HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MYCAMINE® safely and effectively. See Full Prescribing Information for MYCAMINE.

MYCAMINE (micafungin sodium) For Injection; IV Infusion Only
Initial U.S. Approval: 2005

----------INDICATIONS AND USAGE ----------
Mycamine is an echinocandin indicated for:
- Treatment of Patients with Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses (1.1)
- Treatment of Patients with Esophageal Candidiasis (1.2)
- Prophylaxis of *Candida* Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation (1.3)

----------DOSAGE AND ADMINISTRATION----------

Indication	Recommended Reconstituted Dose Once Daily
Treatment of Candidemia , Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses (1.1)	**100 mg**
Treatment of Esophageal Candidiasis (1.2)	**150 mg**
Prophylaxis of *Candida* Infections (1.3)	**50 mg**

- A loading dose is not required. Infuse over 1 hour. (2.5)

See Full Prescribing Information for IV administration instructions (2)

----------DOSAGE FORMS AND STRENGTHS----------
50 mg and 100 mg single-use vials (3)

----------CONTRAINDICATIONS----------
Mycamine is contraindicated in persons with known hypersensitivity to micafungin, any component of Mycamine, or other echinocandins. (4)

----------WARNINGS AND PRECAUTIONS----------
Hypersensitivity Reactions
- Anaphylaxis and anaphylactoid reactions (including shock) have been observed. Discontinue Mycamine and administer appropriate treatment (5.1)

Hematological Effects
- Isolated cases of acute intravascular hemolysis, hemolytic anemia and hemoglobinuria have been reported (5.2)

Hepatic Effects
- Abnormalities in liver function tests; isolated cases of hepatic impairment, hepatitis, and hepatic failure have been observed (5.3)

Renal Effects
- Elevations in BUN and creatinine; isolated cases of renal impairment or acute renal failure have been reported (5.4)

Monitor closely patients who develop clinical or laboratory evidence of the above reactions and evaluate risk/benefit of continuing Mycamine therapy. (5)

----------ADVERSE REACTIONS----------
- Most common adverse reactions include diarrhea, nausea, vomiting, pyrexia, hypokalemia, thrombocytopenia, and headache (6)
- Histamine-mediated symptoms including rash, pruritus, facial swelling, and vasodilatation (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact: Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Monitor for sirolimus, itraconazole or nifedipine toxicity, and dosage of sirolimus, itraconazole or nifedipine should be reduced, if necessary (7)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy - No human data. Adverse effects in animals. Use if potential benefits of treatment outweigh potential fetal risk (8.1)
- Nursing Mothers - Caution should be exercised if administered to a nursing woman (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Mycamine® is indicated for:

1.1 Treatment of Patients with Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses [see *Clinical Studies* (*14.1*)].

Mycamine has not been adequately studied in patients with endocarditis, osteomyelitis and meningitis due to *Candida* infections.

1.2 Treatment of Patients with Esophageal Candidiasis [see *Clinical Studies (14.2)*].

1.3 Prophylaxis of *Candida* Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation [see *Clinical Studies* (*14.3*)].

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

2 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.

Table 1. Mycamine Dosage

Indication	**Recommended Reconstituted Dose Once Daily**
Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses*	**100 mg**
Treatment of Esophageal Candidiasis†	**150 mg**
Prophylaxis of *Candida* Infections in HSCT Recipients‡	**50 mg**

* In patients treated successfully for candidemia and other *Candida* infections, the mean duration of treatment was 15 days (range 10-47 days).
† In patients treated successfully for esophageal candidiasis, the mean duration of treatment was 15 days (range 10-30 days).
‡ 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).

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

No dosing adjustments are required based on race, gender, or in patients with severe renal impairment or in patients with mild, moderate, or severe hepatic impairment. [see *Use in Specific Populations* (*8*)].

No dose adjustment for Mycamine is required with concomitant use of mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, voriconazole, itraconazole, amphotericin B, ritonavir, or rifampin. [see *Drug Interactions* (*7*)].

2.1 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:

2.2 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**.

Mycamine 100 mg vial
Aseptically add 5 mL of 0.9% Sodium Chloride Injection, USP (without a bacteriostatic agent) to each **100 mg vial** to yield a preparation containing approximately **20 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.

2.3 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.

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

- For treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses: add 100 mg of reconstituted Mycamine [see *Dosage and Administration* (*2.1*)] into 100 mL of 0.9% Sodium Chloride Injection, USP or 100 mL of 5% Dextrose Injection, USP.

- For treatment of esophageal candidiasis: add 150 mg of reconstituted Mycamine [see *Dosage and Administration* (*2.1*)] into 100 mL of 0.9% Sodium Chloride Injection, USP or 100 mL of 5% Dextrose Injection, USP.

- For prophylaxis of *Candida* infections: add 50 mg of reconstituted Mycamine [see *Dosage and Administration* (*2.1*)] into 100 mL of 0.9% Sodium Chloride Injection, USP or 100 mL of 5% Dextrose Injection, USP.

Mycamine is preservative-free. Discard partially used vials.

2.5 Infusion Volume and Duration

Mycamine should be administered by intravenous infusion only. Infuse over one hour. More rapid infusions may result in more frequent histamine mediated reactions.

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

3 DOSAGE FORMS AND STRENGTHS
50 mg and 100 mg single-use vials

4 CONTRAINDICATIONS
Mycamine is contraindicated in persons with known hypersensitivity to micafungin, any component of Mycamine, or other echinocandins.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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.

5.2 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 reaction 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.

5.3 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 impairment, hepatitis, and 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.

5.4 Renal Effects

Elevations in BUN and creatinine, and isolated cases of significant renal impairment or acute renal failure have been reported in patients who received Mycamine. In fluconazole-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.

6 ADVERSE REACTIONS

6.1 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 reactions tended to occur more often in patients receiving Mycamine via peripheral intravenous administration.

6.2 Clinical Trials Experience

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.

Candidemia and Other Candida Infections

In a randomized, double-blind study for treatment of candidemia and other *Candida* infections, treatment emergent adverse events occurred in 183/200 (91.5%), 187/202 (92.6%) and 171/193 (88.6%) patients in the Mycamine 100 mg/day, Mycamine 150mg/day, and caspofungin (70/50mg/day) treatment groups, respectively. Treatment emergent adverse events occurring in ≥5% of the patients in any treatment study groups are shown in Table 2.

Table 2. *Treatment Emergent Adverse Events in Patients with Candidemia and Other *Candida* Infections

MedDRA v 5.0 System Organ Class Preferred Term †	Micafungin 100 mg (n = 200)	Micafungin 150 mg (n = 202)	Caspofungin‡ (n = 193)
All Systems, Any Adverse Event	183 (91.5)	187 (92.6)	171 (88.6)
Gastrointestinal Disorders	**81 (40.5)**	**89 (44.1)**	**76 (39.4)**
Diarrhea NOS	15 (7.5)	26 (12.9)	14 (7.3)
Nausea	19 (9.5)	15 (7.4)	20 (10.4)
Vomiting NOS	18 (9)	15 (7.4)	16 (8.3)
Abdominal Pain NOS	5 (2.5)	4 (2)	10 (5.2)
Metabolism and Nutrition Disorders	**77 (38.5)**	**83 (41.1)**	**73 (37.8)**
Hypokalemia	28 (14)	34 (16.8)	28 (14.5)
Hypomagnesaemia	11 (5.5)	17 (8.4)	14 (7.3)
Hypoglycemia NOS	12 (6)	14 (6.9)	9 (4.7)
Hypernatremia	8 (4)	13 (6.4)	8 (4.1)
Hyperkalemia	10 (5)	8 (4)	5 (2.6)
Infections and Infestations	**67 (33.5)**	**81 (40.1)**	**59 (30.6)**
Bacteremia	10 (5)	18 (8.9)	11 (5.7)
Septic Shock	15 (7.5)	9 (4.5)	9 (4.7)
Sepsis NOS	11 (5.5)	10 (5)	11 (5.7)
Pneumonia NOS	3 (1.5)	11 (5.4)	4 (2.1)
General Disorders/Administration Site Conditions	**59 (29.5)**	**56 (27.7)**	**51 (26.4)**
Pyrexia	14 (7)	22 (10.9)	15 (7.8)
Edema Peripheral	11 (5.5)	12 (5.9)	14 (7.3)
Vascular Disorders	**43 (21.5)**	**47 (23.3)**	**36 (18.7)**
Hypotension NOS	20 (10)	12 (5.9)	15 (7.8)
Hypertension NOS	6 (3)	10 (5)	12 (6.2)
Investigations	**36 (18)**	**49 (24.3)**	**37 (19.2)**
Blood Alkaline Phosphatase NOS Increased	11 (5.5)	16 (7.9)	8 (4.1)
Blood/Lymphatic System Disorders	**38 (19)**	**45 (22.3)**	**37 (19.2)**
Thrombocytopenia	8 (4)	8 (4)	11 (5.7)
Anemia NOS	5 (2.5)	6 (3)	13 (6.7)
Anemia NOS Aggravated	4 (2)	10 (5)	5 (2.6)
Cardiac Disorders	**35 (17.5)**	**48 (23.8)**	**36 (18.7%)**
Tachycardia NOS	6 (3)	7 (3.5)	13 (6.7%)
Bradycardia NOS	5 (2.5)	10 (5)	8 (4.1%)
Atrial Fibrillation	5 (2.5)	10 (5)	0
Nervous System Disorders	**21 (10.5)**	**42 (20.8)**	**32 (16.6)**
Headache NOS	4 (2)	10 (5)	11 (5.7)
Skin/Subcutaneous Tissue Disorders	**26 (13)**	**34 (16.8)**	**33 (17.1)**
Decubitus Ulcer	9 (4.5)	12 (5.9)	9 (4.7)
Psychiatric Disorders	**31 (15.5)**	**27 (13.4)**	**33 (17.1)**
Insomnia	11 (5.5)	8 (4)	16 (8.3)

Patient base: all randomized patients who received at least 1 dose of trial drug
Common: ≥5% in any treatment arm.
* During IV treatment + 3 days
† Within a system organ class patients may experience more than 1 adverse event.
‡ 70 mg loading dose on day 1 followed by 50 mg/day thereafter (caspofungin)

In a second, supportive, randomized, double-blind study for treatment of candidemia and other *Candida* infections, treatment emergent adverse events occurred in 245/264 (92.8%) and 250/265 (94.3%) patients in the Mycamine (100 mg/day) and AmBisome (3 mg/kg/day) treatment groups, respectively. The most common treatment emergent adverse events occurring in ≥5% of the Mycamine-treated patients at least 16 years of age were: pyrexia (15.2% vs. 17%); hypokalemia (16.7% vs. 20.8%); nausea (9.5% vs. 8.3%); diarrhea (10.6% vs. 11.3%) and vomiting (12.9% vs. 9.4%), in the Mycamine and AmBisome treatment groups, respectively. Other important treatment emergent adverse events that occurred at <5% frequency were abnormal liver function tests (4.2% vs. 3%); increased aspartate aminotransferase (2.7% vs. 1.9%), and increased blood alkaline phosphatase (3% vs. 2.3%), in the Mycamine and AmBisome treatment groups, respectively.

Esophageal Candidiasis

In a 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. Treatment emergent adverse events resulting in discontinuation were reported in 17 (6.5%) Mycamine treated patients; and in 12 (4.7%) fluconazole treated patients. Treatment emergent adverse events occurring in ≥5% of the patients in either treatment group are shown in Table 3.

Table 3. *Treatment Emergent Adverse Events in Patients with Esophageal Candidiasis

Adverse Events † **(MedDRA System Organ Class and Preferred Term)**	**Mycamine 150 mg/day n (%)**	**Fluconazole 200 mg/day n (%)**
Number of Patients	260	258
All Systems, Any Adverse Event	**202 (77.7)**	**186 (72.1)**
Gastrointestinal Disorders	**84 (32.3)**	**93 (36)**
Diarrhea NOS	27 (10.4)	29 (11.2)
Nausea	20 (7.7)	23 (8.9)
Vomiting NOS	17 (6.5)	17 (6.6)
Abdominal Pain NOS	10 (3.8)	15 (5.8)
General Disorders/Administration Site Conditions	**52 (20)**	**45 (17.4)**
Pyrexia	34 (13.1)	21 (8.1)
Nervous System Disorders	**42 (16.2)**	**40 (15.5)**
Headache NOS	22 (8.5)	20 (7.8)
Blood/Lymphatic System Disorders	**38 (14.6)**	**43 (16.7)**
Anemia NOS	8 (3.1)	16 (6.2)
Vascular Disorders	**54 (20.8)**	**21 (8.1)**
Phlebitis NOS	49 (18.8)	13 (5)
Skin and Subcutaneous Tissue Disorders	**36 (13.8)**	**26 (10.1)**
Rash NOS	14 (5.4)	6 (2.3)
Psychiatric Disorders	**20 (7.7)**	**21 (8.1)**
Insomnia	9 (3.5)	13 (5)

Patient base: all randomized patients who received at least 1 dose of trial drug
Common: ≥5% in either treatment arm.
* During treatment + 3 days.
† 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 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. Treatment emergent adverse events resulting in Mycamine discontinuation were reported in 18 (4.2%) patients; while those resulting in fluconazole discontinuation were reported in 33 (7.2%). Treatment emergent adverse events occurring in ≥15% of the patients in either treatment group are shown in Table 4.

Table 4. *Treatment Emergent Adverse Events During Prophylaxis of *Candida* Infection in Hematopoietic Stem Cell Transplant Recipients

Adverse Events † (MedDRA System Organ Class and Preferred Term)	Mycamine 50 mg/day n (%)	Fluconazole 400 mg/day n (%)
Number of Patients	425	457
All Systems, Any Adverse Events	**425 (100)**	**457 (100)**
Gastrointestinal Disorders	**421 (99.1)**	**449 (98.2)**
Diarrhea NOS	302 (71.1)	348 (76.1)
Nausea	296 (69.6)	309 (67.6)
Vomiting NOS	281 (66.1)	307 (67.2)
Constipation	129 (30.4)	143 (31.3)
Dyspepsia	104 (24.5)	122 (26.7)
Abdominal Pain NOS	115 (27.1)	107 (23.4)
General Disorders/Administration Site Conditions	**410 (96.5)**	**440 (96.3)**
Mucosal Inflammation NOS	322 (75.8)	360 (78.8)
Pyrexia	191 (44.9)	218 (47.7)
Fatigue	126 (29.6)	145 (31.7)
Rigors	112 (26.4)	118 (25.8)
Edema Peripheral	88 (20.7)	100 (21.9)
Blood and Lymphatic System Disorders	**408 (96)**	**429 (93.9)**
Neutropenia	320 (75.3)	327 (71.6)
Thrombocytopenia	307 (72.2)	304 (66.5)
Anemia NOS	151 (35.5)	173 (37.9)
Febrile Neutropenia	155 (36.5)	166 (36.3)
Metabolism and Nutrition Disorders	**385 (90.6)**	**428 (93.7)**
Hypomagnesaemia	214 (50.4)	256 (56)
Hypokalemia	209 (49.2)	232 (50.8)
Anorexia	116 (27.3)	121 (26.5)
Appetite Decreased NOS	87 (20.5)	93 (20.4)
Fluid Overload	74 (17.4)	96 (21)
Hyperglycemia NOS	68 (16)	92 (20.1)
Hypocalcemia	72 (16.9)	82 (17.9)
Fluid Retention	69 (16.2)	66 (14.4)
Respiratory, Thoracic and Mediastinal Disorders	**291 (68.5)**	**336 (73.5)**
Cough	98 (23.1)	112 (24.5)
Epistaxis	49 (11.5)	84 (18.4)
Dyspnea NOS	54 (12.7)	64 (14)
Skin and Subcutaneous Tissue Disorders	**290 (68.2)**	**316 (69.1)**
Rash NOS	110 (25.9)	102 (22.3)
Pruritus NOS	75 (17.6)	87 (19.)
Erythema	48 (11.3)	71 (15.5)
Nervous System Disorders	**261 (61.4)**	**268 (58.6)**
Headache NOS	179 (42.1)	165 (36.1)
Dizziness	55 (12.9)	83 (18.2)
Psychiatric Disorders	**257 (60.5)**	**249 (54.5)**
Insomnia	152 (35.8)	146 (31.9)
Anxiety	95 (22.4)	92 (20.1)
Vascular Disorders	**224 (52.7)**	**267 (58.4)**
Hypertension NOS	91 (21.4)	113 (24.7)
Hypotension NOS	79 (18.6)	89 (19.5)
Flushing	47 (11.1)	70 (15.3)
Infections and Infestations	**178 (41.9)**	**208 (45.5)**
Bacteremia	66 (15.5)	86 (18.8)
Cardiac Disorders	**147 (34.6)**	**162 (35.4)**
Tachycardia NOS	105 (24.7)	102 (22.3)

Patient base: all randomized patients who received at least 1 dose of trial drug
Common: ≥15% in either treatment arm.
* During treatment + 3 days
† Within a system organ class patients may experience more than 1 adverse event.

Overall Mycamine Safety Experience in Clinical Trials

The overall safety of Mycamine was assessed in 3083 patients and 501 volunteers in 41 clinical studies, including the invasive candidiasis, esophageal candidiasis and prophylaxis studies, who received single or multiple doses of Mycamine, ranging from 12.5 mg to ≥150 mg/day. Treatment emergent adverse events which occurred in ≥ 5% of all patients who received Mycamine in these trials are shown in Table 5.

Overall, 2810 of 3083 (91.1%) patients who received Mycamine experienced an adverse event.

Clinically significant adverse events regardless of causality or incidence which occurred in these trials are listed below:

- *Blood and lymphatic system disorders*: coagulopathy, febrile neutropenia, hemolysis, hemolytic anemia, pancytopenia, thrombotic thrombocytopenic purpura
- *Cardiac disorders*: arrhythmia, atrial fibrillation, cardiac arrest, cyanosis, hypotension, myocardial infarction, tachycardia
- *Gastrointestinal disorders*: abdominal pain upper, dyspepsia
- *General disorders and administration site conditions*: injection site thrombosis
- *Hepatobiliary disorders*: hepatocellular damage, hepatomegaly, jaundice, hepatic failure
- *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

Table 5. *Treatment Emergent Adverse Events in Patients Who Received Mycamine in Clinical Trials

Adverse Events † **(MedDRA System Organ Class and Preferred Term)**	**Mycamine** **n (%)**
Number of Patients	**3083**
All Systems, Any Adverse Event	**2810 (91.1)**
Gastrointestinal Disorders	**1764 (57.2)**
Diarrhea NOS	718 (23.3)
Nausea	679 (22)
Vomiting NOS	669 (21.7)
Constipation	341 (11.1)
Abdominal Pain	300 (9.7)
Dyspepsia	176 (5.7)
General Disorders/Administration Site Conditions	**1407 (45.6)**
Pyrexia	618 (20)
Mucosal Inflammation NOS	438 (14.2)
Rigors	281 (9.1)
Edema Peripheral	209 (6.8)
Fatigue	198 (6.4)
Metabolism and Nutrition Disorders	**1316 (42.7)**
Hypokalemia	556 (18)
Hypomagnesemia	409 (13.3)
Hypocalcemia	201 (6.5)
Anorexia	190 (6.2)
Hyperglycemia NOS	173 (5.6)
Fluid Overload	155 (5)
Infections and Infestations	**1227 (39.8)**

Bacteremia	185 (6)
Sepsis NOS	156 (5.1)
Respiratory, Thoracic and Mediastinal Disorders	**1108 (35.9)**
Cough	251 (8.1)
Dyspnea NOS	182 (5.9)
Epistaxis	172 (5.6)
Blood and Lymphatic System Disorders	**1047 (34)**
Thrombocytopenia	474 (15.4)
Neutropenia	436 (14.1)
Anemia NOS	302 (9.8)
Febrile Neutropenia	187 (6.1)
Investigations	**989 (32.1)**
Aspartate Aminotransferase Increased	172 (5.6)
Blood Alkaline Phosphatase NOS Increased	168 (5.4)
Alanine Aminotransferase Increased	165 (5.4)
Skin and Subcutaneous Tissue Disorders	**940 (30.5)**
Rash NOS	269 (8.7)
Pruritus NOS	187 (6.1)
Nervous System Disorders	**889 (28.8)**
Headache NOS	489 (15.9)
Psychiatric Disorders	**727 (23.6)**
Insomnia	303 (9.8)
Anxiety	198 (6.4)
Vascular Disorders	**867 (28.1)**
Hypotension NOS	279 (9.1)
Hypertension NOS	214 (6.9)
Phlebitis NOS	172 (5.6)
Musculoskeletal and Connective Tissue Disorders	**579 (18.8)**
Back Pain	166 (5.4)
Cardiac Disorders	**563 (18.3)**
Tachycardia NOS	231 (7.5)

Patient base: all randomized patients who received at least 1 dose of trial drug
Common: Incidence of adverse event ≥5%.
* During treatment + 3 days
† Within a system organ class patients may experience more than 1 adverse event

6.3 Postmarketing Adverse Reactions

The following adverse reactions have been identified during the post-approval use of micafungin sodium for injection. 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 reactions, which included:

- *Blood and lymphatic system disorders*: white blood cell count decreased, hemolytic anemia, disseminated intravascular coagulation
- *Hepatobiliary disorders:* hyperbilirubinemia, hepatic function abnormal, hepatic disorder, hepatocellular damage
- *Renal and urinary disorders*: acute renal failure and renal impairment
- *Skin and subcutaneous tissue disorders:* Stevens-Johnson syndrome, toxic epidermal necrolysis
- *Vascular disorders*: shock

7 DRUG INTERACTIONS

A total of 14 clinical drug-drug interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between Mycamine and amphotericin B, mycophenolate mofetil, cyclosporine, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, itraconazole,

voriconazole, 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, fluconazole, and voriconazole 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. Itraconazole AUC and C_{max} were increased by 22% and 11%, respectively.

Patients receiving sirolimus, nifedipine or itraconazole in combination with Mycamine should be monitored for sirolimus, nifedipine or itraconazole toxicity and the sirolimus, nifedipine or itraconazole dosage should be reduced if necessary [see *Clinical Pharmacology* (*12*)].

Micafungin is neither a substrate nor an inhibitor of P-glycoprotein and, therefore, would not be expected to alter P-glycoprotein-mediated drug transport activity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of micafungin in pregnant women. Animal reproduction studies in rabbits showed visceral abnormalities and increased abortion at 4 times the recommended human dose. However, animal studies are not always predictive of human response. Micafungin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When pregnant rabbits were given 4 times the recommended human dose, there were increased abortion and visceral abnormalities including abnormal lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian artery, and dilatation of the ureter [see *Nonclinical Toxicology (13.2)*].

8.3 Nursing Mothers

It is not known whether micafungin is excreted in human milk. Caution should be exercised when Mycamine is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

A total of 418 subjects in clinical studies of Mycamine were 65 years of age and older, and 124 subjects were 75 years of age and older. No overall differences in safety and 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.

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.

8.6 Use in Patients with Renal Impairment

Mycamine does not require dose adjustment in patients with renal impairment. Supplementary dosing should not be required following hemodialysis [see *Pharmacokinetics* (*12.3*)].

8.7 Use in Patients with Hepatic Impairment

Dose adjustment of Mycamine is not required in patients with mild, moderate, or severe hepatic impairment [see *Pharmacokinetics* (*12.3*)].

8.8 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 19% in Japanese subjects compared to blacks, due to smaller body weight.

9 DRUG ABUSE AND DEPENDENCE

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

10 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.

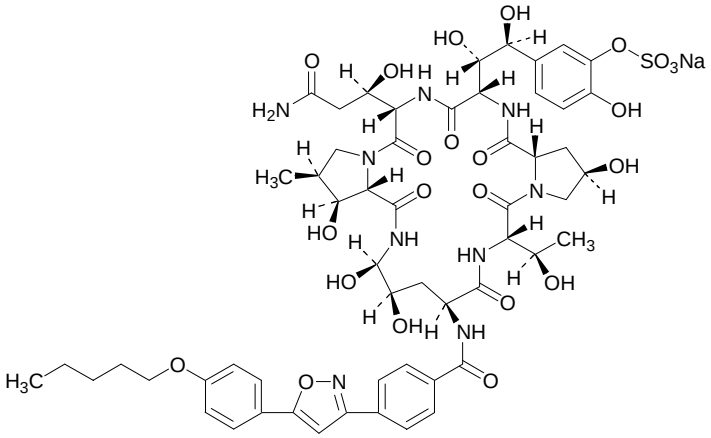
11 DESCRIPTION

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 or 100 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* (*2*)]. Following reconstitution with 0.9% Sodium Chloride Injection, USP, the resulting pH of the solution is between 5-7.

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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Micafungin is a member of the echinocandin class of antifungal agents [see *Clinical Pharmacology, Microbiology (12.4)]*.

12.3 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 6. Pharmacokinetic Parameters of Micafungin in Adult Patients

Population	n	Dose (mg)	Pharmacokinetic Parameters (Mean ± Standard Deviation)			
			C_{max} (mcg/mL)	$AUC_{0\text{-}24}$* (mcg·h/mL)	$t_{½}$ (h)	Cl (mL/min/kg)
Patients with IC† [Day 1]	20	100	5.7±2.2	83±51	14.5±7.0	0.359 ±0.179
[Steady State]	20	100	10.1±4.4	97±29	13.4±2.0	0.298 ±0.115
HIV‡-Positive Patients with EC§ [Day 1]	20	50	4.1±1.4	36±9	14.9±4.3	0.321 ±0.098
	20	100	8.0±2.4	108±31	13.8±3.0	0.327 ±0.093
	14	150	11.6±3.1	151±45	14.1±2.6	0.340 ±0.092
[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
		per kg				
HSCT¶ Recipients [Day 7]	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

* $AUC_{0\text{-infinity}}$ is presented for day 1; $AUC_{0\text{-}24}$ is presented for steady state.
† candidemia or other *Candida* Infections
‡ human immunodeficiency virus
§ esophageal candidiasis
¶ hematopoietic stem cell transplant

Patients with Renal Impairment

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 impairment (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.

Patients with Hepatic Impairment

- A single 1-hour infusion of 100 mg Mycamine was administered to 8 subjects with moderate hepatic impairment (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 impairment compared to normal subjects. This difference in micafungin exposure does not require dose adjustment of Mycamine in patients with moderate hepatic impairment.

- A single 1-hour infusion of 100 mg Mycamine was administered to 8 subjects with severe hepatic impairment (Child-Pugh score 10-12) and 8 age-, gender-, ethnic- and weight-matched subjects with normal hepatic function. The mean C_{max} and AUC values of micafungin were lower by approximately 30% in subjects with severe hepatic impairment compared to normal subjects. The mean C_{max} and AUC values of M-5 metabolite were approximately 2.3-fold higher in subjects with severe hepatic impairment compared to normal subjects; however, this exposure (parent and metabolite) was comparable to that in patients with systemic *Candida* infection. Therefore, no micafungin dose adjustment is necessary in patients with severe hepatic impairment.

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 α1-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% of the administered dose).

12.4 Microbiology

Mechanism of Action

Micafungin 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. guilliermondii, C. krusei, C. parapsilosis* and *C. tropicalis.* Standardized susceptibility testing methods for 1,3-β-D-glucan synthesis inhibitors have recently been proposed by the CLSI, however, the correlation between the results of susceptibility studies and clinical outcome has not been established.

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

Mutants of *Candida* with reduced susceptibility to micafungin have been identified in some patients during treatment suggesting a potential for development of drug resistance. The incidence of drug resistance by various clinical isolates of *Candida* species is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Hepatic carcinomas and adenomas were observed in a 6-month intravenous toxicology study with an 18-month recovery period of micafungin sodium in rats designed to assess the reversibility of hepatocellular lesions.

Rats administered micafungin sodium for 3 months at 32 mg/kg/day (corresponding to 8 times the highest recommended human dose [150 mg/day], based on AUC comparisons), exhibited colored patches/zones, multinucleated hepatocytes and altered hepatocellular foci after 1 or 3 month recovery periods, and adenomas were observed after a 21-month recovery period. Rats administered micafungin sodium at the same dose for 6 months exhibited adenomas after a 12-month recovery period; after an 18-month recovery period, an increased incidence of adenomas was observed, and additionally, carcinomas were detected. A lower dose of micafungin sodium (equivalent to 5 times the human AUC) in the 6-month rat study resulted in a lower incidence of adenomas and carcinomas following 18 months recovery. The duration of micafungin dosing in these rat studies (3 or 6 months) exceeds the usual duration of Mycamine dosing in patients, which is typically less than 1 month for treatment of esophageal candidiasis, but dosing may exceed 1 month for *Candida* prophylaxis.

Although the increase in carcinomas in the 6-month rat study did not reach statistical significance, the persistence of altered hepatocellular foci subsequent to micafungin dosing, and the presence of adenomas and carcinomas in the recovery periods suggest a causal relationship between micafungin sodium, altered hepatocellular foci, and hepatic neoplasms. Whole-life carcinogenicity studies of Mycamine in animals have not been conducted, and it is not known whether the hepatic neoplasms observed in treated rats also occur in other species, or if there is a dose threshold for this effect.

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.

13.2 Animal Toxicology and/or Pharmacology

High doses of micafungin sodium (5 to 8 times the highest recommended human dose, based on AUC comparisons) have been associated with irreversible changes to the liver when administered for 3 or 6 months, and these changes may be indicative of pre-malignant processes [see *Nonclinical Toxicology (13.1)*].

Reproductive Toxicology Studies

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.

14 CLINICAL STUDIES

14.1 Treatment of Candidemia and Other *Candida* Infections

Two dose levels of Mycamine were evaluated in a randomized, double-blind study to determine the efficacy and safety versus caspofungin in patients with invasive candidiasis and candidemia. Patients were randomized to receive once daily intravenous infusions (IV) of Mycamine, either 100 mg/day or 150 mg/day or caspofungin (70 mg loading dose followed by 50 mg maintenance dose). Patients in both study arms were permitted to switch to oral fluconazole after at least 10 days of intravenous therapy, provided they were non-neutropenic, had improvement or resolution of clinical signs and symptoms, had a *Candida* isolate which was susceptible to fluconazole, and had documentation of 2 negative cultures drawn at least 24 hours apart. Patients were stratified by APACHE II score ($\leq$ 20 or >20) and by geographic region. Patients with *Candida* endocarditis were excluded from this analysis. Outcome was assessed by overall treatment success based on clinical (complete resolution or improvement in attributable signs and symptoms and radiographic abnormalities of the *Candida* infection and no additional antifungal therapy) and mycological (eradication or presumed eradication) response at the end of IV therapy. Deaths that occurred during IV study drug therapy were treated as failures.

In this study, 111/578 (19.2%) of the patients had baseline APACHE II scores of >20, and 50/578 (8.7%) were neutropenic at baseline (absolute neutrophil count less than 500 cells/mm^3). Outcome, relapse and mortality data are shown for the recommended dose of Mycamine (100 mg/day) and caspofungin in Table 7.

Table 7. Efficacy Analysis: Treatment Success in Patients in Study 03-0-192 with Candidemia and other *Candida* Infections

	Mycamine 100 mg/day n (%) % treatment difference (95%CI)	**Caspofungin 70/50 mg/day* n (%)**
Treatment Success at End of IV Therapy†	135/191 (70.7) 7.4 (-2.0, 16.3)	119/188 (63.3)
Success in Patients with Neutropenia at Baseline	14/22 (63.6)	5/11 (45.5)
Success by Site of Infection		
Candidemia	116/163 (71.2)	103/161 (64)
Abscess	4/5 (80)	5/9 (55.6)
Acute Disseminated‡	6/13 (46.2)	5/9 (55.6)
Endophthalmitis	1/3	1/1
Chorioretinitis	0/3	0
Skin	1/1	0
Kidney	2/2	1/1
Pancreas	1/1	0
Peritoneum	1/1	0
Lung/Skin	0/1	0
Lung/Spleen	0/1	0
Liver	0	0/2
Intraabdominal abscess	0	3/5
Chronic Disseminated	0/1	0
Peritonitis	4/6 (66.7)	2/5 (40)
Success by Organism§		
C. albicans	57/81 (70.4)	45/73 (61.6)
C. glabrata	16/23 (69.6)	19/31 (61.3)
C. tropicalis	17/27 (63)	22/29 (75.9)
C. parapsilosis	21/28 (75)	22/39 (56.4)
C. krusei	5/8 (62.5)	2/3 (66.7)
C. guilliermondii	1/2	0/1
C. lusitaniae	2/3 (66.7)	2/2
Relapse through 6 Weeks¶		
Overall	49/135 (36.3)	44/119 (37)
Culture confirmed relapse	5	4
Required systemic antifungal therapy	11	5
Died during follow-up	17	16
Not assessed	16	19
Overall study mortality	58/200 (29)	51/193 (26.4)
Mortality during IV therapy	28/200 (14)	27/193 (14)

* 70 mg loading dose on day 1 followed by 50 mg/day thereafter (caspofungin)
† All patients who received at least one dose of study medication and had documented invasive candidiasis or candidemia. Patients with *Candida* endocarditis were excluded from the analyses.
‡ A patient may have had >1 organ of dissemination
§ A patient may have had >1 baseline infection species
¶ All patients who had a culture confirmed relapse or required systemic antifungal therapy in the post treatment period for a suspected or proven *Candida* infection. Also includes patients who died or were not assessed in follow-up.

In two cases of ophthalmic involvement assessed as failures in the above table due to missing evaluation at the end of IV treatment with Mycamine, therapeutic success was documented during protocol-defined oral fluconazole therapy.

14.2 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 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 8, endoscopic cure, clinical cure, overall therapeutic cure, and mycological eradication were comparable for patients in the Mycamine and fluconazole treatment groups.

Table 8. 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 9.

Table 9. 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]).

14.3 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 $\geq$ 38.5ºC after having at least one prior temperature > 38ºC; or having two days of temperatures > 38ºC 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 10, 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 10. 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†	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) †	6 (1.4%)	8 (1.8%)
Suspected fungal infection ‡	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]
† Through end-of-study (4 weeks post-therapy)
‡ Through end-of-therapy

16 HOW SUPPLIED/STORAGE AND HANDLING

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).

- cartons of 10 individually packaged 100 mg single-use vials, coated with a light protective film and sealed with a red flip-off cap. (NDC 0469-3211-10)

Storage
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.]

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).

17 PATIENT COUNSELING INFORMATION

Patients should be advised of the potential benefits and risks of Mycamine. Patients should be informed about the common adverse effects of Mycamine including hypersensitivity reactions (anaphylaxis and anaphylactoid reactions including shock), hematological effects (acute intravascular hemolysis, hemolytic anemia and hemoglobinuria), hepatic effects (abnormal liver function tests, hepatic impairment, hepatitis or worsening hepatic failure) and renal effects (elevations in BUN and creatinine, renal impairment or acute renal failure). Patients should be instructed to inform their health care provider if they develop any unusual symptom, or if any known symptom persists or worsens. Patients should be instructed to inform their health care provider of any other medications they are currently taking with Mycamine, including over-the-counter medications.

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