Micafungin for Injection

13.1000/40-02

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MICAFUNGIN FOR INJECTION safely and effectively. See full prescribing information for MICAFUNGIN FOR INJECTION.
MICAFUNGIN for injection, for intravenous use
Initial U.S. Approval: 2005

RECENT MAJOR CHANGES

Indications and Usage (1) 12/2019
Dosage and Administration, Dosage for Pediatric Patients Younger than 4 Months of Age (2.3) 12/2019
Warnings and Precautions, Infusion and Injection Site Reactions (5.5) 12/2019

INDICATIONS AND USAGE

Micafungin for Injection is an echinocandin indicated in adult and pediatric patients for (1):

- Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses in adult and pediatric patients 4 months of age and older.
- Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses **without** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age.
- Prophylaxis of Candida Infections in adult and pediatric patients 4 months of age and older undergoing Hematopoietic Stem Cell Transplantation (HSCT).

Limitations of Use

- The safety and effectiveness of Micafungin for Injection have not been established for the treatment of candidemia **with** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age as a higher dose may be needed (*see Clinical Studies (14.1)*).
- Micafungin for Injection has not been adequately studied in patients with endocarditis, osteomyelitis or meningoencephalitis due to *Candida*.
- The efficacy of Micafungin for Injection against infections caused by fungi other than *Candida* has not been established.

DOSAGE AND ADMINISTRATION

Recommended Dosage Administered by Indication, Weight and Age (2.1, 2.2, 2.3, 8.4)

Adult	Pediatric Patients 4 Months and Older 30 kg or less	Pediatric Patients 4 Months and Older greater than 30 kg	Pediatric Patients Younger than 4 Months of Age
Treatment of Candidiasis, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses			
100 mg daily	2 mg/kg daily (maximum 100 mg daily)	See below	
Treatment of Candidiasis, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses *without* Meningoencephalitis and/or Ocular Dissemination			
See above	See above	See above	4 mg/kg/day
Treatment of Esophageal Candidiasis			
150 mg daily	3 mg/kg/day	2.5 mg/kg/day (maximum 150 mg daily)	Not approved
Prophylaxis of Candida Infections in HSCT Recipients			
50 mg daily	1 mg/kg/day (maximum 50 mg daily)		Not approved

- Infuse over 1 hour. (2.5)
- See Full Prescribing Information for intravenous (IV) preparation and administration instructions. (2)

DOSAGE FORMS AND STRENGTHS

- For injection: 50 mg single-dose vial. (3)
- For injection: 100 mg single-dose vial. (3)

CONTRAINDICATIONS

Micafungin for Injection is contraindicated in persons with known hypersensitivity to micafungin sodium, any component of Micafungin for Injection, or other echinocandins. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Anaphylaxis and anaphylactoid reactions (including shock) have been observed. Discontinue micafungin and administer appropriate treatment. (5.1)
- Hematological Effects: Isolated cases of acute intravascular hemolysis, hemolytic anemia and hemorrhagic cystitis have been observed. Monitor rate of hemolysis. Discontinue if severe. (5.2)
- Hepatic Effects: Abnormalities in liver tests; isolated cases of hepatic impairment, hepatitis, and hepatic failure have been observed. Monitor hepatic function. Discontinue if severe dysfunction occurs. (5.3)
- Renal Effects: Elevations in BUN and creatinine; isolated cases of renal impairment or acute renal failure have been observed. Monitor renal function. (5.4)
- Infusion and Injection Site Reactions can occur including rash, pruritus, facial swelling, and vasodilatation. Monitor infusion closely, slow infusion rate if necessary. (2.5, 5.5)

ADVERSE REACTIONS

- Most common adverse reactions across adult and pediatric clinical trials for all indications include diarrhea, nausea, vomiting, abdominal pain, pyrexia, thrombocytopenia, phlebitis, and headache. (6.1)
- In pediatric patients younger than 4 months of age, the following additional common adverse reactions were observed: elevation rate of 21% sepsis, acidosis, anemia, oxygen saturation decreased and hypokalemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Monitor for sirolimus, tacrolimus or nifedipine toxicity, and dosage of sirolimus, tacrolimus or nifedipine should be reduced, if necessary. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy – Based on animal data, Micafungin may cause fetal harm. Advise pregnant women of the risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Micafungin for Injection is indicated for:

- Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses in adult and pediatric patients 4 months of age and older *[see Clinical Studies (14.1)] and Use in Specific Populations (8.4)]*.
- Treatment of Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses **without** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age *[see Use in Specific Populations (8.4)]*.
- Treatment of Esophageal Candidiasis in adult and pediatric patients 4 months of age and older *[see Clinical Studies (14.2)]*.
- Prophylaxis of Candida Infections in adult and pediatric patients 4 months of age and older undergoing hematopoietic stem cell transplantation *[see Clinical Studies (14.3)]*.

Limitations of Use

- The safety and effectiveness of Micafungin for Injection have **not** been established for the treatment of candidemia **with** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age as a higher dose may be needed *[see Use in Specific Populations (8.4)]*.
- Micafungin for Injection has not been adequately studied in patients with endocarditis, osteomyelitis and meningoencephalitis due to *Candida*.
- The efficacy of Micafungin for Injection against infections caused by fungi other than *Candida* has not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Adults

The recommended dosage for adult patients based on indications are shown in Table 1.

Table 1. Micafungin for Injection Dosage in Adult Patients

Indication	Recommended Reconstituted Dose Once Daily
Treatment of Candidiasis, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses[1]	**100 mg**
Treatment of Esophageal Candidiasis[2]	**150 mg**
Prophylaxis of Candida Infections in HSCT Recipients[3]	**50 mg**

[1] In patients treated successfully for candidemia and other *Candida* infections, the mean duration of treatment was 15 days (range 10 to 47 days).
[2] In patients treated successfully for esophageal candidiasis, the mean duration of treatment was 15 days (range 10 to 30 days).
[3] In hematopoietic stem cell transplant (HSCT) recipients who experienced success of prophylactic therapy, the mean duration of prophylaxis was 19 days (range 8 to 51 days).

2.2 Dosage for Pediatric Patients 4 Months and Older

The recommended dosage for pediatric patients 4 months of age and older based on indication and weight are shown in Table 2.

Table 2. Micafungin for Injection Dosage in Pediatric Patients (4 Months of Age and Older)

Indication	Dosage for Pediatric Patients 4 Months of Age and Older	
	30 kg or less	Greater than 30 kg
Treatment of Candidiasis, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses	2 mg/kg once daily (maximum daily dose 100 mg)	
Treatment of Esophageal Candidiasis	3 mg/kg once daily	2.5 mg/kg once daily (maximum daily dose 150 mg)
Prophylaxis of Candida Infections in HSCT Recipients	1 mg/kg once daily (maximum daily dose 50 mg)	

2.3 Dosage for Pediatric Patients Younger than 4 Months of Age

Treatment of Candidiasis, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses **without** meningoencephalitis and/or ocular dissemination

The recommended dosage is 4 mg/kg once daily.

The safety and effectiveness of Micafungin for Injection have **not** been established for the treatment of candidemia **with** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age as a higher dose may be needed *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3) and Microbiology (12.4)]*.

2.4 Directions for Reconstitution, Dilution, and Preparation

Do not mix or co-infuse Micafungin for Injection with other medications. Micafungin for Injection has been shown to precipitate when mixed directly with a number of other commonly used medications. Please read this entire section carefully before beginning reconstitution.

Reconstitution

Reconstitute Micafungin for Injection 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 Micafungin for Injection powder by swirling the vial. Do not vigorously shake the vial. Visually inspect the vial for particulate matter.

Micafungin for Injection 50 mg vial: after reconstitution each mL contains 10 mg of micafungin.

Micafungin for Injection 100 mg vial: after reconstitution each mL contains 20 mg of micafungin.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use 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 Micafungin for Injection or in the materials specified for reconstitution and dilution.

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

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 Micafungin for Injection into 100 mL of 0.9% Sodium Chloride Injection, USP or 100 mL of 5% Dextrose Injection, USP.
2. Appropriately dilute the dose.

Pediatric Patients

1. Calculate the total Micafungin for Injection 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 reconstituted micafungin solution (mg/mL) (either 10 mg/mL for the 50 mg vial or 20 mg/mL for the 100 mg vial), see example below:

Using 50 mg vial:

Divide the calculated mg dose (from step 1) by 10 mg/mL to determine the volume (mL) needed.

OR

Using 100 mg vial:

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 Micafungin for Injection 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 diluted solution is less or equal to 1.5 mg/mL.

To dilute doses that result in infusion solutions concentrations above 1.5 mg/mL, should be administered via central catheter *[see Warnings and Precautions (5.5)]*.

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.

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

Micafungin for Injection is preservative-free. Discard partially used vials.

2.5 Infusion Volume and Dosage

Administer Micafungin for Injection by intravenous infusion only. Infuse over one hour. More rapid infusions may result in more frequent histamine-mediated reactions *[see Warnings and Precautions (5.5)]*.

Flush an existing intravenous line with 0.9% Sodium Chloride Injection, USP, prior to infusion of Micafungin for Injection.

Pediatric Patients

Micafungin for Injection should be infused over one hour. To decrease the risk of infusion reactions, concentrations above 1.5 mg/mL should be administered via central catheter *[see Warnings and Precautions (5.5)]*.

3 DOSAGE FORMS AND STRENGTHS

Micafungin for Injection is a sterile, white lyophilized powder for reconstitution for intravenous infusion available as:

- 50 mg single-dose vial
- 100 mg single-dose vial

4 CONTRAINDICATIONS

Micafungin for Injection is contraindicated in persons with known hypersensitivity to micafungin, any component of Micafungin for Injection, 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 micafungin. If these reactions occur, micafungin 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 micafungin (200 mg) and oral prednisolone (20 mg). Cases of significant hemolysis and hemolytic anemia have also been reported in patients treated with micafungin. Patients who develop clinical or laboratory evidence of hemolysis or hemolytic anemia during micafungin therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing micafungin therapy.

5.3 Hepatic Effects

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with micafungin. In some patients with serious underlying conditions who were receiving micafungin 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 micafungin therapy should be monitored for evidence of worsening hepatic function and evaluated for the risk/benefit of continuing micafungin 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 micafungin in uncontrolled clinical trials. The incidence of drug-related renal adverse reactions was 0.4% for micafungin-treated patients and 0.5% for fluconazole-treated patients. Patients who develop abnormal renal function tests during micafungin therapy should be monitored for evidence of worsening renal function.

5.5 Infusion and Injection Site Reactions

Possible histamine-mediated symptoms have been reported with micafungin, including rash, pruritus, facial swelling and vasodilatation. Slow the infusion rate if infusion reaction occurs *[see Dosage and Administration (2.3)]*.

Injection site reactions, including phlebitis and thrombophlebitis have been reported, at micafungin doses of 50 to 150 mg/day. These reactions tended to occur more often in patients receiving micafungin via peripheral intravenous administration *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Hematological Effects *[see Warnings and Precautions (5.2)]*
- Hepatic Effects *[see Warnings and Precautions (5.3)]*
- Renal Effects *[see Warnings and Precautions (5.4)]*
- Infusion and Injection Site Reactions *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of micafungin cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

The overall safety of micafungin was assessed in 520 healthy volunteers and 3417 adult and pediatric patients who received single or multiple doses of micafungin across 50 clinical trials, including the invasive candidiasis, esophageal candidiasis and prophylaxis trials. The doses of micafungin administered included doses above and below the recommended doses *[see Dosage and Administration (2.1, 2.2)]* and ranged from 0.75 mg/kg to 15 mg/kg in pediatric patients and 12.5 mg to 150 mg/day or greater in adults.

Clinical Trials Experience in Adults

In clinical trials with micafungin, 2,497/2,748 (91%) adult patients experienced at least one adverse reaction.

Candidemia and Other Candida Infections

In a randomized, double-blind trial for the treatment of candidemia and other *Candida* infections, adverse reactions occurred in 183/200 (92%) and 171/189 (89%) patients in the micafungin 100 mg/day, and caspofungin (70 mg loading dose followed by 50 mg/day dose) treatment groups, respectively. Selected adverse reactions occurring in 5% or more of the patients and more frequently in the micafungin treatment group, are shown in Table 3.

Table 3. Selected[1] Adverse Reactions in Adult Patients with Candidemia and Other Candida Infections

Adverse Reaction by System Organ Class[2]	Micafungin100 mg n (%)	Caspofungin[3] n (%)
Number of Patients	200	189
Gastrointestinal Disorders	81 (41)	76 (39)
Diarrhea	15 (8)	14 (7)
Vomiting	18 (9)	16 (8)
Metabolism and Nutrition Disorders	77 (39)	73 (38)
Hypoglycemia	12 (6)	9 (5)
Hypokalemia	10 (5)	5 (3)
General Disorders/Administration Site Conditions	59 (30)	51 (26)
Investigations	36 (18)	37 (19)
Blood Alkaline Phosphatase Increased	11 (6)	8 (4)
Cardiac Disorders	35 (18)	36 (19)
Atrial Fibrillation	5 (3)	0

Patient base: all randomized patients who received at least 1 dose of trial drug.
[1] Reported in ≥ 5% of patients.
Within a system organ class, adverse reactions are ordered by decreasing frequency.
[2] mg dosing dose on day 1 followed by 50 mg/day thereafter (caspofungin).

In a second, open-label, randomized, double-blind trial for the treatment of candidemia and other *Candida* infections, adverse reactions occurred in 245/264 (93%) and 250/265 (94%) adult and pediatric patients in the micafungin (100 mg/day) and amphotericin B liposome (3 mg/kg/day) treatment groups, respectively. In this trial, the following adverse reactions were reported in patients at least 16 years of age in the micafungin and amphotericin B liposome treatment groups, respectively: nausea (10% vs. 8%), diarrhea (11% vs. 11%), vomiting (13% vs. 9%), abnormal liver function tests (6% vs. 3%), increased aspartate aminotransferase (3% vs. 2%), and increased blood alkaline phosphatase (3% vs. 2%).

Esophageal Candidiasis

In a randomized, double-blind study for treatment of esophageal candidiasis, a total of 202/260 (78%) patients who received micafungin 150 mg/day and 208/258 (72%) patients who received intravenous fluconazole 200 mg/day experienced an adverse reaction. Adverse reactions resulting in discontinuation were reported in 17 (7%) and 14 (5%) treated patients and in 12 (5%) fluconazole-treated patients. Selected treatment-emergent adverse reactions occurring in 5% or more of the patients and more frequently in the micafungin group, are shown in Table 4.

Table 4. Selected[1] Adverse Reactions in Adult Patients with Esophageal Candidiasis

Adverse Reaction by System Organ Class[2]	Micafungin 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	79 (30)	46 (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	12 (5)	6 (2)

Patient base: all randomized patients who received at least 1 dose of trial drug.
[1] Reported in ≥ 5% of patients.
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 trial was conducted in a total 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 micafungin (382) or fluconazole (409) experienced at least one adverse reaction during the study. Treatment-emergent adverse reactions resulting in micafungin discontinuation were reported in 15 (4%) adult patients; while those resulting in fluconazole discontinuation were reported in 32 (8%). Selected adverse reactions reported in 15% or more of adult patients and more frequently in the micafungin 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	Micafungin 50 mg/day n (%)	Fluconazole 400 mg/day n (%)
Number of Patients	382	409
Gastrointestinal Disorders	277 (99)	404 (99)
Diarrhea	294 (77)	327 (80)
Nausea	270 (71)	290 (71)
Vomiting	252 (66)	274 (67)
Abdominal Pain	142 (37)	93 (23)
Blood and Lymphatic System Disorders	368 (96)	385 (94)
Neutropenia	288 (75)	297 (73)
Thrombocytopenia	286 (75)	280 (68)
Skin and Subcutaneous Tissue Disorders	257 (67)	275 (67)
Rash	95 (25)	91 (22)
Nervous System Disorders	259 (68)	254 (62)
Headache	189 (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	59 (28)	91 (22)

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

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

- *Blood and lymphatic system disorders:* pancytopenia, disseminated intravascular thrombocytopenic purpura
- *Cardiac disorders:* cardiac arrest, myocardial infarction, pericardial effusion
- *General disorders and administration site conditions:* infusion reaction, injection site thrombosis
- *Hepatobiliary disorders:* hepatomegaly, hepatitis, hepatocellular injury, acute, hepatic failure
- *Immune disorders:* hypersensitivity, anaphylactic reaction
- *Metabolism and nutrition disorders:* hypercalcemia, hypokalemia
- *Nervous system disorders:* convulsions, encephalopathy, intracranial hemorrhage
- *Psychiatric disorders:* delirium
- *Skin and subcutaneous tissue disorders:* urticaria

Clinical Trials Experience in Pediatric Patients

The safety of micafungin was assessed in 593 pediatric patients, 425 of whom were 4 months through 16 years of age and 168 of whom were 3 days to less than 4 months of age who received at least one dose of micafungin across 15 clinical trials.

Of the 425 pediatric patients, 4 months through 16 years of age enrolled in 11 clinical trials, 235 (55%) were male, 290 (68%) were white, with the following age distribution: 62 (15%) 4 months to <2 years, 108 (25%) 2 to <6 years, 76 (18%) 6 to <11 years, and 115 (27%) 11 to 16 years of age. The mean treatment duration was 26.1 days. A total of 246 patients received at least one dose of micafungin ranging from 2 to 51 mg/kg. Overall, 389/425 (91%) patients experienced at least one adverse reaction. Adverse reactions occurring in ≥15% or more of micafungin-treated pediatric patients 4 months of age and older are shown in Table 6. Hypokalemia (29%), diarrhea (24%), pyrexia (24%), hypoalbuminemia (22%), nausea (21%), mucosal inflammation (19%), thrombocytopenia (19%), abdominal pain (18%), headache (15%), and hypertension (15%).

Two randomized, double-blind active-controlled trials included pediatric patients. In the invasive candidiasis/candidemia trial, the efficacy and safety of micafungin (2 mg/kg/day for patients weighing 40 kg or less and 100 mg/day for patients weighing greater than 40 kg) was compared to amphotericin B liposome (3 mg/kg/day) in 112 pediatric patients. Treatment-emergent adverse reactions occurred in 51/56 (91%) of patients in the micafungin group and 52/56 (93%) of patients in the amphotericin B liposome group. The most common treatment-emergent adverse reactions resulting in drug discontinuation were reported in 2 (4%) micafungin-treated pediatric patients and in 9 (16%) amphotericin B liposome-treated pediatric patients.

The prophylaxis study in patients undergoing HSCT investigated the efficacy of micafungin (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 8 pediatric patients experienced at least one treatment-emergent adverse reaction. Three (7%) pediatric patients discontinued micafungin due to adverse reaction, while one (2%) patient discontinued fluconazole.

The selected adverse reactions, occurring in 15% or more of the patients and more frequently in a micafungin group, for the two comparative trials are shown in Table 6.

Table 6. Selected Adverse Reactions in Pediatric Patients with Candidemia and Other Candida Infections and Prophylaxis of Candida Infections in Stem-Cell Recipients During Prophylaxis of Candidiasis Infections

Adverse Reactions[1]	Candidemia and Other Candida Infections		Prophylaxis	
	Micafungin n = 58 n (%)	Amphotericin B liposome n = 56 n (%)	Micafungin n = 43 n (%)	Fluconazole n = 48 n (%)
Gastrointestinal disorders	22 (40)	18 (32)	43 (100)	45 (94)
Vomiting	10 (18)	8 (14)	18 (42)	32 (67)
Diarrhea	4 (7)	5 (9)	22 (51)	31 (65)
Nausea	4 (7)	4 (7)	30 (70)	25 (52)
Abdominal pain	2 (4)	2 (4)	15 (35)	12 (25)
Abdominal distension	1 (2)	1 (2)	8 (19)	6 (13)
General disorders and administration site conditions	14 (25)	14 (25)	41 (95)	46 (96)
Pyrexia	5 (9)	9 (16)	26 (61)	31 (65)
Infusion related reaction	0	3 (5)	7 (16)	4 (8)
Skin and subcutaneous tissue disorders	11 (20)	8 (14)	33 (77)	38 (79)
Pruritus	0	1 (2)	14 (33)	15 (31)
Rash	1 (2)	1 (2)	13 (30)	10 (27)
Urticaria	0	1 (2)	6 (19)	4 (8)
Respiratory, thoracic and mediastinal disorders	9 (16)	13 (23)	30 (70)	33 (69)
Dyspnea	0	0	4 (9)	8 (17)
Blood and lymphatic system disorders	17 (30)	13 (23)	40 (93)	46 (96)
Thrombocytopenia	5 (9)	3 (5)	21 (49)	37 (77)
Neutropenia	3 (5)	4 (7)	33 (77)	34 (71)
Anemia	10 (18)	6 (11)	22 (51)	34 (53)
Febrile neutropenia	0	0	7 (16)	7 (15)
Investigations	12 (21)	8 (14)	24 (56)	25 (52)
Aspartate aminotransferase increased	0	0	7 (16)	1 (2)
Urine output decreased	0	0	10 (23)	6 (17)
Cardiac disorders	7 (13)	3 (5)	10 (23)	17 (23)
Tachycardia	4 (7)	1 (2)	7 (16)	12 (25)
Renal and urinary disorders	4 (7)	4 (7)	16 (37)	15 (31)
Hematuria	0	0	10 (23)	7 (15)
Psychiatric disorders	1 (2)	0	20 (47)	9 (19)
Anxiety	0	0	10 (23)	3 (6)

*Study population included 20 pediatric patients younger than 4 months of age (10 in each arm).
[1] Within a system organ class, adverse reactions are ordered by decreasing frequency.

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

- *Hepatobiliary disorders:* hyperbilirubinemia
- *Investigations:* blood lactate increased
- *Renal disorders:* renal failure

Clinical Trials Experience in Pediatric Patients Younger than 4 Months of Age

The safety of micafungin was assessed in 168 pediatric patients younger than 4 months of age who received single doses of micafungin in 9 clinical trials. The mean treatment duration was 16.6 days. A total of 59 patients received micafungin at doses ≤4 mg/kg/day and 109 patients received micafungin doses >4 mg/kg/day (8 to 15 mg/kg/day; approximately 1.3 to 3.8 times the recommended dosage in pediatric patients less than 4 months old).

The adverse reaction profile of micafungin in pediatric patients younger than 4 months of age was generally comparable to that of pediatric patients 4 months of age and older adults. The most frequent adverse reactions (≥15%) in pediatric patients younger than 4 months old receiving a micafungin dose of approximately 4 mg/kg/day included hypokalemia (25%), thrombocytopenia (25%), acidosis (20%), sepsis (20%), anemia (15%), oxygen saturation decreased (15%), and vomiting (15%). No new safety signals were seen in patients who received 5 to 15 mg/kg/day *[see Use in Specific Populations (8.4)]*.

Additional clinically significant adverse reactions reported in less than 15% of pediatric patients younger than 4 months of age who received approximately 4 mg/kg/day are listed below:

- *Blood and Lymphatic System Disorders:* leuko-cytosis, thrombocytosis, coagulation disorder neonatal
- *Gastrointestinal Disorders:* hematochezia, intestinal perforation, ileitis, ileus, intestinal infarction, diarrhea, abdominal distension
- *General Disorders and Administration Site Conditions:* peripheral swelling, generalized edema, pyrexia, infusion site extravasation, edema neonatal
- *Hepatobiliary Disorders:* hyperbilirubinemia
- *Investigations:* blood lactate dehydrogenase increased, blood urea increased, ECG QRS complex prolonged
- *Vascular Disorders:* neonatal hypotension, thrombophlebitis
- *Musculoskeletal and connective tissue disorders:* hypertonia neonatal
- *Respiratory, thoracic and mediastinal disorders:* pleural effusion, respiratory failure, neonatal aspiration, respiratory distress
- *Metabolism and Nutrition disorders:* hyperglycemia, dehydration, hypocalcemia, hypermagnesemia

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of micafungin for injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Blood and lymphatic system disorders:* disseminated intravascular coagulation
- *Hepatobiliary disorders:* hepatic failure
- *Renal and urinary disorders:* renal impairment
- *Skin and subcutaneous tissue disorders:* Stevens-Johnson syndrome, toxic epidermal necrolysis
- *Vascular disorders:* shock

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Micafungin

CYP3A4, CYP2C9 and CYP2C19 Inhibitors

Co-administration of micafungin with cyclosporine, itraconazole, voriconazole and fluconazole did not alter the pharmacokinetics of micafungin.

CYP2C19 and CYP3A4 Inducer

Co-administration of micafungin with rifampin and ritonavir did not alter the pharmacokinetics of micafungin.

Co-administration of Micafungin with Other Drugs

Co-administration of micafungin with mycophenolate mofetil (MMF), amphotericin B, tacrolimus, prednisone, sirolimus and nifedipine did not alter the pharmacokinetics of micafungin.

7.2 Effect of Micafungin on Other Drugs

CYP3A4 Substrates

Co-administration of single or multiple doses of micafungin on cyclosporine, tacrolimus, prednisone, voriconazole and fluconazole pharmacokinetics.

Sirolimus AUC was increased by 21% with no effect on C_{max} in the presence of steady-state micafungin compared with sirolimus alone. Nifedipine AUC and C_{max} were increased by 18% and 42%, respectively, in the presence of steady-state micafungin compared with nifedipine alone. Itraconazole AUC and C_{max} were increased by 22% and 11%, respectively. Patients receiving sirolimus, nifedipine, and itraconazole in combination with micafungin should be monitored for sirolimus, nifedipine, and itraconazole toxicity and the sirolimus, nifedipine, and itraconazole dosage should be reduced if necessary.

UDP-Glucuronyltransferase Substrate

Co-administration of mycophenolate mofetil (MMF) with micafungin did not alter the pharmacokinetics of MMF.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, micafungin may cause fetal harm when administered to a pregnant woman *(see Data)*. There is insufficient human data on the use of micafungin in pregnant women to inform a pharmacodynamic response and adverse reaction in animal reproduction studies, intravenous administration of micafungin sodium to pregnant rabbits during organogenesis at doses four times the adult exposure (based on mg/m² body surface area) resulted in visceral abnormalities and increased abortion *(see Data)*. Advise pregnant women of the risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal toxicity study in pregnant rabbits, intravenous administration of micafungin sodium during organogenesis (days 6 to 18 of gestation) resulted in fetal visceral abnormalities and abortion at 32 mg/kg, a dose equivalent to four times the recommended human dose based on body surface area comparisons. Visceral abnormalities included anomalous origin of the heart, lung, lobe, vena cava, retrocaval ureter, anomalous right subclavian artery, and dilatation of the ureter.

8.2 Lactation

Risk Summary

There are no data on the presence of micafungin in human milk, the effects on the breast-fed infant or the effects on milk production. Micafungin was present in the milk of lactating rats following intravenous administration. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for micafungin, and any potential adverse effects on the breast-fed child from micafungin, or from the underlying maternal condition.

8.4 Pediatric Use

Pediatric Patients 4 Months of Age and Older

The safety and effectiveness of micafungin for the treatment of esophageal candidiasis, candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses, and prophylaxis of *Candida* infections in patients undergoing HSCT have been established in pediatric patients 4 months of age and older. Use of micafungin for these indications and in this age group is supported by evidence from adequate and well-controlled studies in adult and pediatric patients with additional *pharmacokinetic* and safety data in pediatric patients 4 months of age and older [*see Indications and Usage (1), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)*].

Pediatric Patients Younger Than 4 Months of Age

Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses ***Without*** *Meningoencephalitis and/or Ocular Dissemination in Pediatric Patients Younger Than 4 Months of Age*

The safety and effectiveness of micafungin have **not** been established for the treatment of candidemia **with** meningoencephalitis and/or ocular dissemination in pediatric patients younger than 4 months of age.

In a rabbit model of hematogenous *Candida* meningoencephalitis (HCME) with *Candida albicans* (minimum inhibitory concentration of 0.125 mcg/mL), a decrease in mean fungal burden in central nervous system (CNS) compartment assessed as the average of combined fungal burden in the cerebrum, cerebellum, and spinal cord tissues to unbiased estimates, was observed with increasing micafungin dosages administered once daily for 7 days. Data from the rabbit model suggest that a micafungin dose regimen of 4 mg/kg once daily is inadequate to treat meningoencephalitis and that a dose regimen of approximately 10 to 25 mg/kg once daily may be necessary to lower fungal burden in the CNS to 1 log10 colony forming units (CFU) per gram of tissue in immunocompetent rabbits. In this rabbit model, micafungin concentrations could not be reliably detected in cerebrospinal fluid (CSF). Due to limitations of the study design, the clinical significance of a decreased CNS fungal burden in the rabbit HCME model is unknown.

A randomized controlled trial evaluated a micafungin dose regimen of 10 mg/kg once daily in pediatric patients younger than 4 months of age with suspected or proven *Candida* meningoencephalitis. Fungal-free survival at week after end of treatment was defined in 65% of micafungin-treated vs. 70% of amphotericin B-treated patients, and all-cause mortality was 15% vs. 10%, respectively. Micafungin exposure in this study was lower than exposure in adult HSCT recipients receiving more than 4 months of age (20 fungal with neutropenia) and 10 fungal with neutropenia) 8 weeks was 13% of the planned enrollment for the study, no conclusions can be drawn regarding efficacy of micafungin at this dose regimen.

In six uncontrolled, open-label studies, and a neonatal intensive care unit (ICU) medical records database, patients younger than 4 months of age with proven or suspected *Candida* meningoencephalitis or disseminated candidiasis received micafungin at dose regimens ranging from 1 to 5 to 10 mg/kg once daily. Across the entire pediatric population, the majority of these patients with proven *Candida* meningoencephalitis were treated with dosages of 2 mg/kg, 8 mg/kg and 10 mg/kg once daily. Data from these studies suggest that micafungin is active against suspected *Candida* meningoencephalitis. No conclusions regarding the efficacy of a particular dosage of micafungin or the generation of micafungin into the CSF can be drawn due to limitations of the data, including but not limited to, multiple confounding factors, variable study designs, and limited numbers of patients. No new safety signals were observed with the use of micafungin at dosages of 5 to 15 mg/kg once daily in pediatric patients younger than 4 months of age, and there was no discernible dose-response for adverse events.

Although the dosage for the treatment of candidemia with meningoencephalitis has not been established, antifungal activity in various CNS compartments in the rabbit HCME model and limited clinical trial data suggest that in patients younger than 4 months of age, dose regimens 10 mg/kg once daily or higher may be necessary for the treatment of candidemia with meningoencephalitis. Safety data from clinical studies for micafungin at dose regimens of 10 to 15 mg/kg once daily in pediatric patients younger than 4 months of age did not reveal new safety signals.

Treatment of Esophageal Candidiasis and Prophylaxis of Candida Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation in Pediatric Patients Younger Than 4 Months of Age

The safety and effectiveness of micafungin in pediatric patients younger than 4 months of age have not been established for:

- Treatment of esophageal candidiasis
- Prophylaxis of Candida infections in patients undergoing hematopoietic stem cell transplantation

8.5 Geriatric Use

A total of 418 subjects in clinical studies of micafungin 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 micafungin dose administered as a single 1-hour infusion to 10 healthy subjects aged 66 to 78 years were not significantly different from those in 10 healthy subjects aged 20 to 24 years. No dose adjustment is necessary for elderly.

8.6 Use in Patients with Renal Impairment

Micafungin 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 Undergoing Hemodialysis

Dose adjustment of micafungin 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 micafungin 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 observed. Micafungin AUC was greater by 19% in Japanese subjects compared to blacks, due to smaller body weight.

DRUG ABUSE AND DEPENDENCE

There has been no evidence of either psychological or physical dependence or withdrawal or rebound phenomena observed.

10 OVERDOSAGE

Micafungin is highly protein bound and, therefore, is not dialyzable. No cases of micafungin overdosage have been reported. Repeated daily doses up to 8 mg/kg (maximum total dose of 996 mg) in adult patients, up to 4 mg/kg (maximum total dose of 296 mg) in adult patients, and up to 15 mg/kg in pediatric patients younger than 4 months of age have been administered in clinical trials with no reported dose-limiting toxicity [*see Adverse Reactions (6.1) and Use in Specific Populations (8.4)*].

11 DESCRIPTION

Micafungin for injection 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 sp. strain 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 sodium (equivalent to 50 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). Micafungin for injection 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-[(4R,5R)-4,5-dihydroxy-N*-[4-[5-(4-[pentyloxy]phenyl)-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-phenyl-5-oxo-L-leucine], 5-sulfo(phenylmethyl)-L-threonine], monosodium salt.

The chemical structure of micafungin sodium is:

$C_{56}H_{71}N_9Na_2O_{23}S$ M.W. 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 methanol, 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 Microbiology (12.4)*].

12.2 Pharmacodynamics

The pharmacodynamics of micafungin related to hematogenous *Candida* meningoencephalitis are described in other sections of the prescribing information [*see Use in Specific Populations (8.4) and Microbiology (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. Typically, 85% to 95% of steady-state concentration is achieved after three daily micafungin doses.

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	Dose (mg)	Pharmacokinetic Parameters Mean (Coefficient of Variation %)			
		C_{max} (mcg/mL)	AUC_{168} (mcg·hr/mL)*	t½ (hr)	Cl (mL/min/kg)
Patients with IC† [Day 1]	20	100	5.7 ± 22.8	83 ± 51	14.5 ± 7.0	0.359 ± 0.179
[Steady State]	20	100	10.1 ± 4.4	87 ± 29	13.4 ± 2.0	0.298 ± 0.115
HSCT‡ Patients with EC‡ [Day 1]	20	20	4.1 ± 1.4	36 ± 9	14.9 ± 4.3	0.921 ± 0.298
	100	100	8.0 ± 2.4	108 ± 31	13.8 ± 3.0	0.327 ± 0.093
	14	12	11.6 ± 3.1	131 ± 42	14.1 ± 2.8	0.340 ± 0.082
[Day 14 or 21]	20	50	5.1 ± 1.5	54 ± 13	15.6 ± 2.8	0.300 ± 0.063
	100	100	10.1 ± 2.8	110 ± 25	16.6 ± 4.4	0.301 ± 0.088
	14	150	16.4 ± 6.5	187 ± 60	15.2 ± 2.2	0.297 ± 0.081
HSCT‡ Recipients [Day 7]	per kg					
	8	3	21.1 ± 2.8	234 ± 34	14 ± 1.4	0.214 ± 0.031
	4	6	9.8 ± 1.3	139 ± 72	14.2 ± 3.3	0.463 ± 0.239
	2	8	38.4 ± 5.7	479 ± 101	14.9 ± 2.6	0.224 ± 0.064
	1	9	50.8 ± 10.9	565 ± 251	14.2 ± 2.3	0.221 ± 0.098

* AUC_{168} is presented for day 1 AUC_{24} is presented for steady state.
† Invasive candidiasis infection
‡ Immunosuppressive
§ esophageal candidiasis
¶ hepatobiliary stem cell transplant

Pediatric Patients 4 Months of Age and Older

Micafungin pharmacokinetic data in 20 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}† (mcg/mL)	AUC_{24} (mcg·hr/mL)	t½ (hr)	$CL^{\S}$ (mL/min/kg)
30 kg or less	149	2.0	14.2 +/- 9.3	108 +/- 31	12.5 +/- 4.6	0.328 +/- 0.091
		4.0	21.2 +/- 14	204 +/- 47		
		1.0	8.7 +/- 5.6	67 +/- 17		
Greater than 30 kg	20	2.0	17.5 +/- 11.2	134 +/- 33	13.6 +/- 8.8	0.241 +/- 0.061
		4.0	23 +/- 14.8	178 +/- 42		

* Or the equivalent if receiving the adult dose (50, 100, or 150 mg)
† Derived from plots from the population PK model.
‡ Derived from the population PK model.
§ Derived from the population PK model.

Pediatric Patients Younger than 4 Months of Age

Micafungin pharmacokinetic data in 103 pediatric patients less than 4 months of age were assessed using population pharmacokinetics. Predicted micafungin AUC estimates were dose proportional across the dose regimens and age ranges studied. The body weight-normalized micafungin clearance in pediatric patients less than 4 months of age is higher than the body weight-normalized micafungin clearance in older pediatric patients greater than 4 months of age and adults.

Administration of 4 mg/kg once daily micafungin to pediatric patients less than 4 months of age produces a mean (SD) steady-state AUC of 131 (50 mcg·hr/mL) which is comparable to the steady-state AUC in pediatric patients 4 months of age and older administered micafungin 2 mg/kg/day and adults administered 100 mg once daily.

Specific Populations

Adult Patients with Renal Impairment

Micafungin does not require dose adjustment in patients with renal impairment. A single 1-hour infusion of 550 mg micafungin was administered to 10 subjects with severe renal impairment (creatinine clearance 4 to 30 mL/min/1.73 m2 aged 70 to 9 age, gender, and weight-matched subjects with normal renal function (creatinine clearance greater 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 micafungin was administered to 8 adult subjects with moderate hepatic impairment (Child-Pugh score 7 to 9) and 8 age-, gender-, and weight-matched subjects with normal hepatic function. The C_{max} and AUC values of micafungin were approximately 22% in subjects with moderate hepatic impairment compared to normal subjects. This difference in micafungin exposure does not require dose adjustment of micafungin in patients with moderate hepatic impairment.

• A single 1-hour infusion of 100 mg micafungin was administered to 8 adult subjects with severe hepatic impairment (Child-Pugh score 10 to 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, the exposure (and 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 (greater than 99%) protein bound in vitro, independent of plasma concentrations over the range of 10 mcg/mL to 100 mcg/mL. Micafungin binds primarily to albumin; however, nitrofungin, at therapeutically relevant concentrations, does not competitively displace bilirubin binding to albumin. Micafungin also binds to a lesser extent to α1-and β1-globulins.

Micafungin is neither a substrate nor an inhibitor of P-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 the tetrahydropyrimidine moiety. Cytochrome P450 (CYP) isoenzyme, Even though micafungin is a substrate for and a weak inhibitor of CYP3A in vitro, hydroxylation by CYP3A is not a major pathway of micafungin metabolism in vivo. Micafungin is neither a clinically relevant inhibitor nor inhibitor *in vivo*.

In four human liver microsomes, 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 (50 mg) was studied in healthy male subjects. Urinary excretion of radioactivity was minary and fecal recovery of total radioactivity accounted for 82.5% (76.4% to 87.9%) of the administered radioactivity. Feces is the major route of elimination (fecal 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.

Activity in Animal Models of Candidiasis

Activity of micafungin against *Candida* was demonstrated in both mucosal and disseminated murine and rabbit models of candidiasis. Micafungin administered to immunocompetent or immunosuppressed mice or rabbits with disseminated candidiasis demonstrated a dose-response effect on reduction of fungal burden in different organs including brain in a dose-dependent manner (mice and rabbits). Overall, the data from these animal models of candidiasis suggest that 1 mg/kg/day is the minimum dose required in adults with HCME infection caused by a susceptible strain of *C. albicans*; however, the activity varied in different central nervous system and ocular compartments. In the cerebrum, culture negative was achieved at a micafungin dose regimen of 32 mg/kg once daily for 7 days; whereas, in spinal cord, vitreous humor, and choroid, culture negative was achieved at micafungin dose regimen of 32 mg/kg once daily. In a neutropenic rabbit model of candidiasis, micafungin dose regimens between 8 and 24 mg/kg once daily reduced fungal burden in the cerebrum and cerebellum. When cerebrum, cerebellum, and spinal cord data were combined, a decrease in fungal burden relative to untreated controls was evident at micafungin dose regimens between 16 and 32 mg/kg once daily [*see Use in Specific Populations (8.4)*].

Resistance

There have been reports of clinical failures in patients receiving micafungin 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 [*see Indications and Usage (1)*]:

Candida albicans
Candida dubliniensis
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 in male rats administered 2 mg/kg/day and higher doses of micafungin. No hepatocellular lesions.

Male 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, enlarged livers, hepatocytes and altered hepatocellular foci after 1 or 2-month recovery periods, and adenomas were observed after a21-month recovery period. Rats administered micafungin sodium at 8 mg/kg/day (2 times the highest recommended human dose), after a 18-month 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 (2 or 6 months) exceed the usual duration of micafungin dosing in patients, which is typically less than 1 month for treatment of invasive 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 peritoneum of albino hypothermic female rats subjected to micafungin dosing, and the presence of adenomas and carcinomas in the recovery periods suggest a causal relationship between micafungin sodium, albino hypothermic female rat, and hepatic neoplasms. Whole-life carcinogenicity studies of micafungin in animals have not been conducted, and it is not known whether the hepatic neoplasms observed in rodent rats 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. Micafungin sodium (~ 5 g/kg/day, *i.v.*) (*micronucleus assay*) (*female* 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 AUC comparisons) and epididymal tubular degeneration at twice the recommended clinical dose, based on body surface area comparisons) resulted in higher epididymis weights and epididymal sperm counts. At 26-week intervals, epididymal tubular degeneration, seminiferous tubular atrophy and decreased sperm in the epididymis were observed at 10 and 32 mg/kg, (about 0.6 times and 2 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 shown hepatotoxicity in adult rats, manifested by elevated liver enzymes for 3 or 6 months, and these changes may be indicative of pre-malignant processes [*see Nonclinical Toxicity (13.1)*].

14 CLINICAL STUDIES

14.1 Treatment of Candidemia and Other Candida Infections in Adult and Pediatric Patients 4 Months of Age and Older

The efficacy of micafungin was established 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 one daily intravenous infusions (IV) of micafungin, either 100 mg/day or 150 mg/day or caspofungin (70 mg loading dose followed by 50 mg maintenance dose). Patients in both 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). Treatment success occurred during IV study drug therapy were treated as failures.

In this study, 111/578 (20.2%) 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 presented for patients receiving micafungin (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

	Micafungin 100 mg/day (N=215) % treatment difference (95%CI)	Caspofungin 70/50 mg/day* n (%)
Treatment Success at End of IV Therapy†		119/166 (83.3)
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)
Tissue Infection	41/52 (78.8)	16/5 (32.0)
Acute Disseminated‡	**Candidemia**	23/28
Endophthalmitis	1/3 (42.3)	1/1
Chorioretinitis	0/3	0
Skin	1/1	0
Kidney	1/1	0
Spleen	1/1	0
Pancreas	1/1	0
Lung/Sputum	0/1	0
Liver	0/1	0
Intraabdominal abscess	0/1	0/2
Chronic Disseminated		4
Candidemia	4/9 (66.7)	3/6 (40)
Success by Organism‡		
C. albicans	57/81 (70.4)	45/73 (61.6)
C. glabrata	16/23 (69.6)	19/30 (63.3)
C. parapsilosis	12/27 (68)	22/32 (68.8)
C. parapsilosis	12/20 (60)	13/20 (65)
C. inusei	5/9 (62.5)	2/3 (66.7)
C. guilliermondii	1/2 (50)	0/1 (0)
C. lusitaniae	0/3	2/2
Relapse through 6 Weeks‡		
Cured	49/135 (36.3)	44/119 (37)
Culture confirmed relapse	5	4
Required systemic antifungal therapy	11	5
Lost to follow-up	16	11
Not assessed	16	19
Overall study mortality	58/200 (29)	51/193 (26.4)
Mortality during IV therapy	28/200 (14)	27/192 (14)

* 70 mg loading dose on day 1 followed by 50 mg/day thereafter (maintenance dose).
† Patients IV receiving study drug therapy and documented invasive candidiasis or candidemia. Patients with *Candida endocarditis* were excluded from the analysis.
‡ Patients may have had greater than 1 organ of dissemination.
§ A patient may have had greater than 1 baseline infection species.
¶ Patients who received no study drug treatment and received antifungal therapy in the post treatment period for a suspected or proven fungal infection. Also includes patients who died before treatment.

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

14.2 Treatment of Esophageal Candidiasis in Adult and Pediatric Patients 4 Months of Age and Older

In two controlled trials involving 763 patients with esophageal candidiasis, 445 adults with endoscopically-proven candidiasis of the upper gastrointestinal tract (EC) received micafungin for a duration of 14 days (range 1 to 33 days).

The efficacy was evaluated in a randomized, double-blind study which compared micafungin 150 mg/day (n = 266) to intravenous fluconazole 200 mg/day (n = 258) in adults with endoscopically-proven esophageal candidiasis. Patients in this study had HIV infection, 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 the absence of lesions on endoscopy. 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 micafungin and fluconazole treatment groups.

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

Treatment Outcome*	Micafungin 150 mg/day n = 260	Fluconazole 200 mg/day n = 249	% Difference (95% CI)
Endoscopic Cure	228 (87.7%)	227 (88%)	-0.3% (-5.6, +5.3)
Clinical Cure	229 (91.3%)	227 (91.3%)	0.08% (-4.6, +4.8)
Overall Therapeutic Cure	223 (85.8%)	220 (85.3%)	0.5% (-5.6, +6.6)
Mycological Eradication†	141/180 (78%)	140/162 (77.8%)	0% (-11.4, +11.4)

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 Micafungin - fluconazole

Most patients (96%) in this study had *Candida albicans* isolated at baseline. The efficacy of micafungin 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 micafungin 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	Micafungin 150 mg/day (N=260)	Fluconazole 200 mg/day (N=249)	% Difference*
Relapse† at Week 2	40 (17.9%)	30 (13.6%)	4.3% (-2.3, 11.1)
Relapse‡ through Week 4 (cumulative)	73 (32.7%)	62 (28.2%)	4.6% (-4.1, 13.1)

Calculated as Micafungin - 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 antifungal 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 192/350 (83.5%) micafungin-treated patients and 189/229 (82.1%) of fluconazole-treated patients had complete resolution of signs and symptoms of oropharyngeal candidiasis. Of these, 32.3% in the micafungin 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 micafungin group and 39.4% in the fluconazole group (treatment difference = 12.7%, 95% confidence interval [3.5, 22.2]).

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

In a randomized, double-blind study, micafungin 50 mg/day (if 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 pediatrics, except 2 per group, received allogeneic transplants. The status of the patients' underlying malignancy at the time of randomization was: 369 (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 (17%), acute lymphocytic leukemia (13%), and non-Hodgkin's lymphoma (13%). In the 394 autologous and syngeneic transplant recipients the more common baseline underlying diseases were: multiple myeloma (37.5%), non-Hodgkin's lymphoma (36.4%), and Hodgkin's disease (15.6%). During the study, 37 (4.2%) of the 882 patients received a prior fluconazole-based prophylaxis, and 47% 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 10 cells/mm^3 or greater on 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 fluconazole group (mean difference = 1 day). Prophylaxis for duration 32 days compared to the adult patients who received micafungin (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 to week 2 post-therapy (usually 32 days). A suspected systemic fungal infection was diagnosed in patients with neutropenia (ANC less than 500 cells/mm^3), persistent or recurrent fever of at least 96 hours despite at least 4 days of broad-spectrum antibiotics, and the absence of a 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 temperature 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 micafungin recipients, and in 73.7% of adult and pediatric patients who received fluconazole (Table 12) (Mean difference = 7.0%, 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 micafungin and 2 in the fluconazole group.

The efficacy of micafungin 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	Micafungin 50 mg/day (N = 441)	Fluconazole 400 mg/day (N = 441)
Success*	343 (80.7%)	337 (73.7%)
Failures	82 (19.3%)	120 (26.3%)
All Deaths†	18 (4.2%)	26 (5.7%)
Proven/probable fungal infection prior to death	1 (0.2%)	2 (0.7%)
Proven/probable infection (not resulting in death)	6 (1.4%)	6 (1.3%)
Suspected fungal infection ‡	53 (12.5%)	83 (18.2%)
Lost to follow-up	5 (1.2%)	3 (0.7%)

Difference (Micafungin - fluconazole): +7.0%
(95% CI = 1.5, 12.5)
* Success = study (4 weeks post-therapy)
† Through end-of-therapy

16 HOW SUPPLIED/STORAGE AND HANDLING

Micafungin for injection is a sterile, white lyophilized powder for reconstitution for intravenous infusion, and is available in the following packaging configurations:

Product Code	Unit of Sale	Strength	Each
72911/0	NDC 63323-728-10 Unit of 10 packaged in individual cartons.	50 mg	NDC 63323-728-01 10 mL single dose vial coated with a light protective flap and sealed with a red flip off cap.
72910/0	NDC 63323-729-10 Unit of 10 packaged in individual cartons.	100 mg per vial	NDC 63323-729-01 10 mL single dose vial coated with a light protective flap and sealed with a red flip off cap.

Storage

Unopened vials of lyophilized material must be stored at room temperature, 25°C (77°F); excursions permitted to 15°C 30°C (59°F 86°F) [see USP Controlled Room Temperature].

Store the reconstituted product at 25°C (77°F) *[see Dosage and Administration (2.4)]*.

Store the diluted solution at 25°C (77°F) *[see Dosage and Administration (2.4)]*.

Protect from light.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity

Inform patients about the serious adverse effects of Micafungin for injection including hypersensitivity reactions e.g., anaphylaxis and hepatobiliary adverse reactions.

Hepatic

Inform patients about the serious adverse effects of Micafungin for injection including hepatic effects e.g., abnormal liver tests, hepatic impairment, hepatitis or worsening hepatic failure.

Hematologic

Inform patients about the serious adverse effects of Micafungin for injection including hematological effects e.g., acute intravascular hemolysis, hemolytic anemia and hemoglobinuria.

Renal

Inform patients about the serious adverse effects of Micafungin for injection including renal effects e.g., elevations in BUN and creatinine, renal impairment or acute renal failure.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk of Micafungin for injection to a fetus. Advise females to inform their healthcare prov