Fujisawa

Mycamine™

(micafungin sodium) For Injection

INTRAVENOUS INFUSION (not for IV bolus injection)

DESCRIPTION:

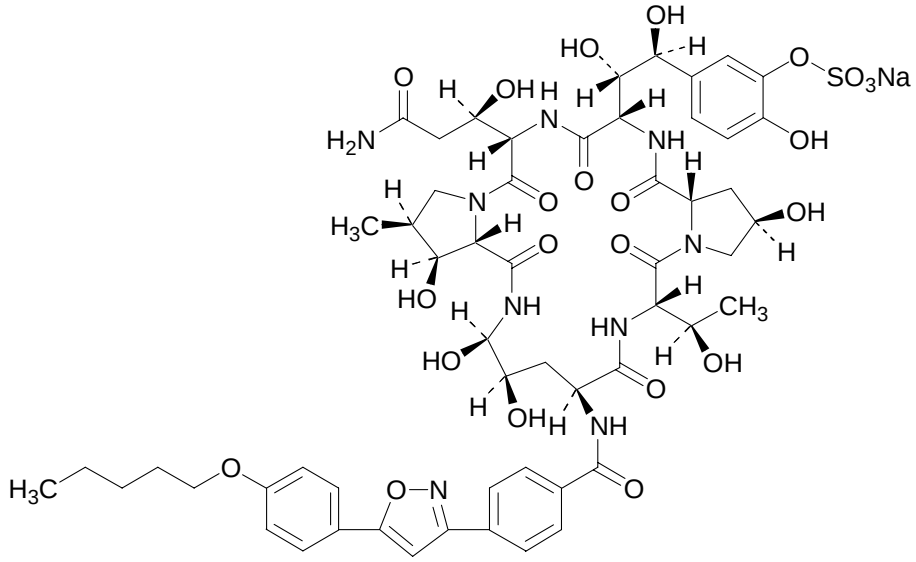
MYCAMINE is a sterile, lyophilized product for intravenous (IV) infusion that contains micafungin sodium. Micafungin sodium is a semisynthetic lipopeptide (echinocandin) synthesized by a chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin inhibits the synthesis of 1, 3-β-D-glucan, an integral component of the fungal cell wall.

Each single-use vial contains 50 mg micafungin sodium, 200 mg lactose, with citric acid and/or sodium hydroxide (used for pH adjustment). MYCAMINE must be diluted with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP (see **DOSAGE AND ADMINISTRATION**). Following reconstitution with 0.9% Sodium Chloride Injection, USP, the resulting pH of the solution is between 5.0-7.0.

Micafungin sodium is chemically designated as:

Pneumocandin A0, 1-[(4*R*,5*R*)-4,5-dihydroxy-N^2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4*S*)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt.

The chemical structure of micafungin sodium is:



The empirical/molecular formula is $C_{56}H_{70}N_9NaO_{23}S$ and the formula weight is 1292.26.

Micafungin sodium is a light-sensitive, hygroscopic white powder that is freely soluble in water, isotonic sodium chloride solution, *N*,*N*-dimethylformamide and dimethylsulfoxide, slightly soluble in methyl alcohol, and practically insoluble in acetonitrile, ethyl alcohol (95%), acetone, diethyl ether and *n*-hexane.

CLINICAL PHARMACOLOGY:

Pharmacokinetics

The pharmacokinetics of micafungin were determined in healthy subjects, hematopoietic stem cell transplant recipients, and patients with esophageal candidiasis up to a maximum daily dose of 8 mg/kg body weight.

The relationship of area under the concentration-time curve (AUC) to micafungin dose was linear over the daily dose range of 50 mg to 150 mg and 3 mg/kg to 8 mg/kg body weight.

Steady-state pharmacokinetic parameters in relevant patient populations after repeated daily administration are presented in the table below.

Table 1: Pharmacokinetic Parameters of Micafungin in Adult Patients

Population	N	Dose (mg)	Pharmacokinetic Parameters (Mean ± Standard Deviation)			
			C_{max} (mcg/mL)	AUC_{0-24} (mcg·h/mL)	$t_{½}$ (h)	Cl (mL/min/kg)
HIV-Positive Patients with EC [Day 14 or 21]	20	50	5.1±1.0	54±13	15.6±2.8	0.300±0.063
	20	100	10.1±2.6	115±25	16.9±4.4	0.301±0.086
	14	150	16.4±6.5	167±40	15.2±2.2	0.297±0.081
HSCT Recipients [Day 7]		*per kg*				
	8	3	21.1±2.84	234±34	14.0±1.4	0.214±0.031
	10	4	29.2±6.2	339±72	14.2±3.2	0.204±0.036
	8	6	38.4±6.9	479±157	14.9±2.6	0.224±0.064
	8	8	60.8±26.9	663±212	17.2±2.3	0.223±0.081

HIV=human immunodeficiency virus; EC = esophageal candidiasis; HSCT = hematopoietic stem cell transplant

Distribution

The mean ± standard deviation volume of distribution of micafungin at terminal phase was 0.39 ± 0.11 L/kg body weight when determined in adult patients with esophageal candidiasis at the dose range of 50 mg to 150 mg.

Micafungin is highly (>99%) protein bound *in vitro*, independent of plasma concentrations over the range of 10 to 100 mcg/mL. The primary binding protein is albumin; however, micafungin, at therapeutically relevant concentrations, does not competitively displace bilirubin binding to albumin. Micafungin also binds to a lesser extent to α_1-acid-glycoprotein.

Metabolism

Micafungin is metabolized to M-1 (catechol form) by arylsulfatase, with further metabolism to M-2 (methoxy form) by catechol-*O*-methyltransferase. M-5 is formed by hydroxylation at the side chain (ω-1 position) of micafungin catalyzed by cytochrome P450 (CYP) isozymes. Even though micafungin is a substrate for and a weak inhibitor of CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for micafungin metabolism *in vivo*. Micafungin is neither a P-glycoprotein substrate nor inhibitor *in vitro*.

In four healthy volunteer studies, the ratio of metabolite to parent exposure (AUC) at a dose of 150 mg/day was 6% for M-1, 1% for M-2, and 6% for M-5. In patients with esophageal candidiasis, the ratio of metabolite to parent exposure (AUC) at a dose of 150 mg/day was 11% for M-1, 2% for M-2, and 12% for M-5.

Excretion

The excretion of radioactivity following a single intravenous dose of ^{14}C-micafungin sodium for injection (25 mg) was evaluated in healthy volunteers. At 28 days after administration, mean urinary and fecal recovery of total radioactivity accounted for 82.5% (76.4 to 87.9%) of the administered dose. Fecal excretion is the major route of elimination (total radioactivity at 28 days was 71.0% of the administered dose).

Special Populations

MYCAMINE disposition has been studied in a variety of populations as described below.

Race and Gender

No dose adjustment of MYCAMINE is required based on gender or race. After 14 daily doses of 150 mg to healthy subjects, micafungin AUC in women was

greater by approximately 23% compared with men, due to smaller body weight. No notable differences among white, black, and Hispanic subjects were seen. The micafungin AUC was greater by 26% in Japanese subjects compared to blacks, due to smaller body weight.

Renal Insufficiency

MYCAMINE does not require dose adjustment in patients with renal impairment. A single 1-hour infusion of 100 mg MYCAMINE was administered to 9 subjects with severe renal dysfunction (creatinine clearance <30 mL/min) and to 9 age-, gender-, and weight-matched subjects with normal renal function (creatinine clearance >80 mL/min). The maximum concentration (C_{max}) and AUC were not significantly altered by severe renal impairment.

Since micafungin is highly protein bound, it is not dialyzable. Supplementary dosing should not be required following hemodialysis.

Hepatic Insufficiency

A single 1-hour infusion of 100 mg MYCAMINE was administered to 8 subjects with moderate hepatic dysfunction (Child-Pugh score 7-9) and 8 age-, gender-, and weight-matched subjects with normal hepatic function. The C_{max} and AUC values of micafungin were lower by approximately 22% in subjects with moderate hepatic insufficiency. This difference in micafungin exposure does not require dose adjustment of MYCAMINE in patients with moderate hepatic impairment. The pharmacokinetics of MYCAMINE have not been studied in patients with severe hepatic insufficiency.

Geriatric

The exposure and disposition of a 50 mg MYCAMINE dose administered as a single 1-hour infusion to 10 healthy subjects aged 66-78 years were not

significantly different from those in 10 healthy subjects aged 20-24 years. No dose adjustment is necessary for the elderly.

MICROBIOLOGY:

Mechanism of Action

Micafungin, the active ingredient in MYCAMINE, inhibits the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls, which is not present in mammalian cells.

Activity *In Vitro*

Micafungin exhibited *in-vitro* activity against *C. albicans, C. glabrata, C. krusei, C. parapsilosis,* and *C. tropicalis.* Standardized susceptibility testing methods for 1,3-β-D-glucan synthesis inhibitors have not been established, and the results of susceptibility studies do not correlate with clinical outcome.

Activity *In Vivo*

Micafungin sodium has shown activity in both mucosal and disseminated murine models of candidiasis. Micafungin sodium, administered to immunosuppressed mice in models of disseminated candidiasis prolonged survival and/or decreased the mycological burden.

Drug Resistance

The potential for development of drug resistance is not known.

INDICATIONS AND USAGE:

MYCAMINE is indicated for:

- Treatment of patients with esophageal candidiasis (see **CLINICAL STUDIES, MICROBIOLOGY**)
- Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (see **CLINICAL STUDIES, MICROBIOLOGY**).

NOTE: The efficacy of MYCAMINE against infections caused by fungi other than *Candida* has not been established.

CONTRAINDICATIONS:

MYCAMINE is contraindicated in patients with hypersensitivity to any component of this product.

WARNINGS:

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

PRECAUTIONS:

Hepatic Effects

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

hepatic function and evaluated for the risk/benefit of continuing MYCAMINE therapy.

Renal Effects

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

Hematological Effects

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

Drug Interactions

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

There was no effect of a single dose or multiple doses of MYCAMINE on mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, and fluconazole pharmacokinetics.

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

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

Carcinogenesis, Mutagenesis and Impairment of Fertility

No life-time studies in animals were performed to evaluate the carcinogenic potential of MYCAMINE. Micafungin sodium was not mutagenic or clastogenic when evaluated in a standard battery of *in-vitro* and *in-vivo* tests (i.e., bacterial reversion - *S. typhimurium*, *E. coli*; chromosomal aberration; intravenous mouse micronucleus).

Male rats treated intravenously with micafungin sodium for 9 weeks showed vacuolation of the epididymal ductal epithelial cells at or above 10 mg/kg (about 0.6 times the recommended clinical dose for esophageal candidiasis, based on body surface area comparisons). Higher doses (about twice the recommended clinical dose, based on body surface area comparisons) resulted in higher epididymis weights and reduced numbers of sperm cells. In a 39-week intravenous study in dogs, seminiferous tubular atrophy and decreased sperm in the epididymis were observed at 10 and 32 mg/kg, doses equal to about 2 and 7

times the recommended clinical dose, based on body surface area comparisons. There was no impairment of fertility in animal studies with micafungin sodium.

Pregnancy Category C

Micafungin sodium administration to pregnant rabbits (intravenous dosing on days 6 to 18 of gestation) resulted in visceral abnormalities and abortion at 32 mg/kg, a dose equivalent to about four times the recommended dose based on body surface area comparisons. Visceral abnormalities included abnormal lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian artery, and dilatation of the ureter.

However, adequate, well-controlled studies were not conducted in pregnant women. Animal studies are not always predictive of human response; therefore, MYCAMINE should be used during pregnancy only if clearly needed.

Nursing Mothers

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

Pediatric Use

The safety and efficacy of MYCAMINE in pediatric patients has not been established in clinical studies.

Geriatric Use

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

subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS:

General

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

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

Clinical Adverse Experiences

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of MYCAMINE cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does provide a basis for identifying adverse events that appear to be related to drug use and for approximating rates.

Esophageal Candidiasis

In a phase 3, randomized, double-blind study for treatment of esophageal candidiasis, a total of 202/260 (77.7%) patients who received MYCAMINE 150 mg/day and 186/258 (72.1%) patients who received intravenous fluconazole 200 mg/day experienced an adverse event. Adverse events considered to be drug-related occurred in 72 (27.7%) and 55 (21.3%) patients in the MYCAMINE and

fluconazole treatment groups, respectively. Drug-related adverse events resulting in discontinuation were reported in 6 (2.3%) MYCAMINE treated patients; and in 2 (0.8%) fluconazole treated patients. Rash and delirium were the most common drug-related adverse events resulting in MYCAMINE discontinuation. Drug-related adverse experiences occurring in ≥0.5% of the patients in either treatment group are shown in Table 2.

Table 2: Common Drug-Related * Adverse Events Among Patients with Esophageal Candidiasis

Adverse Events [(1)] (MedDRA System Organ Class and Preferred Term)	MYCAMINE 150 mg/day n (%)	Fluconazole 200 mg/day n (%)
Number of Patients	260	258
Blood and Lymphatic System Disorders		
Leukopenia	7 (2.7)	2 (0.8)
Neutropenia	3 (1.2)	1 (0.4)
Thrombocytopenia	3 (1.2)	4 (1.6)
Anemia	3 (1.2)	4 (1.6)
Lymphopenia	2 (0.8)	1 (0.4)
Eosinophilia	0	2 (0.8)
Gastrointestinal Disorders		
Nausea	6 (2.3)	7 (2.7)
Abdominal Pain	5 (1.9)	4 (1.6)
Vomiting	3 (1.2)	4 (1.6)
General Disorders and Administration Site Conditions		
Rigors	6 (2.3)	0
Pyrexia	5 (1.9)	1 (0.4)
Infusion Site Inflammation	4 (1.5)	3 (1.2)
Laboratory Tests		
Blood Alkaline Phosphatase Increased	4 (1.5)	4 (1.6)
Aspartate Aminotransferase Increased	2 (0.8)	4 (1.6)
Blood Lactate Dehydrogenase Increased	2 (0.8)	3 (1.2)
Transaminases Increased	2 (0.8)	1 (0.4)
Alanine Aminotransferase Increased	1 (0.4)	5 (1.9)
Metabolism and Nutrition Disorders		
Hypomagnesemia	0	3 (1.2)
Nervous System Disorders		
Headache	7 (2.7)	3 (1.2)
Dizziness	1 (0.4)	2 (0.8)
Somnolence	1 (0.4)	7 (2.7)
Psychiatric Disorders		
Delirium	2 (0.8)	2 (0.8)
Skin and Subcutaneous Tissue Disorders		
Rash	8 (3.1)	5 (1.9)
Pruritus	3 (1.2)	3 (1.2)
Vascular Disorders		
Phlebitis	11 (4.2)	6 (2.3)

Patient base: all randomized patients who received at least 1 dose of trial drug

Common: ≥0.5% in either treatment arm.

*Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.

[(1)] Within a system organ class patients may experience more than 1 adverse event.

Prophylaxis of *Candida* Infections in Hematopoietic Stem Cell Transplant Recipients

A double-blind, phase 3 study was conducted in a total of 882 patients scheduled to undergo an autologous or allogeneic hematopoietic stem cell transplant. The median duration of treatment was 18 days (range 1 to 51 days) in both treatment arms.

All patients who received MYCAMINE (425) and all patients who received fluconazole (457) experienced at least one adverse event during the study. Drug-related adverse events occurred in 64/425 (15.1%) and 77/457 (16.8%) patients in the MYCAMINE and fluconazole treatment groups, respectively. Drug-related adverse events resulting in MYCAMINE discontinuation were reported in 11 (2.6%) patients; while those resulting in fluconazole discontinuation were reported in 16 (3.5%). Drug-related adverse experiences occurring in ≥0.5% of the patients in either treatment group are shown in Table 3.

Table 3: Common Adverse Events Related* to Study Drug in Clinical Study of Prophylaxis of *Candida* Infection in Hematopoietic Stem Cell Transplant Recipients

Adverse Events [(1)] **(MedDRA System Organ Class and Preferred Term)**	**MYCAMINE 50 mg/day n (%)**	**Fluconazole 400 mg/day n (%)**
Number of Patients	425	457
Blood and Lymphatic System Disorders		
Neutropenia	5 (1.2)	4 (0.9)
Anemia	4 (0.9)	3 (0.7)
Febrile neutropenia	4 (0.9)	1 (0.2)
Leukopenia	4 (0.9)	2 (0.4)
Thrombocytopenia	4 (0.9)	5 (1.1)
Gastrointestinal Disorders		
Nausea	10 (2.4)	12 (2.6)
Diarrhea	9 (2.1)	14 (3.1)
Vomiting	7 (1.6)	5 (1.1)
Abdominal pain	4 (0.9)	3 (0.7)
Dyspepsia	3 (0.7)	1 (0.2)
Constipation	1 (0.2)	3 (0.7)
Hiccups	1 (0.2)	3 (0.7)
Abdominal pain upper	0	3 (0.7)
General Disorders and Administrative Site Conditions		
Pyrexia	4 (0.9)	5 (1.1)
Mycosal inflammation	1 (0.2)	3 (0.7)
Rigors	1 (0.2)	5 (1.1)
Fatigue	0	5 (1.1)
Hepatobiliary Disorders		
Hyperbilirubinemia	12 (2.8)	11 (2.4)
Laboratory Tests		
Alanine aminotransferase increased	4 (0.9)	9 (2.0)
Aspartate aminotransferase increased	3 (0.7)	9 (2.0)
Liver function tests abnormal	3 (0.7)	6 (1.3)
Blood creatinine increased	1 (0.2)	3 (0.7)
Drug level increased	1 (0.2)	3 (0.7)
Transaminases increased	1 (0.2)	4 (0.9)
Metabolism and Nutrition Disorders		
Hypokalemia	8 (1.9)	8 (1.8)
Hypophosphatemia	6 (1.4)	4 (0.9)
Hypomagnesemia	5 (1.2)	6 (1.3)
Hypocalcemia	4 (0.9)	4 (0.9)
Appetite decreased	3 (0.7)	0
Nervous System Disorders		
Headache	4 (0.9)	4 (0.9)
Dysgeusia	3 (0.7)	1 (0.2)
Dizziness	0	5 (1.1)
Skin and Subcutaneous Tissue Disorders		
Rash	6 (1.4)	4 (0.9)
Pruritus	4 (0.9)	3 (0.7)

Vascular Disorders		
Flushing	1 (0.2)	6 (1.3)
Hypotension	1 (0.2)	4 (0.9)

Patient base: all randomized patients who received at least 1 dose of trial drug
Common: ≥0.5% in either treatment arm.
*Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.
(1) Within a system organ class patients may experience more than 1 adverse event.

Overall MYCAMINE Safety Experience

The overall safety of MYCAMINE was assessed in 1980 patients and 422 volunteers in 32 clinical studies, including the esophageal candidiasis and prophylaxis studies, who received single or multiple doses of MYCAMINE, ranging from 12.5 mg to ≥150 mg/day.

A total of 606 subjects (patients and volunteers) received at least 150 mg/day MYCAMINE for a minimum of 10 days.

Overall, 2028 of 2402 (84.4%) subjects who received MYCAMINE experienced an adverse event. Adverse events considered to be drug-related were reported in 717 (29.9%) subjects. Drug-related adverse events which occurred in ≥ 0.5% of all subjects who received MYCAMINE in these trials are shown in Table 4.

Table 4: Common Drug-Related* Adverse Events in Subjects† Who Received MYCAMINE in Clinical Trials

Adverse Events [(1)] (MedDRA System Organ Class and Preferred Term)	MYCAMINE n (%)
Number of Patients	2402
Blood and Lymphatic System Disorders	
Leukopenia	38 (1.6)
Neutropenia	29 (1.2)
Thrombocytopenia	20 (0.8)
Anemia	19 (0.8)
Gastrointestinal Disorders	
Nausea	67 (2.8)
Vomiting	58 (2.4)
Diarrhea	38 (1.6)
Abdominal pain	23 (1.0)
Abdominal pain upper	11 (0.5)
General Disorders and Administration Site Conditions	
Pyrexia	37 (1.5)
Rigors	23 (1.0)
Injection site pain	21 (0.9)
Hepatobiliary Disorders	
Hyperbilirubinemia	25 (1.0)
Laboratory Tests	
Aspartate aminotransferase increased	64 (2.7)
Alanine aminotransferase increased	62 (2.6)
Blood alkaline phosphatase increased	48 (2.0)
Liver function tests abnormal	36 (1.5)
Blood creatinine increased	14 (0.6)
Blood urea increased	12 (0.5)
Blood lactate dehydrogenase increased	11 (0.5)
Metabolism and Nutrition Disorders	
Hypokalemia	28 (1.2)
Hypocalcemia	27 (1.1)
Hypomagnesemia	27 (1.1)
Nervous System Disorders	
Headache	57 (2.4)
Dizziness	16 (0.7)
Somnolence	12 (0.5)
Skin and Subcutaneous Tissue Disorders	
Rash	38 (1.6)
Pruritus	18 (0.7)
Vascular Disorders	
Phlebitis	39 (1.6)
Hypertension	14 (0.6)
Flushing	12 (0.5)

Patient base: all randomized patients who received at least 1 dose of trial drug
Common: Incidence of adverse event ≥0.5%.
*Relationship to drug was determined by the investigator to be possibly, probably, or definitely drug-related.
†Subjects included patients and volunteers
(1)Within a system organ class, patients may experience more than 1 adverse event

Other clinically significant adverse events regardless of causality which occurred in these trials are listed below:

- *Blood and lymphatic system disorders*: coagulopathy, hemolysis, hemolytic anemia, pancytopenia, thrombotic thrombocytopenic purpura
- *Cardiac disorders*: arrhythmia, cardiac arrest, cyanosis, myocardial infarction, tachycardia
- *Hepatobiliary disorders*: hepatocellular damage, hepatomegaly, jaundice, hepatic failure
- *General disorders and administration site conditions*: injection site thrombosis
- *Infections and infestations*: infection, pneumonia, sepsis
- *Metabolism and nutrition disorders*: acidosis, anorexia, hyponatremia
- *Musculoskeletal, connective tissue and bone disorders*: arthralgia
- *Nervous system disorders*: convulsions, encephalopathy, intracranial hemorrhage
- *Psychiatric disorders*: delirium
- *Renal and urinary disorders*: anuria, hemoglobinuria, oliguria, renal failure acute, renal tubular necrosis
- *Respiratory, thoracic and mediastinal disorders*: apnea, dyspnea, hypoxia, pulmonary embolism
- *Skin and subcutaneous tissue disorders*: erythema multiforme, skin necrosis, urticaria
- *Vascular disorders*: deep venous thrombosis, hypertension

Postmarketing Adverse Events

The following adverse events have been identified during the post-approval use of micafungin sodium for injection in Japan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency. A causal relationship to micafungin sodium for injection could not be excluded for these adverse events, which included:

- *Hepatobiliary disorders:* hyperbilirubinemia, hepatic function abnormal, hepatic disorder, hepatocellular damage
- *Renal and urinary disorders*: acute renal failure and renal impairment
- *Blood and lymphatic system disorders*: white blood cell count decreased, hemolytic anemia
- *Vascular disorders*: shock

DRUG ABUSE AND DEPENDENCE:

There has been no evidence of either psychological or physical dependence, or withdrawal or rebound effects with MYCAMINE.

OVERDOSAGE:

MYCAMINE is highly protein bound and, therefore, is not dialyzable. No cases of MYCAMINE overdosage have been reported. Repeated daily doses up to 8 mg/kg (maximum total dose of 896 mg) in adult patients have been administered in clinical trials with no reported dose-limiting toxicity. The minimum lethal dose of MYCAMINE is 125 mg/kg in rats, equivalent to 8.1 times the recommended human clinical dose for esophageal candidiasis based on body surface area comparisons.

DOSAGE AND ADMINISTRATION:

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

MYCAMINE DOSAGE

Indication	Recommended Dose (mg per day)
Treatment of Esophageal Candidiasis[1]	150
Prophylaxis of *Candida* Infections in HSCT Recipients[2]	50

[1]In patients treated successfully for esophageal candidiasis, the mean duration of treatment was 15 days (range 10-30 days).

[2]In hematopoietic stem cell transplant (HSCT) recipients who experienced success of prophylactic therapy, the mean duration of prophylaxis was 19 days (range 6-51 days).

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

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

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

Directions for Reconstitution and Dilution

Please read this entire section carefully before beginning reconstitution.

The diluent to be used for reconstitution and dilution is 0.9% Sodium Chloride Injection, USP (without a bacteriostatic agent). Alternatively, 5% Dextrose

Injection, USP, may be used for reconstitution and dilution of MYCAMINE. Solutions for infusion are prepared as follows:

Reconstitution

MYCAMINE 50 mg vial

Aseptically add 5 mL of 0.9% Sodium Chloride Injection, USP (without a bacteriostatic agent) to each 50 mg vial to yield a preparation containing approximately 10 mg micafungin/mL.

As with all parenteral drug products, reconstituted MYCAMINE should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use material if there is any evidence of precipitation or foreign matter. Aseptic technique must be strictly observed in all handling since no preservative or bacteriostatic agent is present in MYCAMINE or in the materials specified for reconstitution and dilution.

Dissolution

To minimize excessive foaming, GENTLY dissolve the MYCAMINE powder by swirling the vial. **DO NOT VIGOROUSLY SHAKE THE VIAL.**

Visually inspect the vial for particulate matter.

Dilution

The diluted solution should be protected from light. It is not necessary to cover the infusion drip chamber or the tubing.

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

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

MYCAMINE is preservative-free. Discard partially used vials.

Infusion Volume and Duration

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

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

STORAGE OF MYCAMINE:

The reconstituted product may be stored in the original vial for up to 24 hours at room temperature, 25° C (77° F).

The diluted infusion should be protected from light and may be stored for up to 24 hours at room temperature, 25° C (77° F).

HOW SUPPLIED:

MYCAMINE is available in cartons of 10 individually packaged 50 mg single-use vials, coated with a light protective film and sealed with a blue flip-off cap. (NDC 0469-3250-10). Unopened vials of lyophilized material must be stored at room temperature, 25° C (77° F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]

ANIMAL TOXICOLOGY:

High doses of micafungin sodium have been associated with irreversible changes to the liver when administered for prolonged periods. In a 13-week intravenous rat study (dosed to 5-times clinical exposure, based on body surface area comparisons), with four- or 13-week recovery periods, colored patches/zones, multinucleated hepatocytes and altered cell foci remained at the end of the recovery period. In a similar 13-week intravenous dog study with 4-week recovery (doses to 10 times clinical exposure), liver discoloration, cellular infiltration and hypertrophy remained visible at the end of the 13-week recovery period.

CLINICAL STUDIES:

Treatment of Esophageal Candidiasis

In two controlled trials involving 763 patients with esophageal candidiasis, 445 adults with endoscopically-proven candidiasis received MYCAMINE, and 318 received fluconazole for a median duration of 14 days (range 1-33 days).

MYCAMINE was evaluated in a phase 3, randomized, double-blind study which compared MYCAMINE 150 mg/day (n=260) to intravenous fluconazole 200 mg/day (n=258) in adults with endoscopically-proven esophageal candidiasis. Most patients in this study had HIV infection, with CD4 cell counts <100 cells/mm^3. Outcome was assessed by endoscopy and by clinical response at the end of treatment. Endoscopic cure was defined as endoscopic grade 0, based on a scale of 0-3. Clinical cure was defined as complete resolution in clinical symptoms of esophageal candidiasis (dysphagia, odynophagia, and retrosternal pain). Overall therapeutic cure was defined as both clinical and endoscopic cure. Mycological eradication was determined by culture, and by histological or cytological evaluation of esophageal biopsy or brushings obtained endoscopically at the end of treatment. As shown in Table 5, endoscopic cure, clinical cure, overall therapeutic cure, and mycological eradication were comparable for patients in the MYCAMINE and fluconazole treatment groups.

Table 5: Endoscopic, Clinical, and Mycological Outcomes for Esophageal Candidiasis at End-of-Treatment

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

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

†calculated as MYCAMINE – fluconazole

Most patients (96%) in this study had *Candida albicans* isolated at baseline. The efficacy of MYCAMINE was evaluated in less than 10 patients with *Candida* species other than *C. albicans*, most of which were isolated concurrently with *C. albicans.*

Relapse was assessed at 2 and 4 weeks post-treatment in patients with overall therapeutic cure at end of treatment. Relapse was defined as a recurrence of clinical symptoms or endoscopic lesions (endoscopic grade > 0). There was no statistically significant difference in relapse rates at either 2 weeks or through 4 weeks post-treatment for patients in the MYCAMINE and fluconazole treatment groups, as shown in Table 6.

Table 6: Relapse of Esophageal Candidiasis at Week 2 and through Week 4 Post-Treatment in Patients with Overall Therapeutic Cure at the End of Treatment

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

*calculated as MYCAMINE – fluconazole; N=number of patients with overall therapeutic cure (both clinical and endoscopic cure at end-of-treatment); †Relapse included patients who died or were lost to follow-up, and those who received systemic anti-fungal therapy in the post-treatment period

In this study, 459 of 518 (88.6%) patients had oropharyngeal candidiasis in addition to esophageal candidiasis at baseline. At the end of treatment 192/230 (83.5%) MYCAMINE treated patients and 188/229 (82.1%) of fluconazole treated patients experienced resolution of signs and symptoms of oropharyngeal candidiasis. Of these, 32.3% in the MYCAMINE group, and 18.1% in the fluconazole group (treatment difference = 14.2%; 95% confidence interval [5.6, 22.8]) had symptomatic relapse at 2 weeks post-treatment. Relapse included patients who died or were lost to follow-up, and those who received systemic antifungal therapy during the post-treatment period. Cumulative relapse at 4 weeks post-treatment was 52.1% in the MYCAMINE group and 39.4% in the fluconazole group (treatment difference 12.7%, 95% confidence interval [2.8, 22.7]).

Prophylaxis of *Candida* Infections in Hematopoietic Stem Cell Transplant Recipients

In a randomized, double-blind study, MYCAMINE (50 mg IV once daily) was compared to fluconazole (400 mg IV once daily) in 882 patients undergoing an autologous or syngeneic (46%) or allogeneic (54%) stem cell transplant.

The status of the patients' underlying malignancy at the time of randomization was: 365 (41%) patients with active disease, 326 (37%) patients in remission, and

195 (22%) patients in relapse. The more common baseline underlying diseases in the 476 allogeneic transplant recipients were: chronic myelogenous leukemia (22%), acute myelogenous leukemia (21%), acute lymphocytic leukemia (13%), and non-Hodgkin's lymphoma (13%). In the 404 autologous and syngeneic transplant recipients the more common baseline underlying diseases were: multiple myeloma (37.1%), non-Hodgkin's lymphoma (36.4%), and Hodgkin's disease (15.6%). During the study, 198 of 882 (22.4%) transplant recipients had proven graft-versus-host disease; and 475 of 882 (53.9%) recipients received immunosuppressive medications for treatment or prophylaxis of graft-versus-host disease.

Study drug was continued until the patient had neutrophil recovery to an absolute neutrophil count (ANC) of $\geq$500 cells/mm^3 or up to a maximum of 42 days after transplant. The average duration of drug administration was 18 days (range 1 to 51 days).

Successful prophylaxis was defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy (usually 18 days), and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-therapy period. A suspected systemic fungal infection was diagnosed in patients with neutropenia (ANC <500 cells/mm^3); persistent or recurrent fever (while ANC <500 cells/mm^3) of no known etiology; and failure to respond to at least 96 hours of broad spectrum antibacterial therapy. A persistent fever was defined as four consecutive days of fever greater than 38ºC. A recurrent fever was defined as having at least one day with temperatures $\geq$ 38.5 ºC after having at least one prior temperature > 38 ºC; or having two days of temperatures > 38 ºC after having at least one prior temperature > 38ºC. Transplant recipients who died or were lost to follow-up during the study were considered failures of prophylactic therapy.

Successful prophylaxis was documented in 80.7% of recipients who received MYCAMINE, and in 73.7% of recipients who received fluconazole (7.0% difference [95% CI = 1.5, 12.5]), as shown in Table 7, along with other study endpoints. The use of systemic antifungal therapy post-treatment was 42% in both groups.

The number of proven breakthrough *Candida* infections was 4 in the MYCAMINE and 2 in the fluconazole group.

The efficacy of MYCAMINE against infections caused by fungi other than *Candida* has not been established.

Table 7: Results from Clinical Study of Prophylaxis of *Candida* Infections in Hematopoietic Stem Cell Transplant Recipients

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

***** Difference (MYCAMINE – Fluconazole): +7.0% [95% CI=1.5, 12.5]

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

[2] Through end-of-therapy

Rx only

Manufactured for:

Fujisawa Healthcare, Inc.
Deerfield, IL 60015-2548

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