National PBM Drug Monograph
Micafungin (Mycamine™)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

EXECUTIVE SUMMARY

Micafungin is the second antifungal in the echinocandin class and was approved in 2005 for treatment of esophageal candidiasis and for prophylaxis of *Candida* infection in patients undergoing hematopoietic stem cell transplantation (HSCT).

Micafungin is fungicidal against most clinically relevant species of *Candida*. It also has activity against many other fungi, including *Aspergillus spp*. In-vitro data show that micafungin is active against fluconazole-resistant *Candida.*

There are 3 published clinical trials evaluating micafungin in the treatment of endoscopically confirmed symptomatic esophageal candidiasis; 1 was a dose-finding study and 2 compared micafungin and fluconazole. In the 2 comparator trials, the primary endpoint was endoscopic cure rate (defined as endoscopy grade=0) at end of therapy. In the intent-to-treat population, the endoscopic cure rate of micafungin 150mg IV daily and fluconazole 200mg IV daily was 87.7-89.8% and 86.7 -88% respectively. The percent of patients who had a clinical response of cleared (defined as clinical grade 0 for all symptoms) was 91.9 - 92.7% and 91.9-93% for micafungin and fluconazole respectively.

A large pivotal trial compared micafungin 50mg IV once daily to fluconazole 400mg IV once daily for prophylaxis of *Candida* infection in patients undergoing HSCT. The primary endpoint was treatment success defined as the absence of proven, probable, or suspected systemic fungal infection through the end of prophylaxis therapy and as the absence of a proven or probable systemic fungal infection through the end of the 4-week post- treatment period. Overall success was achieved in 80.7% and 73.7% of patients receiving micafungin and fluconazole (respectively treatment difference= 6.5% [95%CI 0.9%, 12%] p=.03)

Micafungin has also been evaluated for treatment of severe infections due to *Candida* or *Aspergillus.*

The majority of adverse events (AE) were considered to be mild-moderate in severity. In general, adverse hematologic events occurred slightly more frequently with micafungin compared to fluconazole whereas increased liver function tests were slightly more common with fluconazole than micafungin.

Micafungin is not a substrate for or an inhibitor of P-glycoprotein; therefore, drug interactions via this mechanism are unlikely. Micafungin is a substrate for and a weak inhibitor of CYP3A4; however, this is not a major pathway for micafungin metabolism, so drug interactions via this pathway are not expected.

Micafungin is only available intravenously. For the treatment of esophageal candidiasis, the recommended dose is 150mg/day. In the clinical trials, the mean duration of treatment was 15 days (range 10-30days). For prophylaxis of Candida infections in hematopoietic stem cell transplant recipients, the dose is 50mg/day. The mean duration of prophylaxis was 19 days (range 6-51days).

Micafungin is an alternative to azole antifungals for patients with esophageal candidiasis or for those who require prophylaxis of Candida infections during HSCT who have contraindications, adverse events, significant drug interactions, or fluconazole-resistant *Candida* or for patients unable to tolerate amphotericin B.

INTRODUCTION

Micafungin is in the class of antifungals known as echinocandins. Currently, the only other echinocandin on the market is caspofungin. Another echinocandin, anidulafungin, has recently been submitted to the FDA for review. Micafungin was approved in 2005 for treatment of esophageal candidiasis and for prophylaxis of Candida infection in patients undergoing HSCT. At this time the only other agent FDA approved for prophylaxis of Candida infections in HSCT is fluconazole; however, published data exist for low-dose amphotericin and itraconazole and there is an ongoing study with voriconazole.

PHARMACOLOGY

The echinocandins inhibit the synthesis of (1, 3)-β-D-glucan, an essential component of fungal cell walls, resulting in interference with fungal cell wall synthesis.

PHARMACOKINETICS

The pharmacokinetics of micafungin have been determined in HIV-positive patients with esophageal candidiasis (n=54) and in patients undergoing HSCT (n=34). The concentration of micafungin increases proportionally with increasing dose. The data presented in table 1 were obtained from the product package insert.

Table 1: Pharmacokinetics

	HIV + with esophageal candidiasis (day 14 or 21)			HSCT (day 7)			
Dose	**50mg**	**100mg**	**150mg**	**3mg/kg**	**4mg/kg**	**6mg/kg**	**8mg/kg**
Cmax (μg/mL)	5.1 ± 1.0	10.1 ± 2.6	16.4 ± 6.5	21.1 ± 2.84	29.2 ± 6.2	38.4 ± 6.9	60.8 ± 26.9
AUC_{0-24} (μg • h/mL)	54 ± 13	115 ± 25	167 ± 40	234 ± 34	339 ± 72	479 ± 157	663 ± 212
t1/2 (h)	15.6 ± 2.8	16.9 ± 4.4	15.2± 2.2	14 ± 1.4	14.2 ± 3.2	14.9 ± 2.6	17.2 ± 2.3
Cl (mL/min/kg)	0.300 ± 0.063	0.301 ± 0.086	0.297 ± 0.081	0.214 ± 0.031	0.204 ± 0.036	0.224 ± 0.064	0.223 ± 0.08
Distribution (L/kg)		0.39 ± 0.11			ND		

Micafungin is highly protein bound (> 99%) primarily to albumin and to a lesser extent to α_1-acid-glycoprotein. There are 3 metabolites (M-1, M-2, M-3). M-1 and M-2 are formed via arylsulfatase and catechol-O-methyltransferase respectively. M-5 is formed by hydroxylation via CYP3A (minor pathway). Fecal excretion is the major route of elimination.

IN-VITRO SUSCEPTIBILITY

Micafungin is fungicidal against most clinically relevant species of Candida. In-vitro susceptibility of micafungin against the most common Candida spp. is shown in table 2. Higher MIC values were seen for *C. parapsilosis* and *C. lusitaniae.* Please note that methods for susceptibility testing and interpretive breakpoints for the echinocandins have not been established. Cross-resistance to amphotericin B and the azole antifungals is not expected due to differing mechanisms of action.

Takakura et al. reported that the micafungin MICs for fluconazole- or voriconazole-resistant isolates (median 0.016mcg/ml; range ≤0.008-1) were not higher than those for susceptible isolates (median 0.031mcg/ml; range ≤0.008-4).[1]

Table 2: In-vitro activity of micafungin against the most common *Candida* spp.

Organism	Study	# isolates	MIC_{90} (μg/mL)	MIC range
C. albicans	Takakura 2004	218	0.016	≤0.008-0.031
	Ostrosky-Zeichner 2003*	733	0.03	NR
	Espinel-Ingroff 2003	966	0.01-0.25	≤0.01-0.5
C. glabrata	Takakura 2004	96	0.031	≤0.008-1
	Ostrosky-Zeichner 2003*	458	0.06	NR
	Espinel-Ingroff 2003	524	0.01-0.5	≤0.01->8
C. parapsilosis	Takakura 2004	123	2	≤0.008-4
	Ostrosky-Zeichner 2003*	391	2	NR
	Espinel-Ingroff 2003	439	1.0->8	0.03->8
C. tropicalis	Takakura 2004	62	0.031	≤0.008-0.25
	Ostrosky-Zeichner 2003*	307	0.06	NR
	Espinel-Ingroff 2003	364	<0.01->8	0.03-2
C. krusei	Takakura 2004	13	0.125	0.063-0.25
	Ostrosky-Zeichner 2003*	50	0.25	NR
	Espinel-Ingroff 2003	82	0.12-0.25	0.06-4
C. lusitaniae	Ostrosky-Zeichner 2003	20	2.0	NR
C. dubliniensis	Ostrosky-Zeichner 2003*	18	0.03	NR
	Espinel-Ingroff 2003	40	0.03-0.5	<0.06-1.0

MIC endpoints after 48 hours of incubation

*data for Ostrosky-Zeichner is included in the review by Espinel-Ingroff. Because data were from isolates obtained in the U.S., results are also shown separately

Micafungin also has fungistatic activity against *Aspergillus* spp. MICs for several Aspergillus species are shown in table 3. Micafungin also has moderate activity against *Cladosporium trichoides, Exophiala dermatitidis, Exophiala spinifera, Fonsecaea pedrosoi* and variable activity against *H. capsulatum, B. dermatitidis, Coccidioides immitis, P. brazilienensis, Penicillium marneffei*, and *Sporothrix schenckii.*[11]

Table 3: In-vitro activity of micafungin against Aspergillus[11]

organism (# isolates)	***A. flavus* (31)**	***A. fumigatus** (99)**	***A. nidulans* (3)**	***A. niger* (18)**	***A. terreus* (12)**	***A. versicolor* (3)**
MIC (mcg/ml)	≤0.0078 – 0.25	<0.0078- >64	≤0.0078	≤0.0078	≤0.0078 – 0.0156	≤0.0078 – 0.0156

*70 isolates had a MIC ranging from ≤0078 – 0.25 and 19 had MIC > 64mcg/ml

FDA INDICATIONS
- Treatment of esophageal candidiasis
- Prophylaxis of Candida infection in patients undergoing hematopoietic stem cell transplantation.

VA FORMULARY ALTERNATIVES
Fluconazole, itraconazole

DOSAGE
For the treatment of esophageal candidiasis, the recommended dose is 150mg/day. In the clinical trials, the mean duration of treatment was 15 days (range 10-30days).

For prophylaxis of Candida infections in hematopoietic stem cell transplant recipients, the dose is 50mg/day. The mean duration of prophylaxis was 19 days (range 6-51days).

No dosing adjustment is needed based on race, gender, renal dysfunction, or mild-moderate hepatic insufficiency. Micafungin has not been studied in patients with severe hepatic dysfunction.

PREPARATION AND ADMINISTRATION
Micafungin is packaged as 50mg single-use vials coated with a light protective film. Each vial should be reconstituted with 5ml of 0.9% sodium chloride injection USP (without bacteriostatic agent). Dextrose 5% may also be used. This will yield approximately 10mg/ml of micafungin.

For prophylaxis of candida infections, one 50mg vial will be needed. The reconstituted solution should be diluted with 100ml of 0.9% sodium chloride injection USP (or 5% dextrose USP).

For the treatment of esophageal candidiasis, three 50mg vials will be needed. The reconstituted solution should be diluted with 100ml of 0.9% sodium chloride injection USP (or 5% dextrose USP).

An existing IV line should be flushed with 0.9% sodium chloride injection USP, prior to micafungin infusion.

Micafungin should be infused over 1 hour. More rapid infusion may result in more frequent histamine mediated reactions.

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

EFFICACY
Treatment of esophageal candidiasis
There are 3 published clinical trials evaluating micafungin in the treatment of endoscopically confirmed symptomatic esophageal candidiasis. One was a dose-response study comparing micafungin 12.5mg, 25mg, 50mg, 75mg, and 100mg administered once daily in HIV-positive patients.[4] The second study compared micafungin 50mg, 100mg, 150mg and fluconazole 200mg IV administered once daily in 245 HIV-positive patients.[5] The third study (n=518) compared once daily IV administration of micafungin 150mg and

fluconazole 200mg (94% were HIV-positive).[6] Treatment was to last for at least 14-days, but may be extended for up to 21 days [4,5] or for 7 days after resolution of symptoms, whichever was longer[6]. Mean CD4 counts ranged from 60-119.5 cells/mm3 [5, 6] and in Pettengell, the median value was 27cells/mm3[4]. At baseline, approximately 10% of patients were receiving antiretroviral therapy.[6] See appendix 1 for baseline symptom and endoscopy scores. Grading of mucosa and clinical symptoms are described in table 4.

Table 4: Mucosal and clinical symptom grades

	0	1	2	3
Mucosal grade	no evidence of EC-associated plaques	individual raised plaques, each ≤ 2mm in size	multiple raised white plaques > 2mm in size	confluent plaques combined with ulceration
Clinical symptom grade				
• Dysphasia • Odonophasia • Retronsternal pain	• swallows food normally • none • none	• swallows solid food with difficulty • food causes pain; little or no pain with liquids • low-grade intermittent or continuous pain	• can swallow soft food or liquid only • liquids cause pain; will not eat solids • continuous pain, soreness, or burning; may require some pain medication	• can swallow small amounts of liquid or cannot swallow • accepts small sips of liquids only or will not swallow • very painful; requires analgesia

Candida albicans was recovered in over 98% of the samples at baseline. *C. glabrata* was the second most common pathogen occurring in 1.8-6.6% of isolates. Other infrequently isolated candidal organisms included *C. tropicalis, C. krusei, C. parpsilosis, C. kefyr,* and *C. inconspicua*. Only 1 study discussed fluconazole resistance, and found two *C. albicans* isolates to be resistant (MIC > 64 μg/ml).[5]

In Pettengell, the primary endpoint was cure or improvement of clinical signs and symptoms at end of therapy (EOT).[4] Primary endpoint for both de Wet studies was endoscopic cure rate (defined as endoscopy grade=0) at EOT.[5, 6] Secondary outcomes include clinical response rate as defined in table 5.

Table 5: Definitions for clinical response

	de Wet 2004	de Wet 2005
• cleared • improved • unchanged • worse	• clinical grade 0 for all symptoms • clinical grade reduction of symptoms by ≥ 2 clinical grades or achievement of a clinical grade of 0 for ≥ 1 symptoms • no change • progression of symptoms	• clinical grade 0 for all symptoms • improvement from total baseline score by ≥ 2 and no grade increase of any symptom • does not meet definition of improved or cleared and no grade increase in any clinical symptom • grade increase in any clinical symptom from baseline

Definitions were not provided in Pettengell et al.

In the first study, Pettengell showed that the 12.5mg and 25mg doses resulted in the lowest clinical response rate (33.3 and 53.8% respectively). The response rate was approximately 85% with both the 50mg and 75 mg doses, followed by the highest response rate with the 100mg dose (94.7%). Improvement in mucosal lesion grade followed a similar trend. Improvement in symptoms occurred within 3-5 days of therapy.[4]

In the second study, a dose-dependent response for endoscopic cure was also seen (68.6%, 77.4%, and 89.8% for the 50mg, 100mg, and 150mg respectively). The response rate for fluconazole was 86.7% and was not significantly different from micafungin 100mg and 150mg. Approximately 93% of patients receiving micafungin 100mg, 150mg or fluconazole had a clinical response of cleared at EOT compared to 75.8% with the 50mg dose. Approximately 75% of patients had improved symptoms scores between 3-7 days of treatment. Relapse occurred in 9 patients in the micafungin groups and none in the fluconazole group. (See appendix 1 for study details and results of other secondary outcomes).[5]

In the third study, micafungin 150mg was found to be non-inferior to fluconazole 200mg (87.7% and 88% respectively) based on endoscopic cure rate. The authors state that baseline severity of mucosal lesions did not result in significant differences in endoscopic cure rates between treatment groups. For both micafungin and fluconazole the clinical response rate of cleared at EOT was 91.9%. Noticeable improvement in symptoms was

seen within 3-5 days of treatment. Relapse rate through post-treatment week 4 was 15.2% and 11.3% for micafungin and fluconazole respectively (p=0.257). In 17 patients who had persistent mucosal lesions, 3 were found to have C*andida* organisms resistant (n=2) or have dose-dependent susceptibility (n=1) to fluconazole. All 3 were randomized to receive fluconazole. (See appendix 1 for study details and results of other secondary outcomes)[6]

Prophylaxis of Candida infection in patients undergoing hematopoietic stem cell transplantation

Micafungin 50mg IV daily was compared to fluconazole 400mg IV daily in patients undergoing HSCT in a large randomized study (n=882) using a non-inferiority design.[7] Treatment was initiated within 48h of the beginning of the transplant-related conditioning regimen and continued until ANC ≥ 500cells/mm3 or up to a maximum of 42 days after transplant. The primary endpoint was treatment success defined as the absence of proven, probable, or suspected systemic fungal infection through the end of prophylaxis therapy and as the absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period.

Table 6: Definitions of systemic fungal infection used in HSCT study*

Proven	Biopsy-proven invasive or disseminated infection. Sinus or pulmonary infection with *Aspergillus, Fusarium, or Zygomycetes* organisms also was considered to be proven if results of cultures of specimens obtained from the respiratory tract were positive in conjunction with compatible diagnostic imaging findings
Probable	Probable pulmonary aspergillosis if lower respiratory tract diagnostic studies revealed fungal elements in conjunction with compatible clinical and radiographic findings
Suspected	fevers (≥ 100.4°F) persisted for > 96h during the neutropenic phase despite broad-spectrum antibacterial therapy, and led to the initiation of empirical antifungal therapy

*Definitions from Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer, National Institute of Allergy and Infectious Diseases Mycosis Study Group

Approximately 46% of patients were to receive an autologous or syngeneic stem cell transplant and the remainder an allogeneic stem cell transplant. During the treatment period, approximately 75% of the patients received growth factor for about 9.3 days. Graft vs. host disease was present in about 22% of patients.

Mean duration of prophylaxis for either drug for adults receiving autologous/ syngeneic and allogenic transplants was approximately 16 days and 21 days respectively.

Overall success was achieved in 80.7% and 73.7% of patients receiving micafungin and fluconazole respectively. The rate of success when broken down by subgroup was lower for either drug in patients receiving allogeneic transplants and in those with graft vs. host disease. For patients > 64 years old, the rate of success was higher with micafungin (97% vs. 69.6%); however, the number of patients in this age group was too small to draw any firm conclusions.

More patients in the fluconazole group required empirical use of systemic antifungals during the treatment period (21.5% vs. 15.1%). The need for systemic antifungal therapy in the posttreatment period was 42% for both groups.

Break-through candidemia occurred in 4 patients receiving micafungin (*C. lusitaniae, C. albicans, C. parapsilosis, and C. glabrata)* and in 2 receiving fluconazole (*C. krusei, C. parapsilosis)*. However, break-through aspergillosis was considered as probable in 3 patients receiving fluconazole and in 1 receiving micafungin. There were 4 proven cases of aspergillosis in the fluconazole group and none in the micafungin group.

The percentage of patients colonized with *C. albicans* decreased during treatment by approximately 23% and 50% in the micafungin and fluconazole groups respectively. In contrast, colonization with C. glabrata increased from 13% to 32.4% in fluconazole patients and decreased from 10.4% to 4.9% in the micafungin patients.

Treatment of aspergillosis or candidiasis

There are 2 published open-label trials and several published abstracts that evaluated micafungin in the treatment of severe infections due to Aspergillus or Candida.[8, 9] Results from abstracts are not included in this review.

Table 7: Studies using micafungin in treatment of *Aspergillosis* or *Candidiasis*

	Infection treated	Dosage	Duration of therapy	Clinical response
Kohno 2004 Open-label	Deep-seated mycosis caused by Aspergillus (n=42) or Candida spp.(n=14)	Micafungin 12.5-150mg/d IV once daily	Aspergillosis: 36 days (range 8-57d) Candidiasis: 16 days (range 7-29d)	**Overall clinical response** Aspergillosis: 24/42 (57%) Candidiasis: 11/14 (79%)
Ostrosky-Zeichner 2005 Open-label	newly diagnosed candidemia (n=72) or refractory candidemia (n=54)	Infections caused by *C. albicans*: Micafungin 50mg daily Infections caused by other *Candida spp*.: Micafungin 100mg daily Patients in the refractory candidemia group were allowed to receive micafungin alone or micafungin + their current antifungal	Range 5- 42 days	**Complete/partial response** Newly diagnosed candidemia: 66/75 (88%) Refractory candidemia: micafungin alone- 20/26 (77%) micafungin + other agent- 24/31 (77%)

SAFETY

Esophageal candidiasis

The majority of adverse events (AE) were considered to be mild-moderate in severity. Pettengell reports 1 serious AE (diarrhea) that was considered to be drug-related.[4] Two patients in this study discontinued treatment due to an AE that was thought to be related to the study medication (increased LFTs, erythema multiforme). In de Wet (2005), 27.7% and 21.3% of the micafungin and fluconazole groups respectively had a treatment-emergent AE. Six patients in the micafungin group and 2 patients in the fluconazole group discontinued treatment due to an AE. Discontinuations in the micafungin group were for rash (n=3), delirium (n=1), rash and delirium (n=1), and progression of AIDS (n=1). Discontinuations in the fluconazole group were for rash (n=1) and delirium (n=1).[6] Treatment-emergent AEs and related discontinuations were not reported in the earlier de Wet study.

There were 81 deaths in all 3 studies combined. None were considered to be related to the use of study drugs, except for 1 patient receiving micafungin, where the investigator could not exclude the possibility that the drug was related to the patient's death.[6]

Adverse events occurring in ≥ 0.5% of patients from de Wet (2005) are presented in table 7.[6, 10] Those AEs occurring more frequently with micafungin than fluconazole are highlighted.

Table 8: Adverse Events in esophageal candidiasis

	Micafungin	Fluconazole
Nausea	6 (2.3%)	7 (2.7%)
Vomiting	3 (1.2%)	4 (1.6%)
Abdominal pain	5 (1.9%)	4 (1.6%)
Headache	7 (2.7%)	3 (1.2%)
Dizziness	1 (0.4%)	2 (0.8%)
Somnolence	1 (0.4%)	7 (2.7%)
Delirium	2 (0.8%)	2 (0.8%)
Rash	8 (3.1%)	5 (1.9%)
Pruritis	3 (1.2%)	3 (1.2%)
Phlebitis	11 (4.2%)	6 (2.3%)
Pyrexia	5 (1.9%)	1 (0.4%)
Rigors	6 (2.3%)	0
Infusion site inflam	4 (1.5%)	3 (1.2%)

	Micafungin	Fluconazole
↑ ALT	1 (0.4%)	5 (1.9%)
↑ AST	2 (0.8%)	4 (1.6%)
↑ alk phos	4 (1.5%)	4 (1.6%)
↑ LDH	2 (0.8%)	3 (1.2%)
↑ transaminases	2 (0.8%)	1 (0.4%)
Hypomagnesemia	0	3 (1.2%)
Leukopenia	7 (2.7%)	2 (0.8%)
Neutropenia	3 (1.2%)	1 (0.4%)
Thrombocytopenia	3 (1.2%)	4 (1.6%)
Anemia	3 (1.2%)	4 (1.6%)
Lymphopenia	2 (0.8%)	1 (0.4%)
Eosinophilia	0	2 (0.8%)

Prophylaxis in HSCT

Adverse events occurring in ≥ 0.5% of patients from the large HSCT study are presented in table 8.[7, 10] Those AEs occurring more frequently with micafungin than fluconazole are highlighted. Drug-related AEs occurred

in 15.1% of patients receiving micafungin and in 16.8% receiving fluconazole. Treatment discontinuation due to a drug-related AE was reported in 2.6% and 3.5% of those receiving micafungin and fluconazole respectively.

Table 9: Adverse Events in HSCT

	Micafungin	Fluconazole
Nausea	10 (2.4%)	12 (2.6%)
Diarrhea	9 (2.1%)	14 (3.1%)
Vomiting	7 (1.6%)	5 (1.1%)
Abdominal pain	4 (0.9%)	3 (0.7%)
Dyspepsia	3 (0.7%)	1 (0.2%)
Constipation	1 (0.2%)	3 (0.7%)
Headache	4 (0.9%)	4 (0.9%)
Dysgeusia	3 (0.7%)	1 (0.2%)
Dizziness	0	5 (1.1%)
Rash	6 (1.4%)	4 (0.9%)
Pruritis	4 (0.9%)	3 (0.7%)
Flushing	1 (0.2%)	6 (1.3%)
Hypotension	1 (0.2%)	4 (0.9%)
Pyrexia	4 (0.9%)	5 (1.1%)
Rigors	1 (0.2%)	5 (1.1%)
Fatigue	0	5 (1.1%)

	Micafungin	Fluconazole
↑ ALT	4 (0.9%)	9 (2%)
↑ AST	3 (0.7%)	9 (2%)
LFTs abnorm	3 (0.7%)	6 (1.3%)
Hyperbilirubinemia	12 (2.8%)	11 (2.4%)
↑ SCr	1 (0.2%)	3 (0.7%)
Hypokalemia	8 (1.9%)	8 (1.8%)
Hypophosphatemia	6 (1.4%)	4 (0.9%)
Hypomagnesemia	5 (1.2%)	6 (1.3%)
Hypocalcemia	4 (0.9%)	4 (0.9%)
Neutropenia	5 (1.2%)	4 (0.9%)
Anemia	4 (0.9%)	3 (0.7%)
Leukopenia	4 (0.9%)	2 (0.4%)
Thrombocytopenia	4 (0.9%)	5 (1.1%)
Febrile neutropenia	4 (0.9%)	1 (0.2%)

Look-alike/Sound-alike drugs

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

Micafungin: caspofungin, Fungizone, Macugen
Mycamine: Micatin (spray), Mysoline (tablets) – low potential for mix-up due to different routes of administration

DRUG INTERACTIONS

Micafungin is not a substrate for or an inhibitor of P-glycoprotein; therefore, drug interactions via this mechanism are unlikely. Micafungin is a substrate for and a weak inhibitor of CYP3A4; however, this is not a major pathway for micafungin metabolism, so drug interactions via this pathway are not expected.

Table 10: Drug interaction studies in healthy volunteers

Micafungin	mycophenolate mofetil, cyclosporine, tacrolimus*, prednisolone, fluconazole,	Single and multiple doses of micafungin	No pharmacokinetic interactions of either drug
Micafungin	Sirolimus	Multiple dose micafungin at steady state	Sirolimus AUC increased by 23%; no effect on Cmax
Micafungin	Nifedipine	Multiple dose micafungin at steady state	Nifedipine AUC increased by 18%; Cmax increased by 42%
Micafungin	ritonovir, rifampin		No interactions affecting p-kinetics of micafungin

*a small study in patients with hematologic disease also found no difference in micafungin blood levels when given concomitantly with tacrolimus compared to micafungin alone. Shimoeda et al. Biol Pharm Bull 205; 28: 477-80.

COST

In table 10, the acquisition cost of micafungin is compared to other antifungals used for treatment of esophageal candidiasis or prophylaxis of Candida infection in HSCT.

Table 11: Cost

Drug	Dose	Dosage forms	Duration of treatment	Cost/ unit	Cost/day
Treatment of esophageal candidiasis					
Micafungin	150mg daily	IV only	Mean duration of treatment 15 days (range 10-30 days)	$66.09/ 50mg vial	$198.27
Caspofungin	50mg daily	IV only	Mean duration of treatment 9 days (range 7-21 days)	$217.96/ 50mg vial	$217.96
Fluconazole	200mg first dose followed by 100mg once daily (up to 400mg/d may be used)	Oral and IV	Minimum treatment of three weeks. Treatment should continue for 2 weeks following resolution of symptoms.	$0.125/100mg tablet (generic) $7.00/ 35ml bottle of 10mg/ml (generic) $14.32/ 35ml bottle of 40mg/ml (generic) $12.50-15.85/ 200mg vial (generic)	$0.125 (tablets) $2.00 (10mg/ml susp) $1.02 (40mg/ml susp) $12.50-15.85 (IV)
Itraconazole oral solution	100mg once daily	Oral and IV	Minimum treatment of three weeks. Treatment should continue for 2 weeks following resolution of symptoms.	$76.09/ 150ml bottle of 10mg/ml	$5.07 (soln)
Voriconazole	200mg every 12 hours	Oral and IV	Minimum treatment of 15 days. Treatment should continue for at least 7 days following resolution of symptoms.	$18.36/ 200mg tablet $382.03/70ml bottle of 40mg/ml susp $65.15/vial	$36.71 (tablets) $54.57 (susp) $130.30 (IV)
Amphotericin B (conventional)	0.3-5mg/kg/day	IV		$5.07/50mg vial	$2.13-3.55/day (based on 70kg)
Prophylaxis of Candida in HSCT					
Micafungin	50mg daily	IV only	Mean duration of treatment 19days (range 6-51 days)	$66.09/50mg vial	$66.09
Fluconazole	400mg daily	Oral and IV		$0.183/200mg tablet (generic) $18.75-37.50/ 400mg vial (generic)	$0.37/ day (tablets) $18.75-37.50 (IV)
Amphotericin B (conventional)	0.2mg/kg/day	IV		$5.07/50mg vial	$1.42/day (based on 70kg)

Does not include the cost of IV diluents, IV lines, preparation, and administration

RECOMMENDATIONS

Micafungin is an alternative to azole antifungals for patients with esophageal candidiasis or for those who require prophylaxis of Candida infections during HSCT who have contraindications, adverse events, significant drug interactions, or fluconazole-resistant *Candida* or for patients unable to tolerate amphotericin B.

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Prepared by Deborah Khachikian, PharmD
January 2006

Appendix 1: Published clinical trials in esophageal candidiasis

<table>
<tr><th>Study</th><th>Inclusion/ exclusion criteria</th><th>Dose</th><th>Demographics and baseline values</th><th>Results</th></tr>
<tr>
<td>Pettengell 2004
R, OL, PR
South Africa

n=120 enrolled
n=84 per protocol population used for efficacy assessment</td>
<td>HIV-positive
≥ 18 years old
Endoscopically confirmed symptomatic esophageal candidiasis

Exclusions: LFTs > 2.5 x ULN, SCr > 2mg/dl, other opportunistic infections, hepatitis, cirrhosis, tx with topical or systemic antifungals w/i 48 or 72 hours of first dose of micafungin respectively, allergy to echinocandins</td>
<td>Micafungin 12.5mg vs. 25mg vs. 50mg vs. 75mg vs. 100mg IV once daily for 14days.

Treatment may be extended up to a total of 21 days if clinically indicated</td>
<td>Males: 51%
% white/black/ other: 14.3/ 81/ 4.8
Age (years): 34 ± 8.67 (range 19-59)
Weight (kg): 54.5 ± 13.87
Median CD4 count (cells/mm^3): 27 (range 0.6-1045)

<u>Values for 12.5mg / 25mg/ 50mg/ 75mg/ 100mg groups</u>

Symptom score (scale 0-9): 5.3 ± 2.8/ 5.1 ± 2.4/ 4.3 ± 1.8/ 5.3 ± 2.7/ 5.1 ± 2.3

Mucosal lesion score (0-3): 2.6 ± 0.7/ 2.4 ± 1.0/ 1.9 ± 0.8/ 2.2 ± 0.7/ 2.6 ± 0.8

Mean ± SD unless otherwise indicated</td>
<td>
<table>
<tr><th></th><th colspan="3">Clinical response</th><th>mucosal lesion grade*</th></tr>
<tr><th></th><th>cleared</th><th>improved</th><th>unchanged/ worse</th><th></th></tr>
<tr><td>12.5mg</td><td>6 (33.3%)</td><td>6 (33.3%)</td><td>6 (33.3%)</td><td>1.8</td></tr>
<tr><td>25mg</td><td>7 (53.8%)</td><td>5 (38.5%)</td><td>1 (7.7%)</td><td>1.8</td></tr>
<tr><td>50mg</td><td>13 (86.7%)</td><td>1 (6.7%)</td><td>0</td><td>1.3</td></tr>
<tr><td>75mg</td><td>16 (84.2%)</td><td>3 (15.8%)</td><td>0</td><td>0.3</td></tr>
<tr><td>100mg</td><td>18 (94.7%)</td><td>1 (5.3%)</td><td>0</td><td>0.2</td></tr>
<tr><td>total</td><td>60 (71.4%)</td><td>16 (19%)</td><td>7 (8.3%)</td><td></td></tr>
<tr><td>mean # of days on drug</td><td colspan="4">15.1 ± 3.72 days (per-protocol group)
13.2 ± 5.05 days (ITT group)</td></tr>
</table>
*Results for mean mucosal lesion grade estimated from graph
</td>
</tr>
<tr>
<td>de Wet 2004
Micafungin vs. fluconazole
R, DB, PR
Brazil, Peru, S. Africa
n=245 (ITT)
n=199 (per-protocol)

analysis done using ITT and per-protocol (≥ 10 doses of drug, baseline and end of treatment endoscopy, no other antifungal agents) populations</td>
<td>HIV-positive
≥ 18 years old
Endoscopically confirmed symptomatic esophageal candidiasis

Exclusions: AST/ALT > 5 x ULN, T. bili or alk phos > 2.5x ULN, other opportunistic fungal infections, tx with topical or systemic antifungals w/i 48 or 72 hours of first dose of micafungin respectively, SCr > 2mg/dl, contraindications to study drugs, esophageal abnormalities preventing endoscopy, life expectancy < 2 months, infection with known fluconazole-resistant strain of Candida spp.</td>
<td>1:1:1:1 randomization micafungin 50mg vs. 100mg vs. 150mg vs. fluconazole 200mg administered IV once daily

Treatment duration minimum of 14 days, which can be extended to a maximum of 21 days for patient not achieving endoscopic clearance by day 14.</td>
<td><u>Values for micafungin 50mg/ 100mg/ 150mg/ fluconazole</u>
Age (years): 33.9 ± 7.5/ 36.8 ± 8.1/ 36.7 ± 8.8/ 35.5 ± 8.1
% male: 46.9/ 41.9/ 55.9/ 46.7
CD4 count (cells/mm3): 60 ± 74.1/ 87.6 ± 142.2/ 69.5 ± 119.5/ 53.8 ± 114.6
Endoscopic grade
% w/ grade 0: 0/ 0/ 0/ 1.7
% w/ grade 1: 17.2/ 21/ 18.6/ 16.7
% w/ grade 2: 65.6/ 59.7/ 62.7/ 51.7
% w/ grade 3: 17.2/ 19.4/ 18.6/ 30
Candida albicans (%): 98.3/ 100/ 100/ 100</td>
<td>
<table>
<tr><th></th><th>M50</th><th>M100</th><th>M150</th><th>FLU</th></tr>
<tr><td>drop-outs (n)</td><td>8</td><td>13</td><td>7</td><td>8</td></tr>
<tr><td>dur of tx (days)</td><td>16.3 ± 4.2</td><td>13.4 ± 4.5</td><td>14 ± 3.5</td><td>14 ± 3.3</td></tr>
<tr><th colspan="5">Endoscopic cure % [95% CI]</th></tr>
<tr><td>EOT ITT pop</td><td>68.8% [57.4, 80.1]*</td><td>77.4% [67, 87.8]</td><td>89.8% [82.1, 97.5]</td><td>86.7% [78.1, 95.3]</td></tr>
<tr><td>EOT PP- pop</td><td>71.2% [58.8, 83.5]*</td><td>91.7% [83.8, 99.5]</td><td>98% [94.2, 100]</td><td>95.8% [90.2, 100]</td></tr>
<tr><td>day 14 ITT-pop</td><td>53.1% [41, 65.4]</td><td>71% [59.7, 82.3]</td><td>84.7% [75.6, 93.9]</td><td>81.7% [71.9, 91.5]</td></tr>
<tr><td>endoscopic grade at EOT</td><td>0.5 ± 0.9</td><td>0.1 ± 0.4</td><td>0.0 ± 0.1</td><td>0.1 ± 0.3</td></tr>
<tr><th colspan="5">Clinical response (ITT-pop)</th></tr>
<tr><td>% cleared/ improved</td><td>75.8/ 24.2</td><td>92.9/ 5.4</td><td>92.7/ 7.3</td><td>93/ 5.3</td></tr>
<tr><td>unchanged</td><td>0</td><td>1.8</td><td>0</td><td>1.8</td></tr>
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<table>
<tr><td>or worse</td><td></td><td></td><td></td><td></td></tr>
<tr><td>fungal eradication</td><td>35.1% (20/57)</td><td>78.3% (36/46)^</td><td>57.1% (28/49)</td><td>67.3% (35/52)</td></tr>
<tr><td>Relapse (n)</td><td>1</td><td>5</td><td>3</td><td>0</td></tr>
</table>
*significant vs. micafungin 100mg, 150mg, fluconazole
^significant vs. micafungin 150mg
</td>
</tr>
<tr>
<td>De Wet 2005
Micafungin vs. fluconazole
R, DB, PR, multicenter
S. Africa, Brazil, Peru
n=518

non-inferiority design

analysis done in modified intent-to-treat group</td>
<td>≥ 16 years old
Endoscopically confirmed symptomatic esophageal candidiasis

Exclusions: AST/ALT > 10 x ULN, T. bili > 5x ULN, other opportunistic fungal infections, tx with topical or systemic antifungals w/i 48 or 72 hours of first dose of micafungin respectively, concomitant esophagitis caused by HSV or CMV, requiring antifungal tx for condition other than EC, h/o of ≥ 2 episodes of EC requiring systemic antifungals, non-response to tx in any prior systemic antifungal clinical trial</td>
<td>1:1 randomization (n=260 micafungin; n=258 fluconazole)

micafungin 150mg IV once daily
fluconazole 200mg IV once daily

Duration of tx: minimum of 14 days or for 7 days after resolution of clinical symptoms whichever was longer</td>
<td><u>Values for micafungin/fluconazole</u>
% male: 50.4/ 45
% white: 14.6/ 13.6
% black: 67.7/ 69
% Mestizo: 12.3/ 11.2
% other: 5.4/ 6.2
Age (years): 37.2 ± 10.59/ 37.5 ± 11.16
% HIV-pos: 94.2/ 93.4
CD4 counts in those with HIV(cells/ml): 109 ± 190.8/ 105.9 ± 176.72
% receiving antiretroviral tx: 8.5/ 11.6
% with no prior episodes of EC: 86.5/ 87.2
% w/ endoscopy grade 1: 33.5/ 37.2
% w/ endoscopy grade 2: 37.7/ 38.4
% w/ endoscopy grade 3: 28.8/ 24.4
Mean symptom grade: 4.2 ± 1.84/ 4.3 ± 1.98 (range=1.0-9.0)
% w/ any Candida organism: 90/ 89.5
% w/ C. albicans: 98.3/ 98.3</td>
<td>
<table>
<tr><th></th><th>Micafungin</th><th>Fluconazole</th><th>tx diff [95%CI]</th></tr>
<tr><td>Endoscopic cure rate</td><td>87.7%</td><td>88%</td><td>-0.3 [-5.9, 5.3]</td></tr>
<tr><td>Clinical cure (cleared/improved)</td><td>91.9%/ 2.3%</td><td>91.9%/ 2.7%</td><td></td></tr>
<tr><td>Clinical unchanged/ worse/ not evaluable</td><td>0.8%/ 0/ 5%</td><td>1.2%/ 0.4%/ 3.9%</td><td></td></tr>
<tr><td>Both endoscopic and clinical cure*</td><td>223/260 (85.8%)</td><td>220/258 (85.3%)</td><td>0.5% [-5.6, 6.6]</td></tr>
<tr><td>mycological eradication*</td><td>141/189 (74.6%)</td><td>149/192 (77.6%)</td><td>-3.0% [-11.6, 5.6]</td></tr>
<tr><td>Relapse at 2-week visit*^</td><td>40/223 (17.9%)</td><td>30/220 (13.6%)</td><td>4.3% [-2.5, 11.1]</td></tr>
<tr><td>Relapse at 4-week visit*^</td><td>17/ 185 (9.2%)</td><td>14/ 188 (7.4%)</td><td>4.6% [-4.0, 13.1]</td></tr>
<tr><td>Mean # days of tx</td><td>14.3 ± 3.68 (range 1-33)</td><td>14.7 ± 3.62 (range 2-29)</td><td></td></tr>
</table>
*data obtained from product package insert
^Relapse was defined as those who received systemic antifungal therapy in the post-treatment period (also includes patients who died or were lost to follow-up)
</td>
</tr>
</table>

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, CMV=cytomegalovirus, DB=double-blind, EC=esophageal candidiasis, EOT=end of treatment, HSV=herpes simplex virus, ITT=intent-to-treat, LFT=liver function test, OL=open-label, PP=per-protocol, PR=parallel, R=randomized, SCr=serum creatinine, ULN=upper limit of normal,

Appendix 2: Published clinical trials in prophylaxis of *Candida* infection in patients undergoing hematopoietic stem cell transplant

Study	Inclusion/ exclusion criteria	Dose	Demographics and baseline values	Results
van Burik 2004 **Micafungin vs. fluconazole** R, DB, PR, multicenter n=882 Canada, U.S. analysis done with ITT and per-protocol groups non-inferiority design	allogenic HSCT for any indication autologous HSCT for hematologic malignancy ≥ 6 months old free of deeply invasive fungal disease no systemic antifungal within 72 hours of first dose of study drug no liver disease (ALT, AST < 5x ULN; Bilirubin < 2.5 x ULN)	Micafungin 50mg IV (or 1mg/kg for those weighing < 50kg) once daily vs. Fluconazole 400mg IV (or 8mg/kg for those weighing < 50kg) once daily Treatment initiated within 48h of the beginning of the transplant-related conditioning regimen. Study drug continued until ANC ≥ 500cells/mm3 or up to a maximum of 42 days after transplant.	**Values presented as micafungin/ fluconazole** **% male:** 59.5/ 60 **% white:** 91.1/ 89.9 **Mean age (years):** 43.2/ 41.9 • % pediatric: 9.2/ 9.8 • % aged 16-64: 83/ 85.1 • % > 64: 7.8/ 5 **%autologous or syngeneic stem cell transplant:** 47.8/ 44 **%allogenic stem cell transplant:** 51.8/ 56 **%underlying malignancy active:** 41.9/ 40.9 **%remission:** 37% **%relapse:** 22% **Underlying disease in allogeneic transplant recipients:** • CML: 22% • AML: 21% • ALL: 13% • non-Hodgkin's lymphoma: 13% **Underlying disease in autologous and syngeneic transplant recipients** • multiple myeloma: 37.1% • non-Hodgkin's lymphoma: 36.4% • Hodgkin's disease: 15.6% **Stem cell source:** % bone marrow: 26.4/ 28.9 % peripheral blood: 69.9/ 67.6 % cord blood: 3.3/3.5 **% receiving growth factor during treatment:** 76.7/ 74.4 **GVHD present:** 22.6%/ 22.3% **Neutrophil recovery achieved:** 95.8%/ 94.5% **Median interval between engraftment and recovery:** 13d (range 3-54)/ 13d (range 7-44) **Baseline colonization with C. albicans:** 71.3%/ 60.1% **Baseline colonization with C. glabrata:** 10.4%/ 13%	<table><tr><th></th><th>Micafungin n=425</th><th>Fluconazole n=457</th></tr><tr><td>dropouts</td><td>24.9%</td><td>32.2%</td></tr><tr><td>d/c due to AE</td><td>4.2%</td><td>7.2%</td></tr><tr><td>Overall success*</td><td>80.7%</td><td>73.7%</td></tr><tr><td>Failure</td><td>19.3%</td><td>26.3%</td></tr><tr><td>Success by subgroup</td><td></td><td></td></tr><tr><td>syngeneic/ autologous</td><td>181/203 (89.2%)</td><td>161/201 (80.1%)</td></tr><tr><td>allogeneic</td><td>157/220 (71.4%)</td><td>175/256 (68.4%)</td></tr><tr><td>ages 16-64</td><td>313/386 (81.1%)</td><td>312/412 (75.7%)</td></tr><tr><td>age > 64</td><td>32/33 (97%)</td><td>16/23 (69.6%)</td></tr><tr><td>graft-vs-host present</td><td>65/96 (67.7%)</td><td>58/102 (56.9%)</td></tr><tr><td>graft-vs-host absent</td><td>275/329 (83.6%)</td><td>278/355 (78.3%)</td></tr><tr><td>received empirical systemic antifungal tx</td><td>15.1%</td><td>21.4%^</td></tr><tr><td>systemic antifungal tx posttreatment</td><td>42%</td><td>42%</td></tr><tr><td>mortality</td><td>4.2%</td><td>5.7%</td></tr><tr><td>Mean duration of tx in adults (autologous/ syngeneic)</td><td>16.8 days</td><td>16.2 days</td></tr><tr><td>Mean duration of tx in adults (allogenic)</td><td>21.6 days</td><td>20.7 days</td></tr><tr><td>Break-through candidemia¶</td><td>n=4</td><td>n=2</td></tr><tr><td>Break-through aspergillosis</td><td>n=1 (probable)</td><td>n=4 (proven) n=3 (probable)</td></tr><tr><td>% with *C. albicans* colonization</td><td>55.1%</td><td>30.2%</td></tr><tr><td>% with *C. glabrata* colonization</td><td>4.9%</td><td>32.4%</td></tr></table>results of evaluable group parallel those of the ITT group *treatment difference [95% CI] = 6.5%[0.9%, 12%] p=.03 ^p=.024 ¶*C. lusitaniae, C. albicans, C. parapsilosis, C. glabrata* (micafungin); *C. krusei, C. parapsilosis* (fluconazole)

Abbreviations: AE=adverse reaction, ALL=acute lymphocytic leukemia, ALT=alanine aminotransferase, AML=acute myelogenous leukemia, ANC=absolute neutrophil count, AST=aspartate aminotransferase, CML=chronic myelogenous leukemia, DB= double-blind, d/c=discontinue. GVHD=graft versus host disease, HSCT=hematicpoietic stem cell transplant, ITT=intent-to-treat, PR=parallel, R=randomized, ULN=upper limit of normal