MYCAMINE- micafungin sodium injection, powder, lyophilized, for solution
Astellas Pharma US, Inc.

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 in adult and pediatric patients 4 months and older 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

Recommended Reconstituted Dose Once Daily By Indication

Indication	Dose		
	Adult	Pediatric 30 kg or less	Pediatric greater than 30 kg
Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses (1.1)	100 mg[a] daily	2 mg/kg/day (maximum 100 mg daily)	
Treatment of Esophageal Candidiasis (1.2)	150 mg daily	3 mg/kg/day	2.5 mg/kg/day (maximum 150 mg daily)
Prophylaxis of *Candida* Infections in HSCT Recipients (1.3)	50 mg[b] daily	1 mg/kg/day (maximum 50 mg daily)	

[a] 100 mg micafungin is equivalent to 101.73 mg micafungin sodium.
[b] 50 mg micafungin is equivalent to 50.86 mg micafungin sodium.

A loading dose is not required. Infuse over 1 hour. (2.1, 2.4)
See Full Prescribing Information for IV administration instructions (2)

DOSAGE FORMS AND STRENGTHS

MYCAMINE (micafungin) for injection is supplied in a single-dose vial containing 50 mg micafungin, equivalent to 50.86 mg micafungin sodium (3)
MYCAMINE (micafungin) for injection is supplied in a single-dose vial containing 100 mg micafungin, equivalent to 101.73 mg micafungin sodium (3)

CONTRAINDICATIONS

MYCAMINE is contraindicated in persons with known hypersensitivity to micafungin sodium, 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, 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)
- Safety and effectiveness in pediatric patients less than 4 months of age have not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2018

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 in adult and pediatric patients 4 months and older 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.
The recommended doses for adult patients based on indications are shown in Table 1.

2.1 Dose and Schedule for Adults

Table 1. MYCAMINE Dosage in Adult Patients

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).

† 100 mg micafungin is equivalent to 101.73 mg micafungin sodium.

‡ 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).

¶ 50 mg micafungin is equivalent to 50.86 mg micafungin sodium.

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)]*.

2.2 Dose and Schedule for Pediatric Patients

The recommended doses for pediatric patients based on indication and weight are shown in Table 2.

Table 2. MYCAMINE Dosage in Pediatric Patients 4 Months or Older

Indication	Pediatric Dose Given Once Daily	
	30 kg or less	**Greater than 30 kg**
Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses (1.1)	2 mg/kg (maximum daily dose 100 mg)	
Treatment of Esophageal Candidiasis (1.2)	3 mg/kg	2.5 mg/kg (maximum daily dose 150 mg)
Prophylaxis of *Candida* Infections in HSCT Recipients (1.3)	1 mg/kg (maximum daily dose 50 mg)	

2.3 Directions for Reconstitution, Dilution, and Preparation

Please read this entire section carefully before beginning reconstitution.

Reconstitution

Reconstitute MYCAMINE vials by aseptically adding 5 mL of one of the following compatible

solutions:

- 0.9% Sodium Chloride Injection, USP (without a bacteriostatic agent)
- 5% Dextrose Injection, USP

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.

MYCAMINE 50 mg vial: after reconstitution **each mL contains 10 mg of micafungin.**
MYCAMINE 100 mg vial: after reconstitution **each mL contains 20 mg of micafungin.**

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.

Dilution and Preparation

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

Adult Patients:

1. Add the appropriate volume of reconstituted MYCAMINE into 100 mL of 0.9% Sodium Chloride Injection, USP or 100 mL of 5% Dextrose Injection, USP.
2. Appropriately label the bag.

Pediatric Patients:

1. Calculate the total MYCAMINE dose in milligrams (mg) by multiplying the recommended pediatric dose (mg/kg) for a given indication *[see Table 2]* and the weight of the patient in kilograms (kg).
2. To calculate the volume (mL) of drug needed, divide the calculated dose (mg) from step 1 by the final concentration of the selected reconstituted vial(s) (either 10 mg/mL for the 50 mg vial **or** 20 mg/mL for the 100 mg vial), see example below:

   Using 50 mg vials:
   Divide the calculated mg dose (from step 1) by **10 mg/mL** to determine the volume (mL) needed.

   OR

   Using 100 mg vials:
   Divide the calculated mg dose (from step 1) by **20 mg/mL** to determine the volume (mL) needed.

3. Withdraw the calculated volume (mL) of drug needed from the selected concentration and size of reconstituted MYCAMINE vial(s) used in Step 2 (ensure the selected concentration and vial size used to calculate the dose is also used to prepare the infusion).
4. Add the withdrawn volume of drug (step 3) to a 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP intravenous infusion bag or syringe. Ensure that the final concentration of the solution is between 0.5 mg/mL to 4 mg/mL.

   Note: To minimize the risk of infusion reactions, concentrations of greater than 1.5 mg/mL should be administered via central catheter *[see Adverse Reactions (6.1)]*.

5. Appropriately label the infusion bag or syringe. For concentrations above 1.5 mg/mL, if required, label to specifically warn to administer the solution via central catheter.

MYCAMINE is preservative-free. Discard partially used vials.

2.4 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.

Pediatric Patients
MYCAMINE should be infused over one hour. To minimize the risk of infusion reactions, concentrations of greater than 1.5 mg/mL should be administered via central catheter *[see Adverse Reactions (6.1)]*.

3 DOSAGE FORMS AND STRENGTHS

50 mg single-dose vial is equivalent to 50.86 mg micafungin sodium
100 mg single-dose vial is equivalent to 101.73 mg micafungin sodium

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 reactions 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

The overall safety of MYCAMINE was assessed in 3227 adult and pediatric patients and 520 volunteers in 46 clinical trials, including the invasive candidiasis, esophageal candidiasis and prophylaxis trials, who received single or multiple doses of MYCAMINE, ranging from 0.75 mg/kg to 10 mg/kg in pediatric patients and 12.5 mg to 150 mg/day or greater in adult patients.

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.

6.1 Infusion Reactions

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 in Adults

In all clinical trials with MYCAMINE, 2497/2748 (91%) adult patients experienced at least one treatment-emergent adverse reaction.

Candidemia and Other Candida Infections

In a randomized, double-blind study for treatment of candidemia and other *Candida* infections, treatment-emergent adverse reactions occurred in 183/200 (92%), 187/202 (93%) and 171/193 (89%) patients in the MYCAMINE 100 mg/day, MYCAMINE 150 mg/day, and caspofungin (a 70 mg loading dose followed by a 50 mg/day dose) treatment groups, respectively. Selected treatment-emergent adverse reactions, those occurring in 5% or more of the patients and more frequently in a MYCAMINE treatment group, are shown in Table 3.

Table 3. Selected[*] Treatment-Emergent Adverse Reactions in Adult Patients with Candidemia and Other Candida Infections

System Organ Class[†] (Preferred Term)[‡]	**MYCAMINE 100 mg n (%)**	**MYCAMINE 150 mg n (%)**	**Caspofungin**[§] **n (%)**
Number of Patients	200	202	193
Gastrointestinal Disorders	**81 (41)**	**89 (44)**	**76 (39)**
Diarrhea	15 (8)	26 (13)	14 (7)
Nausea	19 (10)	15 (7)	20 (10)
Vomiting	18 (9)	15 (7)	16 (8)
Metabolism and Nutrition Disorders	**77 (39)**	**83 (41)**	**73 (38)**
Hypoglycemia	12 (6)	14 (7)	9 (5)
Hypernatremia	8 (4)	13 (6)	8 (4)

Hyperkalemia	10 (5)	8 (4)	5 (3)
General Disorders/Administration Site Conditions	**59 (30)**	**56 (28)**	**51 (26)**
Pyrexia	14 (7)	22 (11)	15 (8)
Investigations	**36 (18)**	**49 (24)**	**37 (19)**
Blood Alkaline Phosphatase Increased	11 (6)	16 (8)	8 (4)
Cardiac Disorders	**35 (18)**	**48 (24)**	**36 (19)**
Atrial Fibrillation	5 (3)	10 (5)	0

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

* During IV treatment + 3 days

† MedDRA v5.0

‡ Within a system organ class patients may experience more than 1 adverse reaction.

§ 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 reactions occurred in 245/264 (93%) and 250/265 (94%) patients in the MYCAMINE (100 mg/day) and AmBisome (3 mg/kg/day) treatment groups, respectively. The following treatment-emergent adverse reactions in the MYCAMINE-treated patients at least 16 years of age were notable: nausea (10% vs. 8%); diarrhea (11% vs. 11%), vomiting (13% vs. 9%), abnormal liver function tests (4% vs. 3%); increased aspartate aminotransferase (3% vs. 2%), and increased blood alkaline phosphatase (3% vs. 2%), 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 (78%) patients who received MYCAMINE 150 mg/day and 186/258 (72%) patients who received intravenous fluconazole 200 mg/day experienced an adverse reaction. Treatment-emergent adverse reactions resulting in discontinuation were reported in 17 (7%) MYCAMINE-treated patients; and in 12 (5%) fluconazole-treated patients. Selected treatment-emergent adverse reactions, those occurring in 5% or more of the patients and more frequently in the MYCAMINE group, are shown in Table 4.

Table 4. Selected* Treatment-Emergent Adverse Reactions in Adult Patients with Esophageal Candidiasis

System Organ Class† (Preferred Term)‡	**MYCAMINE 150 mg/day n (%)**	**Fluconazole 200 mg/day n (%)**
Number of Patients	260	258
Gastrointestinal Disorders	**84 (32)**	**93 (36)**
Diarrhea	27 (10)	29 (11)
Nausea	20 (8)	23 (9)
Vomiting	17 (7)	17 (7)
General Disorders/Administration Site Conditions	**52 (20)**	**45 (17)**
Pyrexia	34 (13)	21 (8)
Nervous System Disorders	**42 (16)**	**40 (16)**
Headache	22 (9)	20 (8)
Vascular Disorders	**54 (21)**	**21 (8)**
Phlebitis	49 (19)	13 (5)
Skin and Subcutaneous Tissue Disorders	**36 (14)**	**26 (10)**
Rash	14 (5)	6 (2)

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

* During treatment + 3 days.

† MedDRA v5.0

‡ Within a system organ class patients may experience more than 1 adverse reaction.

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 adult patients who received MYCAMINE (382) or fluconazole (409) experienced at least one adverse reaction during the study. Treatment-emergent adverse reactions resulting in MYCAMINE discontinuation were reported in 15 (4%) adult patients; while those resulting in fluconazole discontinuation were reported in 32 (8%). Selected adverse reactions, those reported in 15% or more of adult patients and more frequently on the MYCAMINE treatment arm, are shown in Table 5.

Table 5. Selected Adverse Reactions in Adult Patients During Prophylaxis of Candida Infection in Hematopoietic Stem Cell Transplant Recipients

System Organ Class * (Preferred Term) †	**MYCAMINE 50 mg/day n (%)**	**Fluconazole 400 mg/day n (%)**
Number of Patients	382	409
Gastrointestinal Disorders	**377 (99)**	**404 (99)**
Diarrhea	294 (77)	327 (80)
Nausea	270 (71)	290 (71)
Vomiting	252 (66)	274 (67)
Abdominal Pain	100 (26)	93 (23)
Blood and Lymphatic System Disorders	**368 (96)**	**385 (94)**
Neutropenia	288 (75)	297 (73)
Thrombocytopenia	286 (75)	280 (69)
Skin and Subcutaneous Tissue Disorders	**257 (67)**	**275 (67)**
Rash	95 (25)	91 (22)
Nervous System Disorders	**250 (65)**	**254 (62)**
Headache	169 (44)	154 (38)
Psychiatric Disorders	**233 (61)**	**235 (58)**
Insomnia	142 (37)	140 (34)
Anxiety	84 (22)	87 (21)
Cardiac Disorders	**133 (35)**	**138 (34)**
Tachycardia	99 (26)	91 (22)

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

* MedDRA v12.0

† Within a system organ class patients may experience more than 1 adverse reaction.

Other selected adverse reactions reported at less than 5% in adult clinical trials are listed below:

- *Blood and lymphatic system disorders:* coagulopathy, pancytopenia, thrombotic thrombocytopenic purpura
- *Cardiac disorders:* cardiac arrest, myocardial infarction, pericardial effusion
- *General disorders and administration site conditions:* infusion reaction, injection site thrombosis

- *Hepatobiliary disorders:* hepatocellular damage, hepatomegaly, jaundice, hepatic failure
- *Immune disorders:* hypersensitivity, anaphylactic reaction
- *Nervous system disorders:* convulsions, encephalopathy, intracranial hemorrhage
- *Psychiatric disorders:* delirium
- *Skin and subcutaneous tissue disorders:* urticaria

6.3 Clinical Trials Experience in Pediatric Patients

The overall safety of MYCAMINE was assessed in 479 patients 3 days through 16 years of age who received at least one dose of MYCAMINE in 11 separate clinical studies. The mean treatment duration was 24.8 days. A total of 246 patients received at least one dose of MYCAMINE 2 mg/kg or higher.

Of the 479 pediatric patients, 264 (55%) were male, 319 (67%) were Caucasians, with the following age distribution: 116 (24%) less than 2 years, 108 (23%) between 2 and 5 years, 140 (29%) between 6 years and 11 years, and 115 (24%) between 12 and 16 years of age.

In all pediatric studies with MYCAMINE, 439/479 (92%) patients experienced at least one treatment-emergent adverse reaction.

Two studies that included pediatric patients were randomized, double-blind, and active-controlled: The invasive candidiasis and candidemia study investigated the efficacy and safety of MYCAMINE (2 mg/kg/day for patients weighing 40 kg or less and 100 mg/day for patients weighing greater than 40 kg) compared to AmBisome (3 mg/kg/day) in 112 pediatric patients. Treatment-emergent adverse reactions occurred in 51/56 (91%) of patients in the MYCAMINE group and 52/56 (93%) of patients in the AmBisome group. Treatment-emergent adverse reactions resulting in MYCAMINE discontinuation were reported in 2 (4%) pediatric patients; while those resulting in AmBisome discontinuation were reported in 9 (16%).

The prophylaxis study in patients undergoing HSCT investigated the efficacy of MYCAMINE (1 mg/kg/day for patients weighing 50 kg or less and 50 mg/day for patients weighing greater than 50 kg) as compared to fluconazole (8 mg/kg/day for patients weighing 50 kg or less and 400 mg/day for patients weighing greater than 50 kg). All 91 pediatric patients experienced at least one treatment-emergent adverse reaction. Three (7%) pediatric patients discontinued MYCAMINE due to adverse reaction; while one (2%) patient discontinued fluconazole.

The selected treatment-emergent adverse reactions, those occurring in 15% or more of the patients and more frequently in a MYCAMINE group, for all MYCAMINE pediatric studies and for the two comparative studies (candidemia and prophylaxis) described above are shown in Table 6.

Table 6. Selected Treatment-Emergent Adverse Reactions in All Pediatric Patients, in Patients with Candidemia and Other Candida Infections (C/IC), and in Hematopoietic Stem-Cell Recipients During Prophylaxis of Candida Infections

System Organ Class* (Preferred Term)†	All Micafungin-treated Patients n = 479 n (%)	C/IC		Prophylaxis	
		MYCAMINE n = 56 n (%)	AmBisome n = 56 n (%)	MYCAMINE n = 43 n (%)	Fluconazole n = 48 n (%)
Gastrointestinal disorders	285 (60)	22 (40)	18 (32)	43 (100)	45 (94)
Vomiting	146 (31)	10 (18)	8 (14)	28 (65)	32 (67)
Diarrhea	106 (22)	4 (7)	5 (9)	22 (51)	31 (65)
Nausea	91 (19)	4 (7)	4 (7)	30 (70)	25 (52)
Abdominal pain	76 (16)	2 (4)	2 (4)	15 (35)	12 (25)

Abdominal distension	29 (6)	1 (2)	1 (2)	8 (19)	6 (13)
General disorders and administration site conditions	256 (53)	14 (25)	14 (25)	41 (95)	46 (96)
Pyrexia	103 (22)	5 (9)	9 (16)	26 (61)	31 (65)
Infusion-related reaction	24 (5)	0	3 (5)	7 (16)	4 (8)
Skin and subcutaneous tissue disorders	197 (41)	11 (20)	8 (14)	33 (77)	38 (79)
Pruritus	54 (11)	0	1 (2)	14 (33)	15 (31)
Rash	55 (12)	1 (2)	1 (2)	13 (30)	13 (27)
Urticaria	24 (5)	0	1 (2)	8 (19)	4 (8)
Respiratory, thoracic and mediastinal disorders	194 (41)	9 (16)	13 (23)	30 (70)	33 (69)
Epistaxis	45 (9)	0	0	4 (9)	8 (17)
Blood and lymphatic system disorders	161 (34)	17 (30)	13 (23)	40 (93)	44 (92)
Thrombocytopenia	70 (15)	5 (9)	3 (5)	31 (72)	37 (77)
Neutropenia	61 (13)	3 (5)	4 (7)	33 (77)	34 (71)
Anemia	63 (13)	10 (18)	6 (11)	22 (51)	24 (50)
Febrile neutropenia	23 (5)	0	0	7 (16)	7 (15)
Investigations	191 (40)	12 (21)	8 (14)	24 (56)	25 (52)
Alanine aminotransferase increased	45 (10)	0	0	7 (16)	1 (2)
Urine output decreased	18 (4)	0	0	10 (23)	8 (17)
Cardiac disorders	97 (20)	7 (13)	3 (5)	10 (23)	17 (35)
Tachycardia	47 (10)	2 (4)	1 (2)	7 (16)	12 (25)
Renal and urinary disorders	78 (16)	4 (7)	4 (7)	16 (37)	15 (31)
Hematuria	18 (4)	0	0	10 (23)	7 (15)
Psychiatric disorders	80 (17)	3 (5)	1 (2)	20 (47)	9 (19)
Anxiety	35 (7)	0	0	10 (23)	3 (6)

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

* MedDRA v12.0

† Within a system organ class, patients may experience more than 1 adverse reaction.

Other clinically significant adverse reactions reported at less than 15% in pediatric clinical trials are listed below:

- *Hepatobiliary disorders*: hyperbilirubinemia

- *Investigations:* liver function tests abnormal
- *Renal Disorders:* renal failure

6.4 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.

- *Blood and lymphatic system disorders*: disseminated intravascular coagulation
- *Hepatobiliary disorders:* hepatic disorder
- *Renal and urinary disorders*: 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 MYCAMINE 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 MYCAMINE 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. MYCAMINE 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 younger than 4 months of age have not been established.

Safety and effectiveness of MYCAMINE in pediatric patients 4 months of age and older have been demonstrated based on the evidence from adequate and well-controlled studies in adult and pediatric patients and additional pediatric pharmacokinetic and safety data. Two randomized, double-blind, active-control studies investigated the safety and efficacy of MYCAMINE in both adult and pediatric patients: one for the treatment of invasive candidiasis and candidemia and the other for prophylaxis of *Candida* infections in patients undergoing HSCT *[see Dosage and Administration (2), Adverse Reactions (6.3), Clinical Pharmacology (12.3), Clinical Studies (14)]*.

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 Clinical Pharmacology (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 Clinical Pharmacology (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, up to 6 mg/kg in pediatric patients 4 months of age and older, and up to 10 mg/kg in pediatric patients less than 4 months of age 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 times the recommended highest adult clinical dose (150 mg) and approximately 7 times the highest pediatric clinical dose (3 mg/kg), based on body surface area comparisons.

11 DESCRIPTION

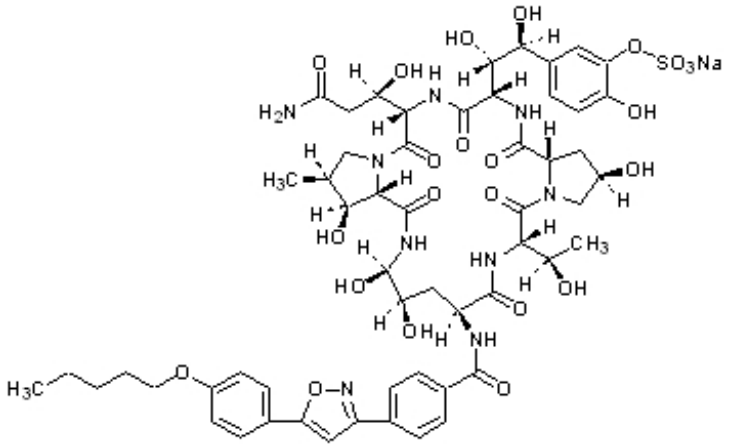
MYCAMINE is a sterile, lyophilized product for intravenous (IV) infusion that contains micafungin sodium. Micafungin sodium is a semisynthetic lipopeptide (echinocandin) synthesized by a chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin inhibits the synthesis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

Each single-dose vial contains 50 mg micafungin (equivalent to 50.86 mg micafungin sodium) or 100 mg micafungin (equivalent to 101.73 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 (12.4)]*.

12.3 Pharmacokinetics

Adults

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 Table 7.

Table 7. 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)
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

* $AUC_{0-infinity}$ is presented for day 1; AUC_{0-24} is presented for steady state.

† candidemia or other *Candida* infections

‡ human immunodeficiency virus

§ esophageal candidiasis

¶ hematopoietic stem cell transplant

Pediatric Patients 4 months of age and older

Micafungin pharmacokinetics in 229 pediatric patients 4 months through 16 years of age were characterized using population pharmacokinetics. Micafungin exposure was dose proportional across the dose and age range studied.

Table 8. Summary (Mean +/- Standard Deviation) of Micafungin Pharmacokinetics in Pediatric Patients 4 Months of Age and Older (Steady-State)

Body weight group	N	Dose* mg/kg	$C_{max.ss}$† (mcg/mL)	$AUC_{.ss}$† (mcg·h/mL)	$t_{½}$‡ (h)	CL‡ (mL/min/kg)
30 kg or less	149	1.0	7.1 +/- 4.7	55 +/- 16	12.5 +/- 4.6	0.328 +/- 0.091
		2.0	14.2 +/- 9.3	109 +/- 31		
		3.0	21.3 +/- 14.0	164 +/- 47		
Greater than 30 kg	80	1.0	8.7 +/- 5.6	67 +/- 17	13.6 +/- 8.8	0.241 +/- 0.061
		2.0	17.5 +/- 11.2	134 +/- 33		
		2.5	23.0 +/- 14.5	176 +/- 42		

* Or the equivalent if receiving the adult dose (50, 100, or 150 mg)

† Derived from simulations from the population PK model

‡ Derived from the population PK model

Special Populations

Adult 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 adult subjects with severe renal impairment (creatinine clearance less than 30 mL/min) and to 9 age-, gender-, and weight-matched subjects with normal renal function (creatinine clearance greater than 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.

Adult Patients with Hepatic Impairment

- A single 1-hour infusion of 100 mg MYCAMINE was administered to 8 adult 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 adult 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 MYCAMINE 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 (greater than 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-beta-D-glucan, an essential component of fungal cell walls, which is not present in mammalian cells.

Resistance

There have been reports of clinical failures in patients receiving MYCAMINE therapy due to the development of drug resistance. Some of these reports have identified specific mutations in the *FKS* protein component of the glucan synthase enzyme that are associated with higher MICs and breakthrough infection.

Antimicrobial Activity

Micafungin has been shown to be active against most isolates of the following *Candida* species, both ***in vitro* and in clinical infections**:

- *Candida albicans*
- *Candida glabrata*
- *Candida guilliermondii*
- *Candida krusei*
- *Candida parapsilosis*
- *Candida tropicalis*

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

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 MYCAMINE 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 Adult 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 (20 or less or greater than 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 greater than 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 9.

Table 9. 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 greater than 1 organ of dissemination

§ A patient may have had greater than 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 Adult 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 less than 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 10, endoscopic cure, clinical cure, overall therapeutic cure, and mycological eradication were comparable for patients in the MYCAMINE and fluconazole treatment groups.

Table 10. Endoscopic, Clinical, and Mycological Outcomes for Esophageal Candidiasis at End-of-Treatment

Treatment Outcome*	**MYCAMINE 150 mg/day n = 260**	**Fluconazole 200 mg/day n = 258**	**% Difference† (95% CI)**
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 or more doses 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 greater than 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 11.

Table 11. 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 [adult (791) and pediatric (91)] patients undergoing an autologous or syngeneic (46%) or allogeneic (54%) stem cell transplant. All pediatric patients, except 2 per group, received allogeneic transplants. 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 500 cells/mm^3 or greater or up to a maximum of 42 days after transplant. The average duration of drug administration was 18 days (range 1 to 51 days). Duration of therapy was slightly longer in the pediatric patients who received MYCAMINE (median duration 22 days) compared to the adult patients who received MYCAMINE (median duration 18 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 less than 500 cells/mm^3); persistent or recurrent fever (while ANC less than 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 38°C. A recurrent fever was defined as having at least one day with temperatures 38.5°C or higher after having at least one prior temperature higher than 38°C; or having two days of temperatures higher than 38°C after having at least one prior temperature higher than

38°C. 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 adult and pediatric MYCAMINE recipients, and in 73.7% of adult and pediatric patients who received fluconazole (7.0% difference [95% CI = 1.5, 12.5]), as shown in Table 12, 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 12. 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† Proven/probable fungal infection prior to death	18 (4.2%) 1 (0.2%)	26 (5.7%) 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-dose vials, coated with a light protective film and sealed with a blue flip-off cap. (NDC 0469-3250-50)
- cartons of 10 individually packaged 100 mg single-dose vials, coated with a light protective film and sealed with a red flip-off cap. (NDC 0469-3211-99)

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 serious 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 healthcare provider if they develop any unusual symptom, or if any known symptom persists or worsens. Patients should be instructed to inform their healthcare provider of any other medications they are currently taking with MYCAMINE, including over-the-counter medications.

Product of Japan

Manufactured by:
Astellas Pharma Tech Co., Ltd. Takaoka Plant
30 Toidesakae-machi, Takaoka city, Toyama 939-1118, Japan

Marketed by:
Astellas Pharma US, Inc.
Northbrook, IL 60062 USA

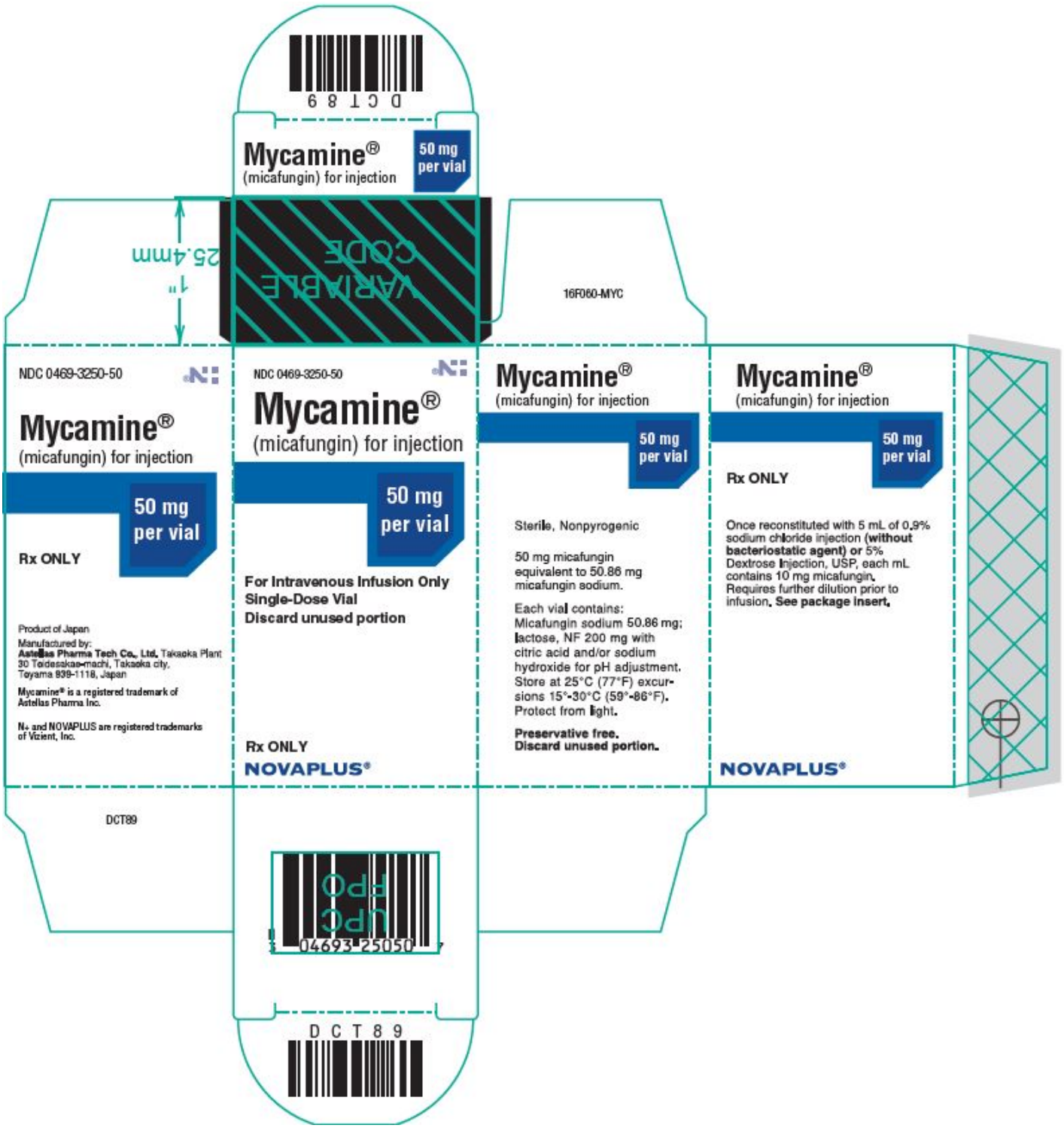
MYCAMINE® is a registered trademark of Astellas Pharma Inc.

Novaplus is a registered trademark of Vizient, Inc.

205923-MYC

Revised: May 2018

PRINCIPAL DISPLAY PANEL – 50 mg/vial



NDC 0469-3250-50

Mycamine®
(micafungin) for injection

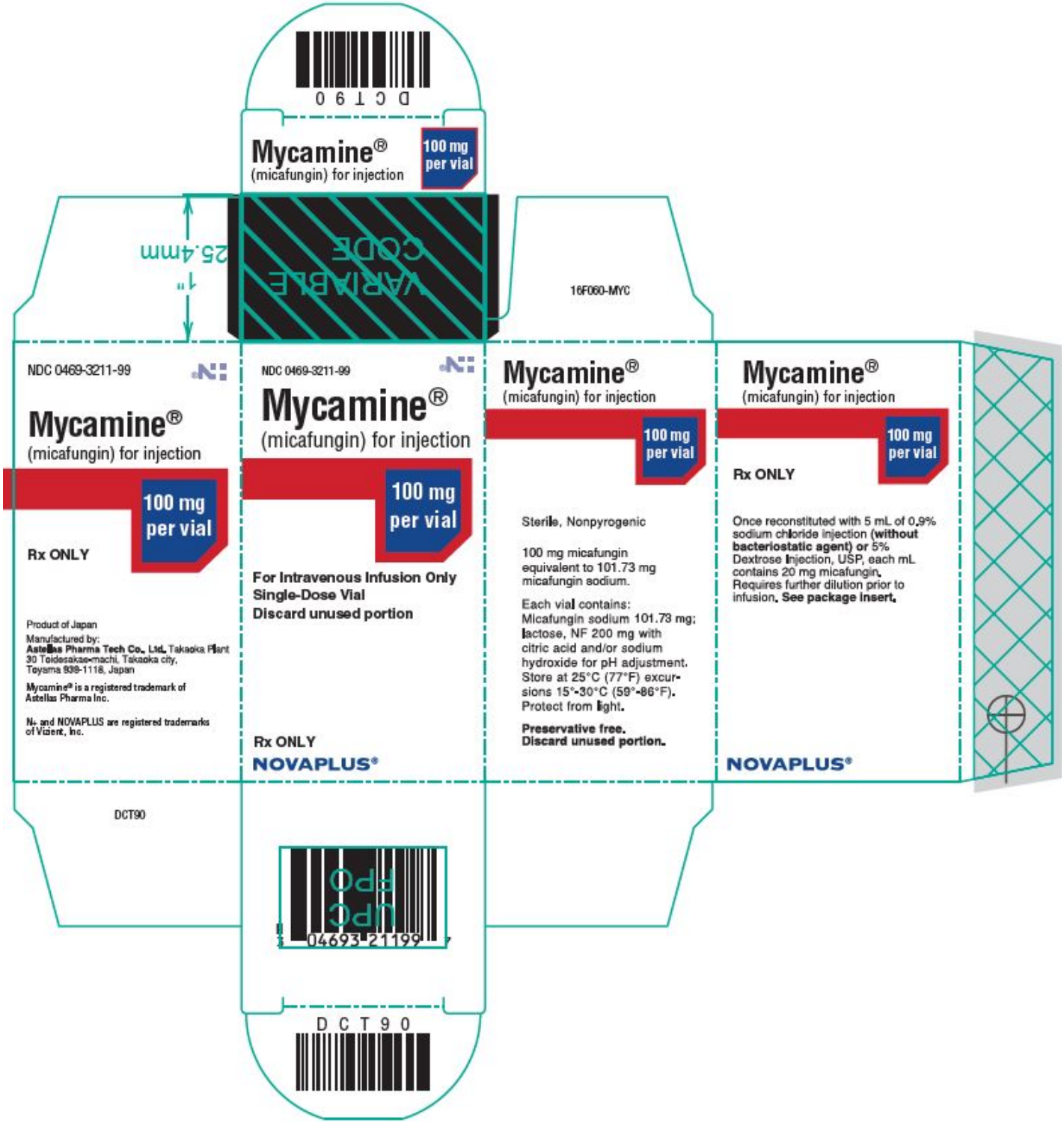
50 mg
per vial

For Intravenous Infusion Only
Single-Dose Vial
Discard unused portion

Rx ONLY

NOVAPLUS®

PRINCIPAL DISPLAY PANEL – 100 mg/vial



NDC 0469-3211-99

Mycamine®
(micafungin) for injection

100 mg

per vial

For Intravenous Infusion Only
Single-Dose Vial
Discard unused portion

Rx ONLY

NOVAPLUS®

MYCAMINE

micafungin sodium injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0469-3250
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
MICAFUNGIN SODIUM (UNII: IS1UP79R56) (MICAFUNGIN - UNII:R10H71BSWG)	MICAFUNGIN SODIUM	10 mg in 1 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0469-3250-50	10 in 1 CARTON	12/01/2014	
1		5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021506	12/01/2014	

MYCAMINE

micafungin sodium injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0469-3211
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
MICAFUNGIN SODIUM (UNII: IS1UP79R56) (MICAFUNGIN - UNII:R10H71BSWG)	MICAFUNGIN SODIUM	20 mg in 1 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0469-3211-99	10 in 1 CARTON	12/01/2014	
1		10 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021506	12/01/2014	

Labeler - Astellas Pharma US, Inc. (605764828)

Revised: 5/2018 Astellas Pharma US, Inc.