable

Medical Officer Comments: Some differences in the number of volunteers who had AST or ALT elevation to $> 2x$ ULN in applicant's table 18, and the data submitted by applicant at request of the agency on 17 December, 2004. Nevertheless, AST and/or ALT elevations to $\geq 2X$ ULN were observed in most of these drug-interaction studies with the exception of the micafungin-sirolimus, -prednisolone, and -rifampin studies. Several patients experienced ALT elevations $> 5x$ ULN after co-administration of mycophenolate, fluconazole, or ritonavir with micafungin.

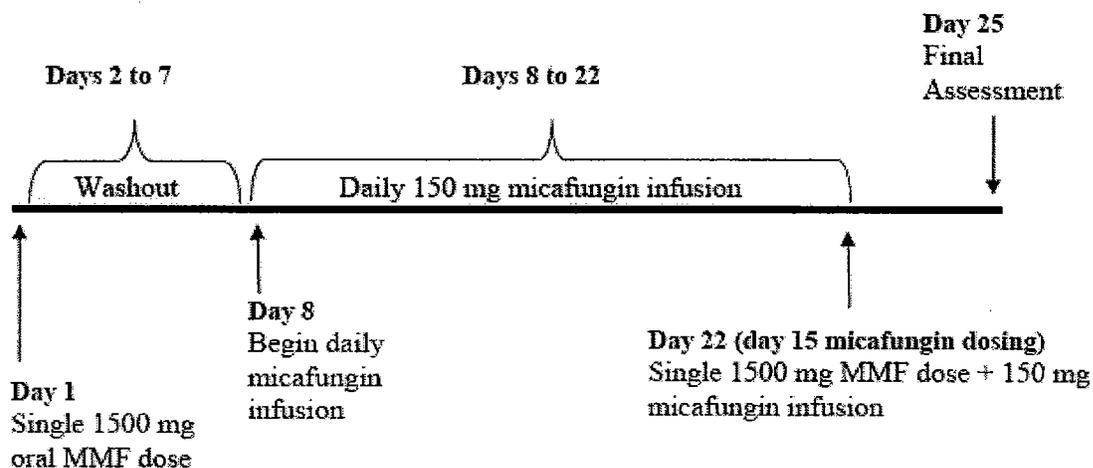
Those drug- interaction studies in which subjects experienced transaminase elevation are summarized briefly, below.

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Transaminase Elevations in study 03-0-176 (Mycophenolate Mofetil-Micafungin Interaction)

In this study in 30 healthy volunteers, mycophenolate mofetil (MMF) 1500 mg was administered as a single oral dose on study day 1, followed by a 1-week washout period. Micafungin 150 mg/day was administered on days 8 through 22, and MMF) 1500 mg orally) was administered concomitantly with the dose of micafungin on day 22. The design for study 03-0-176 is shown in the Figure below.

Figure 3. Study Design for Protocol 03-0-176 (Applicant's Figure 1, study report, 03-0-176)



In this study, 3/30 (10.0%) of subjects had abnormal liver function tests, and 2/30 (6.7%) had increased ALT reported as an adverse event. Eight of 30 subjects (26.6%) had transient increases in AST and/or ALT during the study $\geq 2 \times$ ULN (from day 8 to 25), as shown in the table below.

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Table 87. Hepatic Transaminase Data for Individual Subjects with AST and /or ALT $\geq 2 \times$ ULN during Study 03-0-176 (Applicant's Table 5, study 03-0-176 study report)

Subject Number	Parameter	Screening	Day 1	Day 8	Day 22	Day 25	Follow-up†	
10110102	AST	17	16	33	19	82*	22	
	ALT	15	15	41	16	38	-	
10110103	AST	22	21	34	119*	95*	29	
	ALT	24	23	52	250*	257*	50	
10110106	AST	21	20	38	57	52	-	
	ALT	14	17	39	73*	82*	39	
10110111	AST	18	21	23	56	51	-	
	ALT	19	26	27	84*	101*	36	
10110114	AST	22	24	31	45	39	-	
	ALT	35	43	66	92*	109*	48	
10110115	AST	23	22	115*	29	26	-	
	ALT	31	20	63	41	37	-	
10110119	AST	21	20	33	49	49	-	
	ALT	30	26	51	99*	104*	44	
10110127	AST	28	27	36	45	88*	30	
	ALT	44	39	48	107*	196*	77	
10110129	AST	29	33	28	141*	135*	44	-
	ALT	33	32	31	276*	323*	91*†	74§

Elevated values include subjects with values ≥ 2 times upper limit normal values.

AST (SGOT) normal values are 12 U/L to 31 U/L.

ALT (SGPT) normal values are 9 U/L to 29 U/L (female) and 10 U/L to 45 U/L (male).

* Values at least twice the upper limit normal range.

† Follow-up day varied by the subject: Subjects 10110102, 10110103, 10110111, 10110114, 10110119, 10110127 follow up on day 33; Subject 10110106 follow up on day 32, and Subject 10110129 follow up on days 33† and 36§.

Medical Officer Comments: Most of these subjects had elevations of ALT $> 3 \times$ ULN, and for two of these subjects, numbers 10110103 and 10110129, ALT elevation was 7-8 x ULN. No pharmacokinetic interactions resulting in increased micafungin exposure were noted between mycophenolate mofetil and micafungin. All of the transaminase elevations appeared to be transient, and none was associated with a clinical hepatic adverse event. However, the etiology of transaminase elevation in these subjects is not clear. The applicant attributed the AST and ALT elevations to high calorie or high carbohydrate diets of some of the subjects in this study. This study was limited by the number of observations measuring hepatic laboratory parameters (for example, no hepatic laboratory data was obtained between day 8 and 22 when micafungin and MMF were administered concomitantly), and by lack of control data. Review of data from the clinical studies in the safety database revealed 109 patients who received MMF and micafungin concomitantly. Although transaminase elevations were noted in some of these patients, no serious hepatic failure or liver damage was reported. The data regarding patients who received concomitant immunosuppressive agents with micafungin are described in more detail in this section below.

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Hepatic Transaminase Elevations in Study 03-0-177 (Fluconazole-Micafungin interaction Study)

In this phase 1 study, 30 healthy volunteers received a single dose of fluconazole (200 mg orally) on day 1, followed by a 1 week washout period. Micafungin (150 mg/day) was administered from days 8 through 22, and a second dose of fluconazole (200 mg) was co-administered with micafungin on day 22. Hepatic adverse events in this study included increased ALT in 10 of 28 subjects (35.7%), and increased AST in 9 of 30 subjects (32.1%). There were no clinical hepatic adverse events. Eight subjects (26.6%) experienced increases in AST and or ALT $\geq 2 \times$ ULN during the study (from days 8 to 25). Seven of these subjects are shown in the following table. The eighth subject, not shown below (number 07600125) had an ALT of 83 on study day 22.

Table 88. Hepatic Transaminase Data in Subjects with AST/ALT $\geq 2 \times$ ULN during Study 03-0-177 (applicant's Table 5, study report)

Subject Number	Parameter (U/L)	Screening	Day 1	Day 8	Day 22	Day 25	Follow-up†
07600101	AST	22	22	29	94*	109*	28
	ALT	24	21	40	294*	321*	43
07600106	AST	26	29	21	44	49	-
	ALT	31	32	36	97*	114*	30
07600107	AST	22	25	21	38	39	Not available
	ALT	20	29	24	75*	74*	
07600108	AST	20	19	25	69*	76*	18
	ALT	17	15	36	181*	186*	21
07600110	AST	24	22	28	37	52	20
	ALT	19	15	27	74*	76*	14
07600113	AST	25	25	40	76*	109*	18
	ALT	20	18	26	104*	153*	10
07600118	AST	25	22	44	55	77*	Not available
	ALT	34	31	86	138*	177*	

Elevated values include subjects with values ≥ 2 times upper limit normal values.

AST (SGOT) normal values are 12 U/L to 31 U/L.

ALT (SGPT) normal values are 9 U/L to 29 U/L (female) and 10 U/L to 45 U/L (male).

*Values at least twice the upper limit normal range.

† Post-study values were collected for subjects who agreed to return to the clinic for follow up. Due to the timing of these tests, the data are not available in the data listing, but laboratory reports are archived in the study file. Follow up days varied by subject: Subjects 07600106, 07600108, 07600113 on day 43; Subject 07600101 on day 45, and Subject 07600110 on day 79 (Subjects 107 and 118 did not return for follow up).

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Medical Officer Comments: In one subject (number 07600101) ALT increased to approximately 7 x ULN on day 22 when micafungin and fluconazole were co-administered. In all subjects who had laboratory evaluation at follow-up AST and ALT had normalized. In this case, fluconazole has known potential for hepatotoxicity (See WARNING in Fluconazole label, above). Unfortunately, no laboratory data was available for the time period of micafungin administration alone, prior to the addition of fluconazole, so it is difficult to attribute these laboratory abnormalities to either drug alone or together in combination.

Hepatic Transaminase Elevations in Study Study 03-0-178 (Nifedipine-Micafungin Interaction Study)

In this phase 1 study, 30 healthy volunteers received a single oral dose of nifedipine (10 mg) on study day 1, followed by a 1 week washout period. Micafungin was administered on days 8 through 22, and a second single dose of nifedipine was co-administered with micafungin on day

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22. In this study, 4/30 subjects (13.3%) experienced abnormal liver function tests as an adverse event. There were no clinical hepatic adverse events reported. Additionally, 8/30 (26.7%) subjects experienced elevations in AST and/or ALT, as shown in the table below. One patient, not included in the table (number 10110218) had an ALT of 87 on study day 22 and 88 on study day 25.

Table 89. Hepatic Transaminase Data in in Subjects with AST/ALT $\geq 2 \times$ ULN during Study 03-0-178 (Applicant's Table 5, study report)

Subject Number	Parameter	Screening	Day 1	Day 8	Day 22	Day 25	Follow-up†
10110204	AST	23	24	22	43	47	-
	ALT	12	15	22	54	63*	43
10110208	AST	22	18	22	48	43	-
	ALT	18	17	26	77*	79*	18
10110211	AST	28	25	51	36	40	-
	ALT	37	37	98*	61	68	-
10110214	AST	25	23	37	63*	86*	54
	ALT	32	24	56	125*	166*	122*
10110223	AST	24	18	47	61	36	-
	ALT	25	19	61	153*	98*	25
10110228	AST	18	18	20	63*	81*	-
	ALT	21	19	26	133*	191*	-
10110229	AST	27	29	25	-	-	70*
	ALT	54	43	41	-	-	122*

Elevated values include subjects with values ≥ 2 times upper limit normal values.

AST (SGOT) normal values are 12 U/L to 31 U/L.

ALT (SGPT) normal values are 9 U/L to 29 U/L (female) and 10 U/L to 45 U/L (male).

*Values at least twice the upper limit normal range.

†Follow-up day varied by the subject: Subject Numbers 10110204 and 10110223, follow up on day 33;

Subject Number 10110208 follow-up on day 34; Subject Number 10110214 follow-up on day 28; and

Subject Number 10110229 follow-up on day 11 (discontinued on day 10).

Medical Officer Comments: Most of the ALT elevations in these subjects were in the 2-3 x ULN range. However, in subjects 10110223 and 10110228, ALT elevation was 3-4 x ULN on days 22 and 25. In subjects that had follow-up evaluations, transaminases improved or returned to normal. It is not clear from this study design whether the transaminase elevations are due to micafungin alone, or the combination of nifedipine and micafungin. Nifedipine itself has been associated with rare, usually transient elevations of AST and ALT, and precaution is included in the nifedipine label regarding these laboratory abnormalities.

Hepatic Transaminase Elevations in Study Study FG-21-04 (Steady State Tacrolimus-Micafungin Interaction Study)

In this phase 1 study, 24 healthy volunteers received a single infusion of micafungin 200 mg/day on days 1, 7, and 16, and oral doses of tacrolimus (2 mg twice daily) on days 7 through 16. No hepatic laboratory or clinical adverse events were reported in this study. Five (5) subjects developed AST and/or ALT elevations $\geq 2 \times$ ULN at some point during this study; while none developed AST and/or ALT elevations to $\geq 5 \times$ ULN.

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Hepatic Transaminase Elevations in Study FG-463-21-05 (Steady State Cyclosporine-Micafungin Interaction Study)

In this phase 1 study, 24 subjects received micafungin 200 mg/day on study days 1, 7, and 16. Neoral® 50 mg was administered orally twice daily on days 7 through 16. No subjects experienced any clinical or laboratory hepatic adverse events. Only two of 24 subjects had minimal transient increases in AST and ALT to approximately 2 x ULN after co-administration of cyclosporine and micafungin; while non had transaminase elevations more than 5 x ULN.

Medical Officer Comment: No clinically significant AST or ALT increases were observed with concurrent micafungin and cyclosporine in this study. These results differ from those observed in a study where caspofungin (70 mg on study days 1 through 10) and cyclosporine (two 3 mg/kg doses 12 hours apart on day 10) were co-administered. In that case, a drug interaction resulted in increased caspofungin exposure, and several healthy subjects developed transient ALT elevations that were 2 to 3 times the upper limit of normal. The micafungin-cyclosporine interaction study presented here differed, however, from the caspofungin-cyclosporine interaction study, in that micafungin was administered on several days in the setting of steady state levels of cyclosporine.

Hepatic Transaminase Elevation in Study FG463-21-09 (Ritonavir-Micafungin Interaction Study)

In this study, 25 subjects received a single 200 mg dose of intravenous micafungin on day 1, followed by a washout period of 5 days, then ritonavir 300 mg, orally, twice daily on days 6-17, and a second dose of intravenous micafungin on day 10. Transaminase values for the 6 subjects with hepatic laboratory abnormalities during the study (AST/ALT \geq 2 x ULN) are shown in the table below. One additional subject (number 17) also had elevated ALT levels from day to post-study. However, ALT was mildly elevated in this subject at screening and pre-dose on day 10.

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Table 90. Liver Transaminase Data for Individual Subjects with Clinically Significant Findings (from applicant's Table 12.4-1. Clinical Study Report, FG-463-21-15)

Subject number	Parameter	Screening	Day 1 pre-dose	Day 1 24 h	Day 6 pre-dose	Day 8 pre-dose	Day 9	Day 10 pre-dose	Day 10 24 h
			Micafungin ↓		Ritonavir →			Micafungin ↓	
1	AST	21	18	20	16	15	-	53*	61*
	ALT	23	25	25	26	22	-	73*	115*
9	AST	20	21	18	17	21	-	38	74*
	ALT	11	11	8	8	9	-	25	65*
10	AST	21	22	24	47*	53*	41*	31	29
	ALT	25	35	33	69*	102*	94*	72*	64*
15	AST	19	22	20	20	20	-	54*	84*
	ALT	17	17	16	15	15	-	56*	111*
17	AST	45*	29	34	41	39	-	103*	115*
	ALT	47	50*	57*	74*	71*	-	163*	245*
21	AST	19	15	16	17	19	-	50*	46*
	ALT	20	16	16	18	19	-	64*	88*

Source: Section 16.2.3 (Appendix 3)

AST reference range: 16 – 41 IU/L

ALT reference range: 10 – 49 IU/L

* Values above the reference range

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Table 91. (Continued) Liver Transaminase Data for Individual Subjects with Clinically Significant Findings in Study FG463-21-15)

Subject number	Parameter	Day 12		Day 13	Day 14 pre-dose	Day 16 pre-dose	Day 19	Post-study	Repeat	Repeat
		Ritonavir	→	→	→					
1	AST	34	27	25	29	51*	26	-	-	-
	ALT	91*	77*	73*	73*	125*	86*	43	-	-
9	AST -	-	-	47*	59*	87*	40	-	-	-
	ALT -	-	-	68*	80*	128*	75	17	-	-
10	AST -	-	-	23	22	23	27	-	-	-
	ALT -	-	-	53*	41	41	46	-	-	-
15	AST -	-	-	52*	54*	52*	30	-	-	-
	ALT -	-	-	102*	105*	106*	59*	48	-	-
17	AST -	65*	69*	61*	90*	52*	51*	27	-	-
	ALT -	193*	204*	187*	238*	163*	89*	35	-	-
21	AST -	-	25	21	25	21	-	-	-	-
	ALT -	-	48	38	41	30	-	-	-	-

Source: Section 16.2.3 (Appendix 3)

AST reference range: 16 – 41 IU/L

ALT reference range: 10 – 49 IU/L

* Values above the reference range

None of these six subjects had concomitant bilirubin elevation; while subject 17 had an elevated GGT on day 19 and the post-study visit. As noted previously, subject 17 had mild AST and ALT elevation prior to receiving either micafungin or ritonavir. In subject number 10, AST and ALT elevations were noted approximately 5 days after the first dose of micafungin and prior to ritonavir, and increased further upon addition of ritonavir, indicating a possible relationship to micafungin. For the other subjects, however, transaminase increases were noted after 5 days of ritonavir dosing, and prior to the micafungin dose on day 10, indicating a possible relationship to ritonavir. However, in subjects number 1, 9, 15, 17, and 21, further increases in AST and/or ALT occurred 24 hours after co-administration of micafungin and ritonavir, indicating a potential exacerbation of transaminase abnormalities with co-administration of the two drugs. AST and ALT elevations resolved over variable lengths of time post-study. The maximum ALT in these subjects was approximately 5 x the upper limit of normal (ULN); while the maximum AST elevation was approximately 2 X ULN. The applicant concluded that the transaminase elevations in all six subjects were related to ritonavir; but were unlikely to be related to micafungin.

Medical Officer Comments: Ritonavir itself is known to be potentially hepatotoxic; however, in this study, transaminase elevations with micafungin increased with addition of ritonavir (patients 10 and 17); and transaminase elevations with ritonavir were exacerbated after addition of the second dose of micafungin (patients 1, 9, 15, 17, 21). These data suggest a potential exacerbation of hepatic transaminases increased with this drug combination. This potential "interaction" may be important for patients with HIV

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who frequently receive ritonavir as a component of highly active antiretroviral therapy (HAART). Notably, there is no pharmacokinetic interaction between ritonavir and micafungin resulting in increased micafungin exposure; however, the effect of micafungin on ritonavir exposure was not studied.

Conclusions Regarding Drug-Interaction Studies

Transient, usually mild-moderate transaminase elevations (usually ALT) were observed in a number of healthy volunteers. In several studies (micafungin + mycophenolate mofetil, or fluconazole, or ritonavir), 1 or more subjects developed transaminase elevations ≥ 5 x ULN. No pharmacokinetic interactions have been observed between micafungin and mycophenolate or fluconazole. However, the nifedipine AUC is increased with micafungin. Nifedipine has been associated with liver function test abnormalities. Likewise, fluconazole has known potential for hepatotoxicity. Mycophenolate mofetil, however, has not been associated with hepatotoxicity. The applicant interpreted these results (ALT elevation) in the micafungin-mycophenolate study as being consistent with dietary effects on ALT. However, the magnitude of ALT elevation in 2 subjects (7-8 x ULN) was higher than we would expect with dietary changes alone.

Mycophenolate mofetil is an immunosuppressive agent used for treatment of graft-versus-host disease in hematological and solid organ transplant recipients. Because these patients could also receive micafungin for *Candida* prophylaxis or for esophageal candidiasis, we further evaluated patients in the clinical studies who received concomitant micafungin and mycophenolate, as well as cyclosporine, tacrolimus, nifedipine, ritonavir and fluconazole, in an attempt to correlate the findings in healthy volunteers with transaminase elevations or hepatic adverse events in patients. These analyses are described below at the end of this section.

Phase 1 Study in Volunteers with Hepatic Dysfunction (Study 01-0-111)

Study 01-0-111 was a phase 1 study to evaluate the pharmacokinetics of single dose micafungin in healthy subjects (n=8) with normal liver function and in volunteers (n=8) with moderate hepatic dysfunction (Child-Pugh score 7-9). All subjects received a single 100 mg dose of micafungin. No subjects experienced a clinical hepatic adverse event in this study. Laboratory data was obtained at screening, the day prior to dosing, and on 72 hours after the micafungin dose. Seven (7) of the 8 subjects with baseline hepatic dysfunction had AST and/or ALT elevation at baseline, (4 subjects had baseline ALT < 2 x ULN; while 1 subject had a baseline ALT of approximately 10 x ULN; and 2 subjects had baseline AST elevation of < 2 x ULN). None of the healthy volunteers had an elevated AST or ALT at baseline. After receipt of micafungin, no significant increases from baseline AST or ALT were observed in normal subjects, or in those volunteers with baseline hepatic dysfunction.

Medical Officer Comments: For single dose micafungin in normal subjects and in those with hepatic impairment at baseline, no significant increased in hepatic transaminases were seen up to 72 hours post-dosing.

Conjoint Elevation of Bilirubin and Transaminases in Healthy Volunteers

Several subjects experienced conjoint elevation of transaminases and bilirubin. Although none of the subjects had conjoint elevation of bilirubin and AST or ALT to > 3 times the ULN, 3

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subjects of 336 (0.9%) had conjoint elevations to ≤ 3 times ULN at the end-of-therapy, as shown in the table below. Nine subjects also had bilirubin elevation ≤ 3 times ULN, without concomitant transaminase elevation. According to the applicant, all transaminase elevations observed in healthy volunteers were transient, reversible, and not associated with clinical symptoms or bilirubin elevations.

Table 92. Conjoint frequency of Elevated Transaminases and Total Bilirubin at the End of Therapy in Healthy Volunteers* (Appendix 13.2.1, requested data 14 December, 2004)

Total Bilirubin	AST/ALT \leq ULN	AST/ALT $>$ ULN and $\leq 3x$ ULN	AST/ALT $>$ 3x ULN	Total
\leq ULN	258	54	12	324
$>$ ULN and $\leq 3x$ ULN	9	3	0	12
$>$ 3x ULN	0	0	0	0
Total	267	57	12	336

*subjects had normal transaminases values at baseline

ULN= upper limits of normal range

Medical Officer Comments: A total of 54/336 (16.1 %) healthy volunteers developed AST and/or ALT elevation ≤ 3 times normal without concurrent bilirubin elevation; while twelve subjects (3.6%) also had AST/ALT levels $>$ 3 times normal with a normal bilirubin. Nine of 336 subjects (2.7%) had bilirubin elevation ≤ 3 times normal without concurrent transaminase elevation. The incidence of transaminase or bilirubin elevation alone in this healthy population is significant. However, conjoint elevation of total bilirubin and transaminases is considered a significant signal of potential drug hepatotoxicity. In this case, moderate conjoint bilirubin and transaminase elevation was seen in 3 healthy volunteers, a potential signal of micafungin hepatotoxicity.

When the worst bilirubin or transaminase value for subjects at any time during the study was considered (rather than end-of-therapy values), 7/339 (2.1%) subjects had conjoint elevation of AST/ALT and bilirubin to values ≤ 3 times ULN; while one subject had conjoint elevation of bilirubin to ≤ 3 times ULN with AST/ALT $>$ 3 times ULN. No subjects had conjoint elevation of bilirubin and transaminases $>$ 3 times ULN for both.

Table 93. Conjoint elevation of Hepatic transaminases in Healthy Volunteers at any time during Micafungin Treatment in Subjects with normal transaminases at baseline (applicant's Appendix 13.1.1, requested data, 14 December, 2004)

Worst Bilirubin	Worst AST/ALT \leq ULN	Worst AST/ALT $>$ ULN $\leq 3 x$ ULN	Worst AST/ALT $>$ 3x ULN	Total
\leq ULN	241	63	13	317
$>$ ULN $\leq 3 x$ ULN	14	7	1	22
$>$ 3x ULN	0	0	0	0
Total	255	70	14	339

ULN= upper limit of normal

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Medical Officer Comments: Because the numbers of subjects with at least moderate conjoint elevation of bilirubin and transaminases is somewhat higher in this analysis 2.4% (8/339) subjects, than that seen at the end-of-therapy, 0.9% (3 of 336) as shown above, this suggest that conjoint elevations of bilirubin and transaminases are transient during micafungin treatment.

Additional Phase 1 Studies included in 120-day Safety Update

Study 04-0-193 was a phase 1 study of the safety and pharmacokinetics of steady-state micafungin and voriconazole in healthy volunteers. Thirty five subjects received a loading dose of 800 mg voriconazole, then 400 mg twice daily for days 1 through 4, then day 21 through 24. Twenty three of these subjects also received micafungin on days 11 through 24; and 12 subjects received placebo on days 21 through 24. Data from this study were provided with the 120-day safety update, but was not included in the pooled safety database. The full study report was not provided. No clinical or laboratory hepatic adverse events were attributed to micafungin alone or to the combination of micafungin plus voriconazole. One subject, during treatment with voriconazole alone, developed abnormal liver function tests reported as an adverse event. Further details of these study results were not provided.

Summary of hepatic safety in Healthy Volunteers

No clinical hepatic adverse events were reported in healthy volunteers, however, elevations of AST, ALT and bilirubin were observed in a significant proportion of healthy subjects who received one or more doses of micafungin. None of the healthy subjects developed conjoint transaminase and bilirubin elevation to $> 3 \times$ ULN. However, 3 subjects had moderate (≤ 3 times ULN) concurrent elevation of bilirubin and hepatic transaminases, indicating some potential for micafungin hepatotoxicity.

Transient, usually mild-moderate transaminase elevations (usually ALT) were observed in a number of healthy volunteers. In several drug interaction studies (micafungin + mycophenolate mofetil, or fluconazole, or ritonavir), one or more subjects developed transaminase elevations $\geq 5 \times$ ULN. Further evaluation of patients who received concomitant micafungin with mycophenolate, cyclosporine, tacrolimus, nifedipine, fluconazole, or ritonavir is found below in this section.

Hepatic Safety in Clinical Studies with Patients

Hepatic Adverse Events (Pooled Safety Database)

The applicant combined data from phase 1, 2, and 3 clinical studies into a combined safety database which included micafungin-treated 2402 subjects (patients and volunteers) and 1980 micafungin-treated patients. The hepatic adverse events (as defined by the applicant) are shown in the following table. A total of 481/2402 (20.0%) subjects experienced at least one hepatic adverse event; in comparison to 447/1980 (22.6%) patients.

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Table 94. Incidence of Hepatic Adverse Events in Micafungin-Treated Subjects in Pooled Safety Database (adapted from applicant's Appendix 11.1.1.1, 120-day Safety Update,)

Adverse Event COSTART Term	Subjects N=2402	Patients N=1980	Volunteers N=422
	n (%)	n (%)	n (%)
Any hepatic AE*	481 (20.0)	447 (22.6)	34 (8.1)
AST increased	135 (5.6)	124 (6.3)	11 (2.6)
Alkaline phosphatase increased	103 (4.3)	103 (5.2)	0 (0)
ALT increased	136 (5.7)	121 (6.1)	15 (3.6)
Bilirubinemia	162 (6.7)	161 (8.1)	1 (0.2)
Liver function tests abnormal	105 (4.4)	88 (4.4)	17 (4.0)
Jaundice	62 (2.6)	62 (3.1)	0 (0)
GGT increased	16 (2.6)	16 (0.8)	0 (0)
Hepatitis, nonspecific	3 (0.1)	3 (0.2)	0 (0)
Liver damage	4 (0.2)	4 (0.2)	0 (0)
Hepatic failure	10 (0.4)	10 (0.5)	0 (0)
Hepatitis	1 (0.04)	1 (0.1)	0 (0)

* Hepatic adverse events, as defined by applicant included increased AST, ALT, alkaline phosphatase, GGT, bilirubinemia, abnormal liver function tests, jaundice, hepatitis, liver damage, and hepatic failure.

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

GGT= gamma glutamyl transpeptidase

Medical Officer Comment: Notably, no volunteers experienced a clinical hepatic adverse event. The most common hepatic adverse events in patients were laboratory abnormalities; however, clinically significant events such as jaundice and hepatic failure were reported.

The following additional hepatobiliary adverse events, shown in the table below, were not classified as hepatic adverse events by the applicant.

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Table 95. Other Hepatobiliary Adverse Events* in Micafungin-treated Subjects

Adverse Event COSTART Term	Subjects N=2402
Hepatomegaly	32 (1.3)
Ascites	31 (1.3)
Venoocclusive liver disease	22 (0.9)
Hepatosplenomegaly	9 (0.4)
Cholelithiasis	8 (0.3)
Cholecystitis	7 (0.3)
Cholestatic jaundice	5 (0.2)
Bile duct disorder	3 (0.1)
Cirrhosis of liver	2 (0.1)
Cholangitis	1 (0.1)
Liver fatty deposit	1 (0.1)
Hyperammonemia	3 (0.1)

*Other adverse events (considered to be hepatobiliary adverse events by medical officer) were obtained from Appendix 2.7.4.3.1

Hepatic Adverse Events (Pooled Fluconazole-Controlled Studies)

Hepatic adverse events were compared between treatment groups in the fluconazole-controlled studies (03-7-005, FG463-21-09, 98-0-050, and 97-0-041) are shown in the following table. The incidence of specific hepatic adverse events was similar for micafungin- or fluconazole-treated patients.

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Table 96. Hepatobiliary Adverse Events in Fluconazole-Controlled Studies (adapted from Applicant's Appendix 11.1.2.1, Safety Update, July 2004)

Adverse Event COSTART Term	Micafungin N=932	Fluconazole N=787
	n (%)	n (%)
Any hepatic adverse event*	177 (19.0)	165 (21.0)
Bilirubinemia	76 (8.2)	73 (9.3)
ALT increased	40 (4.3)	42 (5.3)
Liver function tests abnormal	37 (4.0)	48 (6.1)
AST increased	37 (4.0)	35 (4.4)
Alkaline phosphatase increased	30 (3.2)	23 (2.9)
Jaundice	27 (2.9)	34 (4.3)
GGT increased	0 (0)	2 (0.3)
Hepatic failure	2 (0.2)	3 (0.4)
Liver damage	1 (0.1)	2 (0.3)
Venoocclusive liver disease	15 (1.6)	15 (1.9)
Hepatomegaly	9 (1.0)	11 (1.4)
Hepatitis, nonspecific	3 (0.2)	2 (0.3)
Cholecystitis	2 (0.2)	1 (0.1)
Cholelithiasis	4 (0.4)	1 (0.4)
Cholestatic jaundice	0 (0)	1 (0.1)
Bile duct disorder	1 (0.1)	0 (0)
Ascites	9 (1.0)	6 (0.8)
Hyperammonemia	0 (0)	1 (0.1)

* Hepatic adverse events as defined by applicant includes only increased AST, ALT, alkaline phosphatase, GGT, bilirubinemia, abnormal liver function tests, jaundice, liver damage, and hepatic failure. Other COSTART Terms (considered to be hepatic adverse events by the medical officer) were obtained from Appendices 2.7.4.3.3.

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

GGT= gamma glutamyl transpeptidase

Medical Officer Comments: Hepatic adverse events which occurred somewhat more frequently in patients treated with micafungin than in those who received fluconazole included increased alkaline phosphatase, cholecystitis, bile duct disorder, and ascites. These differences are not significant, however. It should be noted that fluconazole is known to have potential hepatotoxicity, and the hepatic adverse effect profile for micafungin looks very similar to that observed with fluconazole.

Serious Hepatic Adverse Events (Pooled Safety Database)

No serious hepatic adverse events were reported in volunteers. Serious hepatic adverse events occurred in 28/1980 (1.4%) patients treated with micafungin. Eleven (11) of 1980 (0.6%) patients had serious hepatic adverse events which were considered drug-related. The table below

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shows all serious hepatic adverse events, and those considered related to micafungin in patients in the pooled safety database.

Table 97. Serious Hepatobiliary Adverse Events in Patients in Pooled Safety Database
(adapted from applicant's Table 11.1.1.2, Safety Update, July, 2004)

Serious Adverse Event (SAE) COSTART Term	Micafungin-treated Patients N=1980 n (%)	Related SAE in Micafungin-treated Patients N=1980 n (%)
Any serious hepatic AE*	28 (1.4%)	11 (0.6)
Bilirubinemia	11 (0.6)	5 (0.3)
Alkaline phosphatase increased	3 (0.2)	3 (0.2)
AST increased	2 (0.1)	2 (0.1)
Liver damage	3 (0.2)	1 (0.1)
Liver function tests abnormal	6 (0.3)	1 (0.1)
ALT increased	1 (0.05)	1 (0.1)
Hepatic failure	8 (0.3)	0 (0)
Jaundice	1 (0.05)	0 (0)
Ascites	3 (0.1)	0 (0)
Venoocclusive liver disease	4 (0.2)	0 (0)
Bile duct disorder	1	0 (0)
Cholecystitis	1	0 (0)
Cholelithiasis	1	0 (0)
Hepatomegaly	1	0 (0)

* Hepatic adverse events as defined by applicant includes only increased AST, ALT, alkaline phosphatase, GGT, bilirubinemia, abnormal liver function tests, jaundice, liver damage, and hepatic failure. Other COSTART Terms considered to be hepatic adverse events by MO were obtained from Appendices 8.1 and 8.8.

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

Medical Officer Comments: Bilirubinemia, hepatic failure, and liver function test abnormalities were the most common serious hepatobiliary adverse events; while bilirubinemia, increased alkaline phosphatase, and increased AST were the most common drug-related serious adverse events. All cases of serious hepatic failure and liver damage were reviewed individually (see table below and narrative summaries).

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Table 98. Summary of Selected Serious Hepatic Adverse Events in Pooled Studies

Serious Hepatic AE	Patient Number	Protocol	Underlying Disease	Micafungin Daily dose (cumulative dose)	Micafungin Duration (days)	Onset (day)	SAE Drug-Related †	Outcome
Liver failure	02194007	01-0-124	Massive blood loss after abdominal aortic aneurysm-ectomy	100 mg/day (1300 mg)	13	6	Unlikely*	Death day 13 due to cardiopulmonary arrest
Liver failure	10745035	03-7-005	HIV/AIDS; CD4 97; EC	150 mg/day (750 mg)	5	4	Unlikely*	Death day 17 due to MDR TB
Liver failure	020785	98-0-046	AML/IA	75 mg/day (5775 mg)	77	77	Not related	Death day 89 due to veno-occlusive disease
Liver failure	059777	98-0-046	Leukemia/IA	12.0 to 45 mg/day (4653 mg)	20	114	Not related	Resolved day 91
Liver failure	063786	98-0-046	IA	75 mg/day (525 mg)	7	8	Not related*	Death day 8 due to end-stage liver disease

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Table 98. *(continued) Summary of Selected Serious Hepatic Adverse Events in Pooled Studies (continued)

Liver failure	262780	98-0-046	BMT for leukemia/IA	27.9 to 43 mg/day (1077 mg)	29	27	Not related*	Death day 31 due to interstitial pneumon-itis
Liver failure	262788	98-0-046	BMT/AML	75 mg/day (750 mg)	10	2	Not related*	Death day 10 due ARDS
Liver failure	474177	98-0-046	ALL/IA	75 mg/day (2250 mg)	34	5	Not related*	Death day 38 due to multi-organ failure
Liver failure	287674	98-0-047	Lymphoma/candidemia	50 to 175 mg/day (3350 mg)	27	14	Not related*	Death day 28 due to cardiac failure
Liver failure	1008	FG463-21-09	HIV/CD ₄ count 290/EC	150 mg/day (2100 mg)	14	13	Unlikely*	Death day 15 due to tuberculosis
Liver damage	3103	FG463-21-09	HIV/AIDS/CD ₄ count 90/EC	50 mg/day (700 mg)	14	10	Not related	SAE persistent at end of study
Liver damage	585271	98-0-047	Mantel cell lymphoma/chemo/invasive candidiasis	100 mg/day (800 mg)	8	8	Probable	Death day 22 due to heart failure*
Liver damage	033885	98-0-047	Duodenal malignancy /invasive candidiasis	50 to 100 mg/day (1050 mg)	13	6	Not related	Death day 15 due to sepsis

† Investigator's assessment of drug-relatedness to SAE (serious adverse event)

IA = invasive aspergillosis; AML= acute myelocytic leukemia; ALL = acute lymphocytic leukemia; MDR TB = multidrug resistant tuberculosis

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***Medical Officer Comments:** Each of the serious adverse events categorized as hepatic failure or liver damage was reviewed. Narratives for those from studies 03-7-005 and FG463-21-09 are found in individual study reports. In the investigator's assessment all but one of these cases were considered unrelated to micafungin. The narrative summaries for these patients are included below.*

Narrative Summaries for Patients with Serious Hepatic Adverse Events of Hepatic Failure and Liver Damage

Study 01-0-124 (Antifungal Prophylaxis Study in Intensive Care Patients)

The applicant provided safety tables and narrative summaries for this study in the NDA submission, but not the full study report or database.

Patient number 02194007 was a 77 year old diabetic male in study 01-0-124 who had an abdominal aortic aneurysm repair complicated by massive blood loss, acute renal failure, and respiratory failure. He received micafungin 100 mg/day for 13 days as prophylaxis/pre-emptive antifungal therapy. Other past medical history included hypertension, coronary artery disease, peripheral vascular disease; and other baseline conditions on enrollment included thrombocytopenia, hypotension, and tachycardia. At the time of enrollment he was receiving cefazolin, midazolam, insulin, fresh frozen plasma, platelets, packed red blood cells, and dopamine. Additional concomitant medications included protonix, amiodarone, epinephrine, cisatracurium, fentanyl, raglan, magnesium sulfate, dextrose, cortisol, potassium sulfate, vitamin K, and epogen. Baseline laboratories included bilirubin 2.0 mg/dl, creatinine 3.0 mg/dl, AST 546 U/L, and ALT 117 U/L. Liver failure was reported as a serious adverse event on day 6, and was considered unlikely to be related to micafungin. Other serious adverse events reported included hypoglycemia, hypomagnesemia, atrial fibrillation and fever, none of which were considered related to micafungin. On day 12, bilirubin was 16.3 mg/dl, creatinine was 4.4 mg/dL, AST 116 U/L, and ALT 22 U/L. Severe acute renal failure, shock and life-threatening cardio-respiratory arrest and acute respiratory distress syndrome were reported as serious adverse events on day 13. Support was withdrawn due to lack of improvement despite vasopressor therapy and supportive care and the patient died on day 13. The primary cause of death was considered cardiopulmonary arrest, with acute renal failure, acute respiratory distress syndrome, and liver failure considered contributory conditions. No autopsy was performed. The death was considered not related to study drug by the investigator.

***Medical Officer Comments:** The etiology of hepatic failure in this patient was likely multifactorial, including hypotension, shock, and other drugs, including amiodarone which was started at the same time as micafungin. Additionally, the patient had baseline elevation of bilirubin and transaminases. The role of micafungin in the progressive decline of hepatic function in this patient cannot be ruled out.*

Study 98-0-046 (Micafungin for treatment of Invasive Aspergillosis):

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Patient Number 020785 was a 30 year-old Caucasian female who received chemotherapy and a mini cord blood transplant for acute myelogenous leukemia. Probable invasive pulmonary Aspergillosis was diagnosed and the patient initially received amphotericin B, then amphotericin plus itraconazole for treatment of aspergillosis. Itraconazole was stopped after 8 days, and micafungin 75 mg/day was added to amphotericin B due to failure of prior antifungal therapy. The patient received a total of 5775 mg micafungin over 77 days. Bilirubinemia developed on day 44, and amphotericin B was discontinued on day 46. Liposomal amphotericin B (Abelcet®) was administered days 47 to 75. The patient developed renal failure requiring dialysis on day 77. The patient died on day 94 due to venoocclusive disease and liver failure. A liver biopsy performed on day 83 revealed early venoocclusive liver disease. Neither bilirubinemia nor hepatic failure was considered related to micafungin. Bilirubin was normal at baseline, but increased to 6.0 mg/dL (day 47), and increased progressively to 51.3mg/dL by day 77. AST was normal at baseline and throughout the study. ALT was normal at baseline, and increased only minimally over time. Alkaline phosphatase was somewhat elevated at baseline (183 U/L), and reached a maximum level of 844 U/L on day 77. The patient received multiple concomitant medications prior to the onset of liver failure, including: percocet, ativan, Tylenol, benadryl, hydrocortisone, dilaudid, senekot, zantac, zofran, phenergan, Demerol, ambient, morphine, compazine, dilantin, novinyll, decadron, busulfan, vioxx, anusol, amlodipine, fludarabine, Demerol, restoril, acyclovir, Maalox, cellcept, cyclosporine, flexeril, carafate, cipro, fentanyl, total parenteral nutrition, penicillin VK, ceftazidime, tobramycin, vancomycin, neupogen, flagyl, ancef, haldol, lansoprazole, simethicone, diltiazem, ursodiol, and nifedipine.

Medical Officer Comments: This is a highly confounded case, with the patient receiving multiple concomitant medications which could cause hepatic adverse events. Additionally, the finding of venoocclusive liver disease on liver biopsy and the concomitant alkaline phosphatase elevation consistent with biliary obstruction, point to venoocclusive liver disease rather than micafungin as the cause of hepatic failure in this patient. This case of hepatic failure, which appeared more cholestatic than due to hepatocellular damage, was not likely related to micafungin.

Patient 059777 was a 34 week-old black male who received chemotherapy for leukemia. Invasive aspergillosis involving the sinuses and left nasal orbit was diagnosed, and the patient underwent left nasal orbital decompression. He was treated initially with AmBisome®, and subsequently received micafungin in addition to AmBisome® due to “efficacy failure”. Significant baseline conditions included anorexia, Klinefelter’s syndrome, valvular heart disease, facial edema, typhlitis, respiratory distress, hypotension, thrombocytopenia, tachycardia, neutropenia, arrhythmia, diarrhea, hypokalemia, atelectasis, alopecia, fluid overload, anemia, respiratory acidosis, abdominal distention, fever, and hypophosphatemia. At the time of enrollment the patient was receiving perdid, Tylenol, GCSF, lipids, total parenteral nutrition, bactrim, imipenem, amikacin, ativan, bacitracin and oxygen. He was also receiving transfusions

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of platelets and packed red blood cells. The patient received 114 days of micafungin dosed at 12 mg/day. Liver failure was reported as an adverse event (not serious) on day 20. At that time, AST was 117 U/L, ALT, 123 U/L, total bilirubin, 10.0 mg/dL, and alkaline phosphatase, 305 U/L. At baseline, AST, ALT, and alkaline phosphatase were normal, but bilirubin was elevated at 8.2 mg/dL. Bilirubin increased to a maximum of 51.1 mg/dL (day 10), and subsequently declined. Liver failure resolved on day 91.

Medical Officer Comments: This is a highly confounded case, but the resolution of hepatic laboratory abnormalities and hyperbilirubinemia while the patient continued on micafungin therapy, makes it unlikely that the liver failure was related to micafungin.

Patient 063786 was a 58 year old Caucasian male with end-stage liver disease receiving solumedrol, who developed invasive pulmonary aspergillosis, initially treated with fluconazole (single dose), then Ambisome®. Micafungin (75 mg/day) was added due to efficacy failure. The cumulative dose of micafungin was 525 mg over 7 days. Other concomitant medications included prevacid, lactulose, aldactone, albumin, cefepime, haldol, potassium chloride, neomycin, vitamin K, albuterol, lasix, and multivitamins. All treatment was electively withdrawn on day 7, and the patient died on day 8. The death was not considered related to micafungin. The primary cause of death was end stage liver disease, and contributing conditions were listed as *Aspergillus* pneumonia, renal failure and hepatic encephalopathy. The patient had elevated liver function tests and bilirubinemia at baseline (AST 158 U/L, ALT 102 U/L, total bilirubin 30.5 mg/dL, alkaline phosphatase 332 U/L), which had worsened on day 7 (AST 266 U/L, ALT 132 U/L, bilirubin 43 mg/dL, and alkaline phosphatase, 471 U/L).

Medical Officer Comments: Transaminases and bilirubin levels increased after starting micafungin in this patient. However, the baseline liver disease and concomitant medications in this patient make it difficult to ascribe the worsening liver disease to micafungin.

Patient 262780 was a 4 year-old Caucasian male who received an allogeneic bone marrow transplant for leukemia. At baseline the patient was noted to have neutropenia, hepatomegaly, anorexia, and ascites. He developed invasive pulmonary aspergillosis and a necrotizing fungal (*Aspergillus flavus*) dermatitis. He had been treated empirically with Abelcet® prior to onset of these fungal infections. He was subsequently treated with Abelcet® in addition to itraconazole, then micafungin (initial dose 27.9 mg/day, then increased to 36, and 43 mg/day) was added due to efficacy failure. He received 1077mg micafungin over 29 days. Multiple concomitant medications were administered during this time period, including itraconazole. The patient developed bilirubinemia on day 24, and hepatic failure on day 27 of micafungin therapy and micafungin was discontinued on day 29. Jaundice was reported as an adverse event on day 30, and the patient died on day 31. The primary cause of death was considered to be interstitial pneumonitis, with contributing conditions of hepatic, renal and respiratory failure. Hepatic laboratory data for this patient are shown in the table below.

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Selected hepatic laboratory data for patient 262780 during micafungin treatment*

Study day	AST (U/L)	ALT (U/L)	Alkaline phosphatase (U/L)	Bilirubin (mg/dL)
Baseline	32	38	335	1.7
Day 8	25	35	345	2.4
Day 16	20	33	236	4.1
Day 23	35	57	314	2.2
Day 31	196	178	581	9.8

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

Medical Officer Comments: *No significant transaminase elevation was noted until after micafungin was discontinued on day 29. Bilirubin was noted to be elevated by day 8, and alkaline phosphatase was elevated at baseline and during the entire course of therapy. This is a highly confounded case, particularly because of multiple concomitant medications, including itraconazole, which is known to be potentially hepatotoxic. Additionally, the patient had hepatomegaly and ascites at baseline suggesting significant underlying liver disease. Despite these caveats, micafungin could have contributed to worsening hepatic laboratory abnormalities and liver disease.*

Patient 262788 was a 16 year-old black male who received an allogeneic bone marrow transplant for acute myelogenous leukemia. He received prophylactic fluconazole, then Ambisome®, but developed invasive pulmonary aspergillosis. Micafungin (75 mg/day) was added to Ambisome® (600 mg/day) for efficacy failure. The patient received a total of 750 mg micafungin over 10 days. Baseline conditions included hyperbilirubinemia, jaundice, respiratory failure, anemia, thrombocytopenia, fever, hypocalcemia, hyperphosphatemia, abnormal renal function, hypertension (and hypotension). Acute respiratory distress syndrome (ARDS) was reported as a serious adverse event on study day 1, and hepatic failure and worsened hyperbilirubinemia were reported as serious adverse events on day 2. Other serious adverse events included acute renal failure (day 4), and pneumothorax (day 5). None of these adverse events were considered related to study drug. Micafungin was discontinued on day 10 due to respiratory failure and acute respiratory distress syndrome. The patient expired of day 10 due to ARDS; and contributing conditions included multisystem organ failure, bone marrow transplantation, and possible aspergillosis. Autopsy showed severe diffuse pulmonary alveolar damage with no evidence of persistent pulmonary aspergillosis, enlarged heart with left ventricular hypertrophy, and dilated left ventricle, and passive congestion of the liver and spleen. There was no evidence of graft-versus-host disease or veno-occlusive disease in the liver, but a moderate non-specific hepatitis was noted. The patient was also noted to have a horseshoe kidney with focal glomerulosclerosis.

Additional concomitant medications included oxacillin, vancomycin, cyclosporine, intravenous immunoglobulin, solumedrol, total parenteral nutrition, meropenem, dopamine, benadryl, lasix, reglan, hydralazine, metolazone, itraconazole (dosed on days 1 and 2), septria, tobramycin, mannitol, morphine, ursodiol, calcium carbonate, and sodium

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bicarbonate. Selected hepatic laboratories during the course of therapy are shown in the table below.

Hepatic laboratories for patient 262788 during micafungin treatment*

Study Day	AST (U/L)	ALT (U/L)	Alkaline phosphatase (U/L)	Total bilirubin (mg/dL)
Baseline	87	58	156	5.7
Day 9	118	49	279	21.1
Day 10	134	56	353	24.8

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

***Medical Officer Comments:** This case is highly confounded primarily because of multiple concomitant medications, some of which may cause hepatotoxicity (itraconazole, cyclosporine, and others). Additionally, the patient had a significantly elevated bilirubin and jaundice at baseline. However, it is possible that micafungin could have contributed to the patient's deterioration of liver function.*

Patient 474177 was a 40 year-old Caucasian male with acute lymphatic leukemia who was diagnosed with pulmonary aspergillosis. He was initially treated with amphotericin B, but developed renal insufficiency, and subsequently received micafungin (75 mg/day) over 34 days for a total dose of 2550 mg. Antineoplastic chemotherapy (cyclophosphamide and cytarabine) was started 2 days prior to micafungin. Bilirubinemia and jaundice were reported as serious adverse events on study day 8, and hepatic failure, on day 36. Other adverse events included abnormal liver function tests (day 18), renal failure (day 35), shock, and coma (day 36). None of the adverse events were considered related to micafungin. Significant baseline conditions included pancytopenia, hypocalcemia, abnormal liver function tests, bilirubinemia, fever and neutropenia, and withdrawal syndrome secondary to alcohol. He received multiple concomitant medications including Ambisome® (days 34-38) and caspofungin (days 35-38), and others. The patient died on day 38 due to multiorgan failure related to progressive leukemia, with contributin conditions including thrombocytopenia resulting in gastrointestinal and retinal bleeding, and pneumonia. No autopsy was performed. Hepatic laboratory data obtained during the course of micafungin therapy for this patient are shown in the table below.

Hepatic Laboratory Values for Patient 474177 during Micafungin Treatment*

Study Day	AST (U/L)	ALT (U/L)	Alkaline phosphatase (U/L)	Total bilirubin (mg/dL)
Baseline	85	66	696	5.2
Day 7	79	29	638	11.9
Day 14	99	52	691	14.5
Day 21	134	66	657	19.4
Day 28	444	510	1680	25.0
Day 34	419	381	1470	40.4

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Day 38	363	298	1442	41.8
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*Normal laboratory values are provided in the appendix, section 10.1.5

Medical Officer Comments: *This case is complicated by the underlying disease, baseline bilirubinemia and other liver function test abnormalities, concomitant medications, and possibly underlying alcoholic liver disease in this patient. However, a contributory role of micafungin in worsening liver disease in this patient cannot be excluded.*

Study 98-0-047 (Open-label study of micafungin for treatment of candidemia or invasive candidiasis):

Patient 287674 was a 48 year-old Caucasian male who received chemotherapy and bone marrow transplant for a malignant lymphoma. He developed candidemia (*Candida rugosa*), and received 2 days of amphotericin B, then micafungin (initial dose was 50 mg/day, which was increased stepwise to 175 mg/day) for 27 days (3350 mg total). Hepatic failure, renal failure, respiratory failure, atrial fibrillation and metabolic encephalopathy were reported on day 14, and pneumonia on day 17. None of the serious adverse events were attributed to micafungin. The patient developed refractory heart failure on day 28 and died the same day. The primary cause of death was considered cardiac failure, and secondary contributing conditions were pneumonia, renal failure and lymphoma. Significant baseline conditions included hematemesis, stomach ulcer, thrombocytopenia, and sepsis. He received multiple concomitant medications including cyclophosphamide (day 2), dexamethasone, cyclosporine (day 8), phenergan, zantac, rifampin (days 13-14), isoniazid (days 13-14), voltaren, codeine, fluconazole (days 14-19), solumedrol, prednisone, ganciclovir, lactulose, flagyl, bactrim, total parenteral nutrition, and others. Hepatic laboratories during the course of micafungin therapy are shown in the following table.

Hepatic Laboratory Values for Patient 287674 during micafungin therapy*

Study Day	AST (U/L)	ALT (U/L)	Alkaline phosphatase (U/L)	Total bilirubin (mg/dL)
Baseline	22	18	74	0.59
Day 7	51	26	87	0.59
Day 14	257	356	110	8.42
Day 21	54	65	117	25.74

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

Medical Officer Comments: *Normal transaminases and bilirubin were seen at baseline, and the patients developed liver function test abnormalities by day 14. However, he received several other potentially hepatotoxic medications prior to development of hepatic failure, namely, cyclosporine, isoniazid, and rifampin, although the latter drugs were received only one day prior to onset of*

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transaminase elevation and bilirubinemia. Micafungin, however, can not be excluded as a possible cause of hepatic deterioration and failure.

Patient number 033885 was a 62 year-old black female with a duodenal malignancy. The patient received micafungin (initially 50 mg/day for 5 days, then 100 mg/day) for 13 days (1050 mg total). Respiratory failure and septic shock were reported as serious adverse events on study day 1 and liver damage on study day 6. The liver damage was actually CT findings of liver lesions considered consistent with metastatic carcinoid or abscesses. Other serious adverse events reported were congestive heart failure, sepsis, increased AST, and abnormal thinking (all on day 14), convulsion, cardiac arrest, and hyperkalemia on day 15. Except for AST elevation, considered possibly related, none of the serious adverse events were attributed to micafungin. Micafungin was discontinued on day 14 due to AST elevation. The patient died on day 15, with the primary cause of death considered to be sepsis, with secondary contributing conditions, carcinoid tumor and end-stage renal disease. Significant baseline conditions included diabetes, end-stage renal disease, hypertension, jaundice, ascites, pancreatitis, sepsis, hypotension, and others. The received multiple concomitant medications including levophed, zosyn, gentamycin, vancomycin, total parenteral nutrition, ibuprofen (day 7 only), Tylenol (day 12 only), and others. Selected hepatic laboratory results for this patient are shown in the table below.

Hepatic Laboratory Values for Patient 033885 during micafungin therapy*

Study Day	AST (U/L)	ALT (U/L)	Alkaline phosphatase (U/L)	Total bilirubin (mg/dL)
Baseline	44	41	652	2.7
Day 7	82	55	540	2.3
Day 14	5836	783	1155	3.2

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

***Medical Officer Comments:** It would appear that the liver damage noted on day 6 was either metastatic tumor or liver abscess, unlikely related to micafungin treatment. However, the AST and ALT elevation noted on day 14 may have been related to the other confounding factor in this case, including shock, sepsis, and hypotension.*

Patient 585271 was a 73 year-old Caucasian male receiving chemotherapy for mantle cell lymphoma. He developed pneumonia presumably secondary to *Candida* and received fluconazole initially, followed by micafungin 100 mg/day for 8 days. At baseline, the patient had diabetes, abdominal pain, splenomegaly, and "coronary insufficiency". On study day 8, worsening abdominal pain, hepatic tenderness and palpable liver were noted, and reported as the serious adverse event, "liver damage", and micafungin was discontinued at that time. The investigator considered the relationship of micafungin to liver damage as highly probable. The patient died on day 22, with the primary cause of death described as circulatory insufficiency and acute heart failure, with secondary

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contributing conditions of immunodeficiency, pneumonia, progression of lymphoma, and respiratory insufficiency. The patient had received multiple other concomitant medications, including metformin, metoprolol, dalacin (clindamycin), amikin (amikacin), aminophyllin, lasix, morphine, digoxin, solumedrol, ciprinol (ciprofloxacin), mesna, clemastine (antihistamine) and ketoconazole on day 15. At autopsy, microscopic examination of the lungs revealed *Aspergillus* colonies in the left lower lobe, without invasion into vessels or peribronchial tissues. Additionally the liver and spleen were enlarged, and there was a question regarding fungal lesions in the liver, although this was not clarified. Hepatic laboratories were normal at baseline; but on day 8, AST was 439 U/L, ALT, 118 U/L, total bilirubin 2.18 mg/dL, and alkaline phosphatase 928 U/L.

Medical Officer Comments: This case is confounded by progressive malignancy, and multiple concomitant medications, particularly metformin which is potentially hepatotoxic. Ketoconazole, also has the potential hepatotoxicity, but was not administered until after the "liver damage", and elevated bilirubin and transaminases were noted on day 8. I would agree that micafungin is possibly related to the "liver damage, but the autopsy report was not very useful in making that determination.

Serious Hepatic Adverse Events (Pooled Fluconazole-Controlled Studies)

The incidence of serious hepatic adverse events in the fluconazole-controlled studies (03-7-005, FG463-21-09, 98-0-050, and 97-0-041) was similar in fluconazole- and micafungin-treated patients. These events are listed in the following table.

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Table 99. Serious Hepatic Adverse Events in Fluconazole-controlled Studies† (adapted from Applicant's Appendix 11.1.2.2)

Serious Adverse Event (SAE)	Micafungin-treated patients N=932	Drug-Related* SAE in Micafungin-treated patients N=932	Fluconazole-treated patients N=787	Drug-Related* SAE N=787 Fluconazole-treated-patients
	n (%)	n (%)	n (%)	n (%)
Any serious hepatic AE	10 (1.1)	1 (0.1)	11 (1.4)	7 (0.9)
Bilirubinemia	4 (0.4)	1 (0.1)	4 (0.5)	2 (0.3)
Liver function tests abnormal	3 (0.3)	0 (0)	2 (0.3)	2 (0.3)
Hepatic failure	2 (0.2)	0 (0)	3 (0.4)	1 (0.1)
Hepatitis, nonspecific	0	0 (0)	1 (0.1)	1 (0.1)
AST increased	0	0 (0)	2 (0.3)	1 (0.1)
ALT increased	0	0 (0)	2 (0.3)	1 (0.1)
Liver damage	1 (0.1)	0 (0)	0 (0)	0 (0)

n (%)= number and percentage of subjects (patients or volunteers) with adverse event.

Note that one person could experience more than 1 adverse event within a body system.

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

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

Medical Officer Comments: In addition to those events shown in this table, 3 patients who received micafungin, and 3 who received fluconazole experienced veno-occlusive liver disease, which was reported as a serious adverse event. The overall the incidence of serious hepatic events was similar in the micafungin and fluconazole groups; however more events were attributed to fluconazole than to micafungin in these studies (only 1 serious adverse event was considered related to micafungin, while 7 were attributed to fluconazole).

Serious hepatic adverse events in patients treated with micafungin in these studies are summarized in the table below.

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Table 100. Summary of Serious Hepatic Adverse Events in Fluconazole-controlled studies*

Patient number	Study	Serious Hepatic Adverse Event	Underlying Disease & Indication for Micafungin	Micafungin Daily and Cumulative Dose	Micafungin duration (days)	Onset of SAE (study day)	Outcome
0122004	98-0-050	Bili-rubinemia	ALL/HSCT prophylaxis	50 mg/day (800 mg)	16	8	Persistent at end of study
0132504	98-0-050	Bili-rubinemia	CML/HSCT Prophylaxis	50 mg/day (750 mg)	15	14	Persistent at end of study
0133501	98-0-050	Bili-rubinemia	Myelo-dysplasia	50 mg/day (750 mg)	15	19	Persistent at end of study
0572502	98-0-050	Liver function tests abnormal	Renal cell carcinoma/transplant	50 mg/day (350 mg)	7	4	Resolved day 14
0702002	98-0-050	Liver function tests abnormal	AML/HSCT	50 mg/day (950 mg)	19	14	Persistent at end of study
1413001	98-0-050	Liver function tests abnormal	CML/HSCT	50 mg/day (1400 mg)	28	25	Resolved by day 64
2492001	98-0-050	Bili-rubinemia	ALL/HSCT	50 mg/day (650 mg)	13	13	Progressive; Death day 36
1008	FG-21-09	Hepatic failure	HIV EC	150 mg/day (2100 mg)	14	13	Persistent at death day 15
3103	FG-21-09	Liver damage	HIV/AIDS	50 mg/day (700)	14	11	persistent
10745035	03-7-005	Hepatic failure	HIV/AIDS EC	150 mg/day (750 mg)	5	5	Persistent at death day 17

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

ALL= acute lymphocytic leukemia, HSCT = hematopoietic stem cell transplant; CML = chronic myelogenous leukemia; EC= esophageal candidiasis

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Medical Officer Comments: No serious hepatic adverse events were reported in study 97-0-041 in 62 micafungin-treated bone marrow transplant patients who received micafungin at doses of 12.5 to 200 mg/day for antifungal prophylaxis.

Serious Hepatic Adverse Events in Fluconazole-controlled Studies

Narrative summaries for patients who experienced serious hepatic adverse events in the fluconazole-controlled studies are provided by study below.

Study 98-0-050 Micafungin as Antifungal Prophylaxis:

Patient 0122004 was a 35 year old Caucasian male with acute lymphocytic leukemia who underwent an allogeneic matched donor bone marrow transplant. He received prophylactic micafungin 50 mg/day for 16 days (800 mg total). Baseline conditions included asthenia, nausea, increased AST, thrombocytopenia, vomiting, leucopenia, and anemia. At the time of enrollment, the patient was receiving total body irradiation, zofran, and ativan. Baseline AST was 28 U/L, ALT, 49 U/L, bilirubin 1.1 mg/dL and alkaline phosphatase 62 U/L. Bilirubinemia requiring hospitalization was reported as a serious adverse event on day 8, but was not considered related to micafungin. Bilirubin was 2.2 mg/dL on day 10 (day 8 bilirubin was not reported); 2.1 mg/dL. AST, ALT and alkaline phosphatase were normal on days 10 and 13. The bilirubinemia was assessed by the investigator to be unlikely related to micafungin. The patient received multiple other medications during the study (prior to bilirubin elevation on day 8), including chemotherapy (etoposide, dexamethasone), tylenol, norfloxacin, valtrex, lasix, vancomycin, cyclosporine, methotrexate, benadryl and oxycodone. Multiple other adverse events were reported, none of which were considered serious. Micafungin therapy was stopped on day 16 due to lack of efficacy. The patient developed grade II graft versus host disease (GVHD) on day 34, and a bilirubin of 7.3 mg/dL was reported at that time.

Medical Officer Comments: This patient had isolated bilirubinemia. Hemolysis was not reported as an adverse event in this patient. No significant anemia was seen upon review of the hematologic laboratory data in this case. The patient was receiving a number of other medications which could cause liver function test abnormalities, including bilirubinemia (methotrexate, cyclosporine). Thus, the role of micafungin in the development of bilirubinemia in this case is not clear, but cannot be excluded.

Patient 0132504 was a 56 year-old Caucasian male with chronic myelogenous leukemia, who underwent an allogeneic matched-donor bone marrow transplant. His conditioning regimen included pentostatin, total body irradiation, and cyclosporine plus methotrexate for GVHD prophylaxis. He received micafungin 50 mg/day for 15 days per the prophylaxis protocol (one dose was held on the day of BMT). Baseline conditions included coronary artery disease, anemia, splenomegaly, and hyperkalemia. Prior to initiation of micafungin, the patient received ciprofloxacin, acyclovir and nystatin,

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accupril, metoprolol, blood transfusions for anemia, and actigall. Moderate bilirubinemia developed on day 14 and micafungin was discontinued on day 16 due to hyperbilirubinemia. The bilirubinemia was considered possibly related to micafungin. Other serious adverse events included pulmonary alveolar hemorrhage (day 21), and grade II GVHD (day 25). Baseline bilirubin was 0.80 mg/dL, 2.6 mg/dL on day 14, 7.6 mg/dL on day 17, and 9.0 mg/dL on day 44. AST and ALT were normal at baseline and until day 44, when AST was 85 U/L, and ALT 194 U/L. Alkaline phosphatase was normal until day 17, when a value of 140 U/L was reported, then 430 U/L on day 44. Multiple other non-serious adverse events were also reported. Other concomitant medications received prior to the development of bilirubinemia included zofran, folate, ativan, compazine, lasix, acyclovir, topical clotrimazole, decadron, zantac, total parenteral nutrition, intralipids, and morphine.

***Medical Officer Comments:** Because the patient was receiving concomitant medications which may cause hepatotoxicity including methotrexate and cyclosporine, the role of micafungin in the development of bilirubinemia in this patient is not clear. Bilirubinemia may have been related to pulmonary hemorrhage and subsequent resorption of hemoglobin.*

Patient 0133501 was a 47 year-old Caucasian female with myelodysplastic syndrome who received an allogeneic bone marrow transplant (BMT). She received micafungin 50 mg/day for 15 days (therapy interrupted one day for BMT). Baseline conditions included anxiety, constipation, anemia, rash, hypoproteinemia, headache, thrombocytopenia, increased LDH, esophagitis, dysuria, inflammation of the catheter site, insomnia, anorexia, asthenia, leukopenia, and pulmonary infiltrate with possible early pneumonia. Medications at the time of enrollment included trazadone, prilosec, valium, colace, oxycodone, benadryl, Tylenol, multivitamin, actigall, vancomycin, calcium phosphate, pentostatin, zofran, triamcinolone, and folic acid. Additionally, she was receiving transfusions of packed red blood cells and platelets. GVHD occurred on day 8, and hyperbilirubinemia was reported as a serious adverse event on day 19. A time course of hepatic laboratory data for this patient is shown in the table below. The bilirubinemia was considered unlikely related to micafungin. Micafungin was discontinued on day 16 due to lack of efficacy. Other concomitant medications prior to development of bilirubinemia included vancomycin, lasix, ativan, decadron, imipenem, compazine, cyclosporine, methotrexate, zantac, total parenteral nutrition, intralipids, magnesium sulfate, solumedrol, morphine, Demerol, prednisone, amphotericin B (days 17-18), Ambisome® (days 19-31).

Hepatic Laboratory Values for Patient 0133501*

Study Day	AST (U/L)	ALT (U/L)	Total bilirubin (mg/dL)	Alkaline phosphatase (U/L)
Baseline	31	49	0.70	60
Day 3	26	40	0.70	58
Day 7	19	26	0.60	55
Day 10	15	15	0.60	44

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Day 14	15	13	0.90	49
Day 18	45	35	1.40	64
Day 45	56	99	15.00	223

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

***Medical Officer Comments:** Mild bilirubinemia developed in this patient several days after stopping micafungin, and was progressive despite micafungin discontinuation. Additionally, the patient received other potential hepatotoxic medications including cyclosporine and methotrexate. I would agree with the investigator who determined that the bilirubinemia was unlikely related to micafungin.*

Patient 0572502 was a 49 year-old Caucasian male with renal cell carcinoma who had been hospitalized for a transplant conditioning regimen. He received micafungin 50 mg/day for 7 days (350 mg) per the prophylaxis protocol. Baseline conditions included hematuria, back pain, and hypertension. Renal insufficiency and liver function test abnormalities developed on day 4 of treatment. The former resolved on day 14, and the latter on day 42. AST and ALT were normal at baseline, but ALT increased to 214 U/L on day 6. Bilirubin and Alkaline phosphatase remained within normal range. BUN and creatinine were normal at baseline, but increased to a maximum of 61 mg/dL and 2.7 mg/dL, respectively on day 6. Other serious adverse events reported were dyspnea, fever, and hypotension (day 4). On day 42 AST was 17 U/L, ALT, 20 U/L, BUN 21 mg/dL, and creatinine 1.60 mg/dL. None of the serious adverse events were considered study drug-related by the investigator. Other concomitant medications prior to day 4 of treatment included colace, amlodipine, granisetron (for nausea), lasix, dexamethasone, norfloxacin, acyclovir, cyclophosphamide, mesna, lorazepam, fludarabine, anti-thymocyte globulin, meperidine, and Tylenol.

***Medical Officer Comments:** Despite the fact that the patient had received other potentially hepatotoxic drugs, including cyclophosphamide, it is feasible that micafungin contributed to liver function test abnormalities, particularly because the laboratory abnormalities were reversible after stopping micafungin, although the same could be true of cyclophosphamide. I would consider the liver function test abnormalities seen in this case possibly related to micafungin.*

Patient number 0702002 was a 38 year old male with acute myelogenous leukemia, hospitalized for an allogeneic peripheral stem cell transplant. The pre-transplant conditioning regimen included busulfan, cylophosphamide, and dexamethasone. The only significant baseline medical condition was hypertension. The patient received micafungin 50 mg/day for 19 days (950 mg) per the prophylaxis protocol. Increased liver function tests were reported as a serious adverse event on day 14. This event was considered unrelated to study drug. No other serious adverse events were reported. The patient completed micafungin upon neutrophil recovery. He developed GVHD on day 31, and was discharged from the hospital on day 82. Baseline AST was 26 U/L, ALT, 36 U/L, bilirubin 1.0 mg/dL, alkaline phosphatase, 91 U/L. On day 14, AST was 95 U/L, ALT,

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283 U/L, bilirubin 0.60 mg/dL, alkaline phosphatase 118 U/L. Liver function test abnormalities were persistent at the end of the study. Other concomitant medications received prior to study day 14 included pepcid, potassium chloride, zestril, Tylenol, dilantin, chlorhexidine, heparin, allopurinol, allegro, compazine, clonidine, lasix, ativan, benadryl, granisetron (antiemetic), phenergan, tacrolimus, acyclovir, methotrexate (day 9), remeron, and calcium gluconate.

***Medical Officer Comments:** This patient received other potentially hepatotoxic medications, including methotrexate, cyclophosphamide, busulfan, and remeron (mirtazapine), so attribution of liver function test abnormalities to micafungin is not straightforward, and seems unlikely.*

Patient Number 1413001 was a 21 year-old Caucasian female with chronic myelogenous leukemia in remission, who received a conditioning regimen of cytarabine, cyclophosphamide, methotrexate and total body irradiation in preparation for a bone marrow transplant (unmatched donor, allogeneic). The patient received micafungin (50 mg/day) for 28 days as antifungal prophylaxis. A bone marrow transplant was performed on day 8, and the patient was neutropenic from days 10-27. Graft vs. host disease (GVHD) was reported as a serious adverse event on day 17, and abnormal liver function tests were reported as a serious adverse event on day 25. Micafungin was discontinued on day 28 due to neutrophil recovery. Other adverse events included neutropenic fever, hypomagnesemia, hypophosphatemia, hypervolemia, dyspnea, nausea (day 2 to 25), vomiting (day 2 to 25), headache, dizziness, anorexia (day 4 to 26), mucositis, sinusitis, bilirubinemia (day 18), hypertension, abnormal vision, chest pain, and hypokalemia. All of the adverse events were considered unlikely to be related to micafungin. Hepatic laboratory values for this patient are shown in the following table.

Hepatic Laboratory values for Patient 1413001*

Study day	AST (U/L)	ALT (U/L)	Total bilirubin (mg/dL)	Alkaline phosphatase (U/L)
Baseline	15	8	2.2	79
Day 4	10	6	0.4	69
Day 7	19	9	0.8	61
Day 11	19	24	0.7	71
Day 14	15	21	0.8	68
Day 18	10	13	1.6	53
Day 21	7	7	2.1	43
Day 25	105	214	1.3	56
Day 29	76	368	1.1	69
Day 36	24	14	0.5	124

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

***Medical Officer Comments:** This patient had modest elevations of transaminases and bilirubin; however, nausea, vomiting and anorexia were reported as adverse*

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events which continued from early in the course of micafungin therapy until the stop date, or shortly thereafter. Additionally, mild abdominal pain was noted on day 29. All of these adverse events could have been due to a mild hepatitis. Notably, transaminases and bilirubin returned to normal by day 36 (11 days after stopping micafungin). Certainly this case is confounded by several factors, including GVHD, which can cause elevation of liver enzymes, and concomitant medications, including ciprofloxacin, cyclophosphamide, cyclosporine, methotrexate, and others, which can also cause elevation of liver enzymes or clinical liver disease.

Patient Number 2492001 was a 13 year old Caucasian female with acute lymphocytic leukemia in remission, who received an allogeneic, matched-sibling peripheral stem cell transplant. Micafungin was initiated at 50 mg/day for antifungal prophylaxis. The patient received 13 days of micafungin, which was discontinued due to lack of efficacy.

AmBisome® was started empirically on day 14, and continued until day 36.

Bilirubinemia was reported as a serious adverse event on day 13, but was considered unrelated to micafungin. Total bilirubin at that time was 1.9 mg/dL (baseline was normal, 0.3 mg/dL), and 38.5 mg/dL on day 36. The patient had developed a respiratory infection on day 14 (*Staphylococcus sp.*), respiratory failure on day 16, died on day 36 due to progressive cardiorespiratory failure and hypotension; while bilirubinemia was considered a contributing factor. Shock was listed as a serious adverse event on day 36. AST and ALT were mildly elevated at baseline (197 U/L, and 167 U/L, respectively), were normal by day 10, and were only minimally elevated on the day of death (77 U/L and 63 U/L), respectively. Alkaline phosphatase was somewhat elevated at baseline (219 U/L), and declined throughout the study period, until day 36 when it was 197 U/L). The patient received multiple concomitant medications, including cyclophosphamide, cefepime, bactrim, methotrexate, cyclosporine, and timentin.

***Medical Officer Comments:** No adverse events suggestive of clinical liver disease were noted from day 13 to 36, while the patient had progressive bilirubinemia, and there was no evidence of significant hepatocellular damage (elevated transaminases), or cholestatic jaundice, or anemia due to hemolysis. I think it is unlikely that micafungin was related to bilirubinemia or to this patient's death.*

Study FG-21-09 (Micafungin for Treatment of Esophageal Candidiasis)

Patient Number 1008 was a 48 year old male with HIV, a CD₄ count of 290 cells/mm³, with a history of pneumonia, and ongoing diarrhea and cachexia. He was not on antiretroviral therapy. He was treated with micafungin 150 mg/day for 14 days for EC. On day 13, he developed confusion and disorientation. On the same day, endoscopy was performed with sedation, and the patient subsequently developed respiratory failure, hepatic failure, renal failure, and severe confusion. None of these serious adverse events was attributed to micafungin. A chest X-ray (CXR) revealed bilateral infiltrates with a small pleural effusion, and the attending physician made a presumptive diagnosis of tuberculosis. The patient had already been receiving bactrim for "bronchitis". The patient

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died on day 15, and cause of death was listed as pulmonary tuberculosis. Ongoing adverse events at the time of death included increased cough, confusion, hepatic failure, kidney failure, and respiratory failure. Laboratories performed on day 14 revealed elevated AST and ALT (both > 10 X ULN), a mild elevation of alkaline phosphatase (< 2X ULN), a mildly elevated BUN of 27 mg/dL mmol/L, and a creatinine of 1.8 mg/dL). These laboratory tests were all normal at baseline, except for the mild elevation of alkaline phosphatase, which remained unchanged. Total bilirubin was normal throughout the study. The table below shows liver function test values during the course of the study. Concomitant medications prior to hepatic failure on day 14 included betaclopramide, loperamide, and cotrimoxazole.

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Hepatic laboratory values for Patient 1008 *

Study Day	AST (U/L)	ALT (U/L)	Total bilirubin (mg/dL)	Alkaline phosphate (U/L)
Baseline	40	19	0.35	125
Day 7	49	19	0.76	132
Day 14	2068	322	0.76	122

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

Medical Officer Comments: The medical monitor suggested the following sequence of events that led to this patient's death: progressive deterioration of lung function causing the initial confusion and disorientation. The sedation given at the time of endoscopy, midazolam, caused the respiratory failure. "Liver and renal decompensation ensued, with possible progressive septicemia, resulting in multi-organ failure and death." The patient was hypotensive on day 14, with a blood pressure of 95/66 on day 14 of treatment, in comparison to 118/80 at baseline. Although this sequence of events is certainly feasible, we cannot rule out an association between the transaminitis and micafungin.

Patient 3103 was a 26 year old Caucasian female with HIV and a CD₄ count of 90 cells/mm³. She received micafungin 50 mg/day for 14 days for esophageal candidiasis. Baseline conditions included weight loss, diarrhea, cough, nausea, abdominal pain, anemia, leukopenia, and hypoalbuminemia. Liver damage was reported as a serious adverse event on day 11. AST, ALT, and bilirubin were normal throughout the study (to day 28). Alkaline phosphatase was elevated at baseline, 312 U/L, and decreased throughout the study to 152 U/L on day 14, and 163 U/L on day 28. The liver damage was considered by the investigator to be multiple liver abscesses, but was considered unrelated to study drug. The patient was diagnosed with non-Hodgkins lymphoma on day 42. Concomitant medicants received prior to the onset of this adverse event included acetaminophen, dimenhydrinate, rehydration salts, cotrimoxazole, isoniazid, and metoclopramide.

Medical Officer Comments: The liver damage described in this case, the abnormalities, presumably observed on a radiographic study, would more likely be related to non-Hodgkins lymphoma or liver abscesses than to micafungin.

Study 03-7-005: (Micafungin for Treatment of Esophageal Candidiasis)

Patient number 10745035 was a 34 year-old South African black male with HIV/AIDS, and a CD₄ count of 97 cells/mm³ at baseline. Other conditions at baseline included generalized lymphadenopathy, cachexia, alcohol abuse, acute diarrhea, anemia, atypical lower respiratory tract infection, and multi-drug-resistant tuberculosis. According to the case report form, an antituberculous medication, rifabutin (isoniazid, rifampin, pyrazinamide, plus ethambutol) was started approximately 7 months prior to study entry, and continued until the day before the patient died. At enrollment the patient was

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receiving DS-24 (nutritional supplementation), bactrim, rifinah (isoniazid and rifampin) for pulmonary tuberculosis, stilpane (paracetamol, meprobamate, plus codeine phosphate), and cough syrup. Voltaren was also listed as a concomitant medication (study days 3-5). He received micafungin 150 mg/day for esophageal candidiasis for 5 days. Micafungin was discontinued on day 5 due to acute liver failure. He was hospitalized on day 6 and died on day 17. Multi-drug resistant tuberculosis (diagnosed day 10) was listed as the primary cause of death. Baseline laboratories included total bilirubin of 16 μ moles/L (within normal range), AST, 121 U/L, ALT, 65 U/L. Laboratory values on day 5 (from an outside, non-study laboratory) revealed a bilirubin of 141 μ moles/L, AST 66 U/L, and ALT of 29 U/L. The investigator considered the hepatic laboratory abnormalities unlikely related to study drug, and did not consider the death related to study drug, although acute liver failure was considered a contributing factor in the patient's death.

Medical Officer Comment: Because of the temporal relationship between administration of micafungin and development of acute liver failure, a possible relationship between hepatic failure and micafungin in this patient cannot be dismissed. In addition, the patient had been treated for pulmonary tuberculosis for at least 5 months prior to hepatic failure and death. Certainly, worsening tuberculosis could have resulted in death. However, acute hepatic failure was probably not related to tuberculosis. NSAIDs such as voltaren (diclofenac) can also cause hepatitis and jaundice, and this patient received voltaren starting one day prior to the report of hepatic failure, potentially confounding this interpretation.

Evaluation of Hepatic Adverse Events of Hepatic Failure and Liver Damage by Panel of Expert Hepatologists

At the request of the DSPIDP, the applicant enlisted an expert panel of hepatologists to review all adverse events (serious and non-serious) of hepatic failure and liver damage in the safety database (19 cases identified) for evidence of any relationship to study drug (either micafungin, placebo, or fluconazole). This panel included

The panel received a patient profile and narrative summary, laboratory, radiology, liver biopsy and autopsy reports, when available. The information was blinded to treatment (micafungin, fluconazole, or placebo). The panel's assessment of any relationship to study drug for these 19 cases is shown in the following table. The panel identified 5 cases of hepatic failure which were possibly related to micafungin, and 1 case possibly related to fluconazole; while all other cases were judged unrelated to study drug. The panel concluded that there was no clear signal for micafungin hepatotoxicity, with the acknowledgement that these cases were extraordinarily complex, with serious underlying diseases and multiple concomitant medications.

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Table 101 Expert Hepatologist Panel Review of Hepatic Failure and Liver Damage
 Adverse Events

Patient number	Study Drug	Adverse Event	Assessment of Relationship to Study Drug-
00384301	Placebo	Hepatic failure	Not related
02194007	Micafungin	Hepatic failure (non-serious)	Not related
10665008	Fluconazole	Hepatic failure	Possibly related
10745035	Micafungin	Hepatic failure	Possibly related
020785	Micafungin	Hepatic failure	Not related
059777	Micafungin	Hepatic failure (non-serious)	Not related
063786	Micafungin	Hepatic failure	Not related
262780	Micafungin	Hepatic failure	Possibly related
262788	Micafungin	Hepatic failure	Not related
474177	Micafungin	Hepatic failure	Possibly related
033885	Micafungin	Liver damage	Not related
287674	Micafungin	Hepatic failure	Possibly related
287679	Micafungin	Hepatic failure	Not related
585271	Micafungin	Liver damage	Not related
0203501	Fluconazole	Hepatic failure	Not related
0372501	Fluconazole	Hepatic failure	Not related
0423004	Micafungin	Hepatic failure	Not related
1008	Micafungin	Hepatic failure	Possibly related
3103	Micafungin	Hepatic failure	Not related

Medical officer Comments: Although the expert panel that 10 of these cases were unrelated, micafungin is not fully exonerated as a potentially hepato-toxic agent, because at least 5 of these serious adverse events were considered possibly related to micafungin.

The DSPIDP also requested a consultation from Dr. John Senior, an experienced hepatologist in the ODS, to review these cases. Dr. Senior found that in 10 of the same 10 cases reviewed by the expert panel, there was no clear causal relationship of study drug to hepatic injury; while in 9 cases (6 micafungin and 3 fluconazole), a possible relationship of the antifungal agent to liver injury was found. Because of multiple confounding factors, there were no cases in the series which were definitely or probably related to the study drug. As summarized in the table below, Dr. Senior's assessment of causality in these cases agreed with the expert panel in 5 of the 6 cases considered possibly related to the study drug by the panel. His assessment also concurred in 9 of the 13 cases considered by the expert panel to be unrelated to study drug.

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Table 102. Summary of Dr. John Senior's Consultation regarding Hepatic Adverse Events in the Clinical Studies

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>					

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Table 102.(continued) Summary of Dr. John Senior's Consultation regarding Hepatic Adverse Events in the Clinical Studies

# 585271, M73c Warsaw, Poland	Mantle cell lymphoma Lung aspergillosis & candida	Mixed liver injury, probable tumor in liver, preexisting before micafungin given	M	U <10% <i>concur</i>	NR
# 2194007, M77c Palo Alto CA	Massive blood loss, aneurysm Repair; no fungal infection	Hepatocellular disease, probably ischemic liver injury	M	U <1% <i>concur</i>	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% <i>concur</i>	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% <i>disagree*</i>	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% <i>concur</i>	NR
# 423004, F40c, Portland OR	Chronic myelogenous leukemia Pulmonary aspergillus sp.	Hepatocellular injury, perhaps added to Leukemic infiltrate before drug	F	P 25% <i>disagree*</i>	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% <i>concur</i>	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% <i>concur</i>	NR

Two additional cases were reviewed by Dr. Senior, at the Division's request. Summaries and conclusions regarding these cases from Dr. Senior's consultation are shown below.

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Table 103. Dr. Senior's Review of Additional Cases of Hepatocellular Injury in Micafungin-Treated Patients

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#107450 31 M34b — South Africa	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 inadequat e informatio n	50%, possible
Comment: death may have resulted from renal failure, but did micafungin cause the acute terminal liver injury also?						

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#104450 08 M45c — Brazil	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 tbc therapy started	HIV: no retroviral therapy, cachexia, CD4 = 13/ μ L inv esophageal candidiasis. neurotoxoplasmosis disseminated tuberculosis; died — (26), of reactivated tuberculosis	micafungin — o — (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 inadequat e informatio n	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.

Medical Officer Comments: Some of the cases of hepatic failure or liver damage were possibly related to micafungin, based on two independent assessments. In some of the cases, addition of the antifungal agent (either micafungin or fluconazole) appeared to aggravate pre-existing liver disease. Dr. Senior also noted that serum bilirubin elevations were out of proportion to AST or ALT levels in a number of these cases in which micafungin was the antifungal agent. He suggested that micafungin-accelerated hemolysis may be at least partly responsible for rises in serum bilirubin concentrations.

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Deaths Due to Hepatic Adverse Events

Among 1980 micafungin-treated patients in the safety database, 2 died of hepatic failure, and 3 died due to veno-occlusive liver disease. These patients along with pertinent details are listed in the table below. None of these deaths were considered related to micafungin.

Table 104. Deaths due to Hepatic Adverse Events in Micafungin-Treated Patients (adapted from Applicant's Table "Item 10", 6 January, 2005)

Patient number	Protocol	Primary Cause of Death	Day of final Micafungin dose	Day of Death	Serious Adverse Events
063311	97-0-041	Veno-occlusive liver disease	15	37	Kidney failure; veno-occlusive liver disease; respiratory failure
020785	98-0-046	Veno-occlusive liver disease	77	94	Hepatic failure
063785	98-0-046	Veno-occlusive liver disease	50	51	Veno-occlusive liver Disease; pneumothorax; respiratory failure
063786	98-0-046	Hepatic failure	7	8	Hepatic failure
287679	98-0-047	Hepatic failure	19	30	Hepatic coma, hepatic failure; diarrhea;, hypoglycemia

Medical Officer Comments: These cases are described in further detail below.

Narrative Summaries for Patients who died due to Hepatic Adverse Events

Patient 063311 was a 53 year-old Caucasian male with non-Hodgkin's lymphoma who underwent an allogeneic peripheral stem cell transplant. He received micafungin 50 mg/day plus fluconazole 400 mg/day as antifungal prophylaxis in protocol 97-0-041 for 15 days following transplantation. Baseline conditions included pulmonary edema. Study medications were stopped at that time due to successful engraftment. Concomitant medications included acyclovir, albuterol, ativan, acid, benadryl, carafate, cefepime, colace, dexamethasone, fentanyl, G-CSF, hydrocortisone, insulin, potassium chloride, lasix, leucovorin, levofloxacin, lipids, lomtil, methotrexate, magnesium sulfate, zofran, pepcid, prochlorperazine, rifampin, sennakot, TPN, Tylenol, and vancomycin. Adverse events during treatment included pulmonary edema, fevers, mucositis, graft versus host disease, involving the skin and eyes, renal failure, mental status changes, and elevated liver enzymes, none of which were considered related to fluconazole or micafungin. The

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patient's liver disease worsened with increasing total bilirubin and ascites, and the he received a transjugular portal-systemic shunt. The patient subsequently developed a coagulopathy and further medical treatment was withdrawn except for mechanical ventilation and comfort care. He died of a respiratory arrest on study day 37. Hepatic laboratory values for this patient are shown in the table below.

Hepatic Laboratory Values for Patient 063311*

Study day	AST U/L	ALT U/L	Alkaline phosphatase U/L	Total bilirubin mg/dL
Baseline	23	--	119	0.9
3	27	19	143	1.0
7	17	21	--	0.7
14	25	21	97 (day 15)	3.3
22	210	136	165	1.9

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

***Medical Officer Comments:** This patient did not have liver disease at baseline, but developed bilirubinemia during treatment with both fluconazole and micafungin. He did not have significant transaminase elevation until more than a week after stopping the antifungal therapy. However, the liver disease was severe enough to require a portal-systemic shunt. The etiology of his liver disease was considered veno-occlusive liver disease, often associated with chemotherapy, which this patient received pre-transplantation. I would concur that the liver disease and death in this patient was not likely related to micafungin.*

Patient 020785 was summarized above in section under serious hepatic adverse events.

Patient 063785 was a 19 year-old Caucasian male with acute lymphocytic leukemia, who received a bone marrow transplant. Baseline conditions included confusion, tachycardia, abdominal distention, peripheral edema, jaundice, petechiae, cord blood graft failure, acute renal failure, hyperbilirubinemia, cardiomegaly, pancytopenia, hypernatremia, elevated liver enzymes, hepatic encephalopathy, metabolic acidosis, and coagulopathy. He was enrolled in study 98-0-046 for after failing AmBisome prophylaxis, and micafungin added to AmBisome® presumed pulmonary aspergillosis. The initial micafungin dose was 75 mg/day, but was increased to 150 mg/day on study day 8, then to 225 mg/day on day 17. Micafungin was discontinued on study day 50 (cumulative dose was 9525 mg) due to an adverse event (veno-occlusive liver disease). During treatment with micafungin and AmBisome®, adverse events included pneumonia (day 11), veno-occlusive liver disease (day 26), and pneumothorax, (day 29). None of the adverse events were attributed to study medication. Concomitant medications included cyclosporine, vancomycin, cefepime, acyclovir, methylprednisolone, neomycin, ofloxacin, flagyl, meropenem, ciprofloxacin, hydrocortisone, and gancyclovir. The patient died on day 51 due to veno-occlusive liver disease, with renal failure listed as a contributing factor. An

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autopsy was performed, but results were not available for review. The death in this patient was not attributed to micafungin.

Medical Officer Comments: This is a highly confounded case of a seriously ill patient with presumed pulmonary aspergillosis post-transplant, multiple concomitant medications, and multiple medical conditions, including liver disease prior to starting micafungin. I would concur that this patient's death was probably not related to micafungin, although certainly it may have contributed to worsening liver dysfunction.

Patient 063786 was summarized above under serious hepatic adverse events.

Patient 287679 was a 51 year-old Caucasian female with pancreatic cancer, who received chemotherapy and subsequently developed candidemia, for which she received amphotericin B. Blood cultures were subsequently positive for *Trichosporon cutaneum* and the patient was enrolled in study 98-0-047 as an efficacy failure patient. Micafungin 50 mg/day (initial dose) was added to amphotericin B. Micafungin doses were increased incrementally, to a maximum dose of 150 mg/day, and she received a total of 2125 mg micafungin over 19 days. Blood cultures on day 20 remained positive for *Trichosporon cutaneum*, and amphotericin B was continued through study day 27. Adverse events during treatment included bacterial peritonitis (day 2), severe hypoglycemia (day 14), *Klebsiella pneumonia* (day 20), and diarrhea (day 21). Concomitant medications included mesna, actilyse, vancomycin, tazocin, amikacin, hydrocortisone, and total parenteral nutrition (TPN). Significant baseline conditions in this patient included liver failure, ascites, abdominal pain, anorexia, cholestasis, liver metastasis, and peritonitis. Liver failure worsened throughout the study, and the patient developed hepatic coma (day 30), and died the same day. The cause of death was liver failure, with contributing conditions of hepatic coma, and metastatic pancreatic carcinoma. The investigator did not consider the death related to micafungin. Hepatic laboratory values for this patient are shown in the following table.

Hepatic Laboratory values for Patient 287679*

Study day	AST U/L	ALT U/L	Alkaline phosphatase U/L	Total bilirubin mg/dL	Albumin g/dL
Day 1	50	59	946	3.1	3.1
Day 7	57	26	1217	9.7	2.9
Day 14	134	63	2601	11.7	2.7
Day 20	159	112	3188	19.6	2.8

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

Medical Officer Comments: This patient had significant liver disease prior to starting micafungin, presumably related to liver metastasis of the primary pancreatic carcinoma. I would concur that this patient's death was not likely