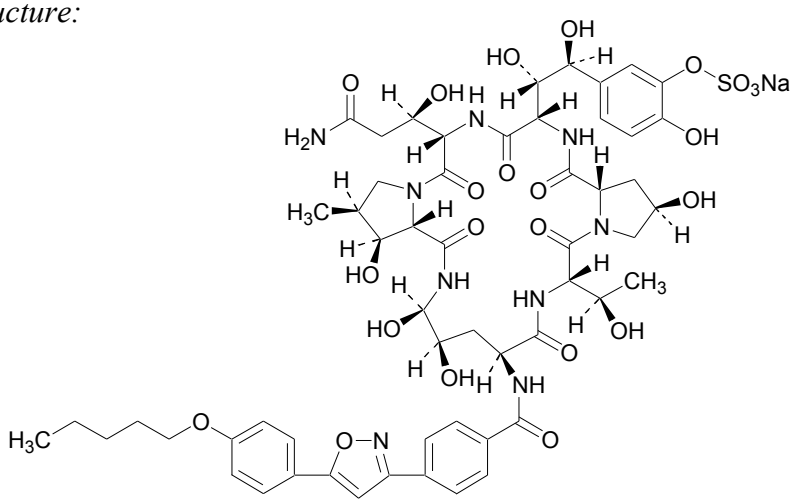
MYCAMINE® POWDER FOR SOLUTION FOR INFUSION 50 mg/vial

NAME OF THE MEDICINE

Active ingredient: micafungin (as sodium)

Chemical structure:



Chemical name: Sodium 5-[(1*S*,2*S*)-2-[(3*S*,6*S*,9*S*,11*R*,15*S*,18*S*,20*R*,21*R*,24*S*,25*S*,26*S*)-3-[(*R*)-2-carbamoyl-1-hydroxyethyl]-11,20,21,25-tetrahydroxy-15-[(*R*)-1-hydroxyethyl]-26-methyl-2,5,8,14,17,23-hexaoxo-18-[4-[5-(4-pentyloxyphenyl)-isoxazol-3-yl]benzoylamino]-1,4,7,13,16,22-hexaazatricyclo-[22.3.0.$0^{9,13}$]heptacos-6-yl]-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate

Molecular formula: $C_{56}H_{70}N_9NaO_{23}S$

CAS registry number: 208538-73-2

DESCRIPTION

Mycamine is a sterile, white powder for solution for infusion containing the active ingredient micafungin as the sodium salt. Micafungin sodium is a light sensitive, hygroscopic, amorphous, white powder that is freely soluble in water, isotonic sodium chloride solution, *N,N*-dimethylformamide and dimethylsulfoxide, slightly soluble in methyl alcohol, and practically insoluble in acetonitrile, ethyl alcohol (95%), acetone, diethyl ether and *n*-hexane.

Mycamine contains the following excipients: lactose monohydrate, citric acid, sodium hydroxide.

Mycamine must be diluted with either sodium chloride 0.9% or glucose 5% solution prior to use (see DOSAGE AND ADMINISTRATION).

PHARMACOLOGY

Pharmacology

Micafungin, the active ingredient of Mycamine, is a member of the echinocandin lipopeptide family and inhibits non-competitively the synthesis of 1,3-β-D-glucan, an essential component of fungal cell walls which is not present in mammalian cells.

Microbiology

Micafungin exhibits fungicidal activity against most *Candida* species and prominently inhibits actively growing hyphae of *Aspergillus* species.

Breakpoints

EUCAST MIC breakpoints for micafungin [susceptible (S); resistant (R)]:

- *Candida albicans*: S ≤0.016 mg/L, R >0.016 mg/L
- *Candida glabrata*: S ≤0.03 mg/L, R >0.03 mg/L
- *Candida parapsilosis*: S ≤0.002 mg/L, R >2 mg/L

MICs for *C. tropicalis* are 1-2 two-fold dilution steps higher than for *C. albicans* and *C. glabrata*. In the clinical study successful outcome was numerically slightly lower for *C. tropicalis* than for *C. albicans* at both dosages (100 and 150 mg daily). However, the difference was not significant and whether it translates into a relevant clinical difference is unknown.
MICs for *C. krusei* are approximately three two-fold dilution steps higher than those for *C. albicans* and, similarly, those for *C. guilliermondii* are approximately eight two-fold dilutions higher. In addition, only a small number of cases involved these species in the clinical trials. This means there is insufficient evidence to indicate whether the wild-type population of these pathogens can be considered susceptible to micafungin.

There are currently insufficient data to set clinical breakpoints for other *Candida* species.

In vivo activity

Micafungin was highly effective in the treatment of disseminated candidiasis, as well as against oropharyngeal and oesophageal candidiasis.

Activity in vitro and in clinical infections

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

Resistance induction

As for all antimicrobial agents, cases of reduced susceptibility and resistance have been reported and cross-resistance with other echinocandins cannot be excluded. Reduced susceptibility to echinocandins has been associated with mutations in the Fks1 and Fks2 genes coding for a major subunit of glucan synthase.

Pharmacokinetics

Absorption

Micafungin is an intravenously administered medication.
Pharmacokinetics are linear over the daily dose range of 12.5 mg to 200 mg and 3 mg/kg to 8 mg/kg. There is no evidence of systemic accumulation with repeated administration and steady-state is generally reached within 4 to 5 days.

Distribution

Following intravenous administration concentrations of micafungin show a biexponential decline. The drug is rapidly distributed into tissues.
In systemic circulation, micafungin is highly bound to plasma protein (> 99%), primarily to albumin. Binding to albumin is independent of micafungin concentration (10-100 µg/mL). The volume of distribution at steady state (Vss) was approximately 18-19 litres.

Biotransformation

Unchanged micafungin is the principal circulating compound in systemic circulation. Micafungin has been shown to be metabolised to several compounds; of these M-1 (catechol form), M-2 (methoxy form of M-1) and M-5 (hydroxylation at the side chain) of micafungin have been detected in systemic circulation. Exposure to these metabolites is low and metabolites do not contribute to the overall efficacy of micafungin.
Even though micafungin is a substrate for CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for micafungin metabolism *in vivo*.

Elimination and excretion

The mean terminal half-life is approximately 10-17 hours and stays consistent across doses up to 8 mg/kg and after single and repeated administration. Total clearance was 0.15-0.3 mL/min/kg in healthy subjects and adult patients and is independent of dose after single and repeated administration.
Following a single intravenous dose of ^{14}C-micafungin (25 mg) to healthy volunteers, 11.6% of the radioactivity was recovered in the urine and 71.0% in the faeces over 28 days. These data indicate that elimination of micafungin is primarily non-renal. In plasma, metabolites M-1 and M-2 were detected only at trace concentrations and metabolite M-5, the more abundant metabolite, accounted for a total of 6.5% relative to parent compound.

Pharmacokinetic characteristics in special populations

Patients with hepatic impairment: A single 1-hour infusion of 100 mg micafungin was administered to eight subjects with moderate hepatic impairment (Child-Pugh score 7 to 9) and eight age, gender and weight matched subjects with normal hepatic function. The pharmacokinetics of micafungin did not differ significantly from those in healthy subjects.

A single 1-hour infusion of 100mg micafungin was administered to eight subjects with severe hepatic impairment (Child-Pugh score 10 to 12) and eight age, gender, ethnic and weight matched subjects with normal hepatic function. The C_{max} and AUC values of micafungin were lower by approximately 30% in subjects with severe hepatic impairment compared to normal subjects. The C_{max} and AUC values of M5 metabolite were approximately 2.3-fold higher in subjects with severe hepatic impairment compared to normal subjects. However, this exposure (parent and metabolite) was comparable to that in patients with systemic *Candida* infection. Therefore, no micafungin dose adjustment is necessary in patients with mild or moderate hepatic impairment.

Patients with renal impairment: A single 1-hour infusion of 100 mg micafungin was administered to nine subjects with severe renal impairment (creatinine clearance < 30 mL/min) and to nine subjects with normal renal function (creatinine clearance > 80 mL/min) who were age, gender and weight matched. The C_{max} and AUC were not significantly altered by severe renal impairment. No dose adjustment is necessary for patients with renal impairment.

Elderly: A single 1-hour infusion of 50 mg micafungin was administered to ten healthy subjects aged 66 to 78 years and ten healthy subjects aged 20 to 24 years. The pharmacokinetics of micafungin showed a similar time-course profile in both the elderly and young, and there were no significant differences in the pharmacokinetic parameters. No dose adjustment is necessary for the elderly.

Paediatric use:
Paediatric Patients 4 months of age and older.

Micafungin pharmacokinetics in 229 paediatric 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 1. Summary (Mean +/- Standard Deviation) of Micafungin Pharmacokinetics in Paediatric Patients 4 Months of Age and older (Steady-State)

Body weight group	N	Dose[§] mg/kg	C_{max}.ss[†] (mcg/mL)	AUC.ss[†] (mcg·h /mL)	t½[‡] (h)	CL[‡] (mL/min/kg)
30 kg or less	149	1.0	7.1 +/- 4.7	55 +/- 16	12.5 +/- 4.6	0.328 +/- 0.091
		2.0	14.2 +/- 9.3	109 +/- 31		
		3.0	21.3 +/- 14.0	164 +/- 47		
Greater than 30 kg	80	1.0	8.7 +/- 5.6	67 +/- 17	13.6 +/- 8.8	0.241 +/- 0.061
		2.0	17.5 +/- 11.2	134 +/- 33		
		2.5	23.0 +/- 14.5	176 +/- 42		

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

Gender and race: Gender or race (Caucasian, Black, Oriental) did not significantly influence the pharmacokinetic parameters of micafungin. No dose adjustment is required based on gender or race.

CLINICAL TRIALS

Candidaemia and Invasive Candidiasis

Micafungin (100 mg/day or 2 mg/kg/day) was as effective as and better tolerated than liposomal amphotericin B (3 mg/kg) as first-line treatment of candidaemia and invasive candidiasis in a randomised, double-blind, multinational non-inferiority study. Micafungin and liposomal amphotericin B were received for a median duration of 15 days (range 4 to 42 days in adults and 12 to 42 days in children).

Non-inferiority was proven for adult patients, and similar findings were demonstrated for the paediatric population. Efficacy findings were consistent, independent of the infective *Candida* species, primary site of infection and neutropenic status (see Table 2). Micafungin demonstrated a smaller mean peak decrease in estimated glomerular filtration rate during treatment ($p < 0.001$) and a lower incidence of infusion-related reactions ($p = 0.001$) than liposomal amphotericin B.

Table 2. Summary of overall treatment success (per protocol set) (Invasive Candidiasis Study)

	Micafungin		**Liposomal Amphotericin B**		**% difference [95% CI]**
	N	**n (%)**	**N**	**n (%)**	
Adult Patients					
Overall Treatment Success	202	181 (89.6)	190	170 (89.5)	0.1 [-5.9, 6.1]†
Overall Treatment Success by Neutropenic Status					
Neutropenia at baseline	24	18 (75.0)	15	12 (80.0)	0.7 [-5.3, 6.7]‡
No neutropenia at baseline	178	163 (91.6)	175	158 (90.3)	
Paediatric Patients					
Overall Treatment Success	48	35 (72.9)	50	38 (76.0)	-2.7 [-17.3, 11.9]§
< 2 years old	26	21 (80.8)	31	24 (77.4)	
Premature Infants	10	7 (70.0)	9	6 (66.7)	
Neonates (0 days to < 4 weeks)	7	7 (100)	5	4 (80)	
2 to 15 years old	22	14 (63.6)	19	14 (73.7)	
Adults and Children Combined, Overall Treatment Success by *Candida* Species					
Candida albicans	102	91 (89.2)	98	89 (90.8)	
Non-*albicans* species: all¶	151	133 (88.1)	140	123 (87.9)	
C. tropicalis	59	54 (91.5)	51	49 (96.1)	
C. parapsilosis	48	41 (85.4)	44	35 (79.5)	
C. glabrata	23	19 (82.6)	17	14 (82.4)	
C. krusei	9	8 (88.9)	7	6 (85.7)	

† Micafungin rate minus the liposomal amphotericin B rate, and 2-sided 95% confidence interval for the difference in overall success rate based on large sample normal approximation.
‡ Adjusted for neutropenic status; primary endpoint.
§ The paediatric population was not sized to test for non-inferiority.
¶ Clinical efficacy was also observed (< 5 patients) in the following *Candida* species: *C. guilliermondii*, *C. famata*, *C. lusitaniae*, *C. utilis*, *C. inconspicua* and *C. dubliniensis*.

Oesophageal Candidiasis

In a randomised, double-blind study of micafungin versus fluconazole in the first-line treatment of oesophageal candidiasis, 518 patients received at least a single dose of study drug. The median treatment duration was 14 days and the median average daily dose was 150 mg for micafungin (N = 260) and 200 mg for fluconazole (N = 258). An endoscopic grade of 0 (endoscopic cure) at the end of treatment was observed for 87.7% (228/260) and 88.0% (227/258) of patients in the micafungin and fluconazole groups, respectively (95% CI for difference: [-5.9%, 5.3%]). The lower limit of the 95% CI was above the predefined non-inferiority margin of -10%, proving non-inferiority. All efficacy findings were consistent and showed micafungin to be as effective as fluconazole in adult oesophageal candidiasis patients, with similar rates of endoscopic cure, clinical resolution of the infection, mycological eradication, dynamics or improvement and incidence of relapse. The nature and incidence of adverse events were also similar between treatment groups.

Prophylaxis of Invasive Fungal Infection

Micafungin was more effective than fluconazole in preventing invasive fungal infections in a population of patients at high risk of developing a systemic fungal infection (patients undergoing haematopoietic stem cell transplantation [HSCT] in a randomised, double-blind, multicentre study). Treatment success was defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy and absence of a proven or probable systemic fungal infection through the end of study. Most patients (97%, N = 882) had neutropenia at baseline (< 200 neutrophils/μL) and neutropenia persisted for a median of 13 days. There was a fixed daily dose of 50 mg (1.0 mg/kg) for micafungin and 400 mg (8 mg/kg) for fluconazole. The mean period of treatment was 19 days for micafungin and 18 days for fluconazole in the adult population (N = 798) and 23 days for both treatment arms in the paediatric population (N = 84). Table 3 summarises the main efficacy findings.

Table 3. Treatment success at end of study (full analysis set; after treatment and 4 weeks of follow-up)

	Micafungin (N = 425)	**Fluconazole (N = 457)**	**Treatment Difference***	**95% CI****
Overall	340 (80.0%)	336 (73.5%)	+ 6.5%	(0.9%, 12.0%)
Type of haematopoietic stem cell transplant				
Allogeneic	157/220 (71.4%)	175/256 (68.4%)	+ 3.0%	
Autologous or syngeneic	181/203 (89.2%)	161/201 (80.1%)	+ 9.1%	
None	2/2 (100.0%)	0	n/a	

* Micafungin rate *minus* the fluconazole rate.
** 95% confidence interval for the difference in overall success rate is based on the large sample normal approximation test.

The rate of treatment success was statistically significantly higher for micafungin than fluconazole (1.6% versus 2.4% breakthrough infections). Breakthrough *Aspergillus* infections were observed in 1 versus 7 patients, and proven or probable breakthrough *Candida* infections were observed in 4 versus 2 patients in the micafungin and fluconazole groups, respectively. Other breakthrough infections were caused by *Fusarium* (1 and 2 patients,

respectively) and *Zygomycetes* (1 and 0 patients, respectively). The nature and incidence of adverse reactions were similar between treatment groups.

INDICATIONS

Mycamine is indicated for:

Adults and paediatric patients 4 months and older for :

- treatment of invasive candidiasis
- treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate
- prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/μL) for 10 or more days.

Mycamine has not been adequately studied in patients with endocarditis, osteomyelitis and meningitis due to *Candida* infections.
The decision to use Mycamine should take into account a potential risk for the development of liver tumours. Mycamine should therefore only be used if other antifungals are not appropriate.

CONTRAINDICATIONS

Mycamine is contraindicated in patients with hypersensitivity to any component of this medication or to other echinocandins (see DESCRIPTION).

PRECAUTIONS

Hepatic effects

The development of foci of altered hepatocytes (FAH) and hepatocellular tumours after a treatment period of 3 months or longer were observed in rats. The assumed threshold for tumour development in rats is approximately in the range of clinical exposure. The relevance of this finding for the therapeutic use in patients cannot be excluded. Liver function should be carefully monitored during micafungin treatment. To minimise the risk of adaptive regeneration and potentially subsequent liver tumour formation, early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended. Micafungin treatment should be conducted on a careful risk/benefit basis, particularly in patients having severe liver function impairment or chronic liver diseases known to represent preneoplastic conditions, such as advanced liver fibrosis, cirrhosis, viral hepatitis, neonatal liver disease or congenital enzyme defects, or receiving a concomitant therapy including hepatotoxic and/or genotoxic properties.

Micafungin treatment was associated with significant impairment of liver function (increase of ALT, AST or total bilirubin > 3 times ULN) in both healthy volunteers and patients. In some patients more severe hepatic dysfunction, hepatitis, or hepatic failure including fatal

cases have been reported.

Hypersensitivity

During administration of micafungin, anaphylactic/anaphylactoid reactions including shock may occur. If these reactions occur, Mycamine should be discontinued and appropriate treatment administered.

Skin Reactions

Exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Haemolysis

Isolated cases of haemolysis including acute intravascular haemolysis or haemolytic anaemia have been reported in patients treated with micafungin. Patients who develop clinical or laboratory evidence of haemolysis during Mycamine therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing therapy.

Renal effects

Micafungin may cause kidney problems, renal failure, and abnormal renal function test. Patients should be closely monitored for worsening of renal function.

Use in pregnancy

There are no adequate and well-controlled studies of micafungin in pregnant women.

Micafungin and/or its metabolites were shown to cross the placental barrier and distribute to the foetus in rats. No effects on embryo foetal development were observed in rats given IV doses of micafungin up to 32 mg/kg/day throughout organogenesis (2-3-fold the anticipated maximum clinical exposure, based on AUC). However, treatment of rabbits at doses of 32 mg/kg/day IV (2-fold the maximum anticipated clinical exposure, based on AUC) throughout organogenesis was associated with visceral abnormalities and increased abortion. Visceral abnormalities included abnormal lobation of the lung, levocardia, retrocaval ureter, anomalous right subclavian artery, and dilation of the ureter.

While animal studies are not always predictive of a human response, Mycamine should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

Use in lactation

Micafungin was found in the milk of lactating micafungin-treated rats. It is not known whether micafungin is excreted in human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Mycamine should be made taking into account the benefit of breast-feeding to the child and the benefit of Mycamine therapy to the mother.

Use in the elderly

No dosage adjustment is necessary for the elderly (see PHARMACOLOGY, Pharmacokinetic characteristics in special populations).

Genotoxicity

Micafungin is considered to have no genotoxic or clastogenic potential based on the negative results of standard genotoxicity tests. Micafungin did not induce gene mutations in bacterial assays and did not induce chromosomal aberrations in Chinese Hamster Lung cells *in vitro*. There was no indication of an induction of micronuclei by micafungin in a micronucleus test in mice or unscheduled DNA synthesis in rat hepatocytes.

Carcinogenicity

The development of foci of altered hepatocytes (FAH) and hepatocellular tumours in rats was dependent on both dose and duration of micafungin treatment. FAH recorded after treatment for 13 weeks or longer persisted after a 13 week withdrawal period and developed into hepatocellular tumours following a treatment free period which covered the life span of rats. No standard carcinogenicity studies have been conducted, but the development of FAH was assessed in female rats after up to 20 and 18 months after cessation of a 3- and 6-month treatment, respectively. In both studies, increased incidences/numbers of hepatocellular tumours were observed after the 18 and 20 month treatment free period in the high dose group of 32 mg/kg/day as well as in a lower dose group (although not statistically significant). The relevance of the hepatocarcinogenic potential of micafungin in humans is not known.

Effects on fertility

Male rats treated intravenously with micafungin for 9 weeks showed vacuolation of the epididymal ductal epithelial cells at 10 and 32 mg/kg/day. A dose of 32 mg/kg/day resulted in higher epididymis weights and reduced numbers of sperm cells. There was no impairment of fertility in rat studies with micafungin. In a 39 week intravenous study in dogs, seminiferous tubular atrophy and decreased sperm in the epididymis were observed at 10 and 32 mg/kg/day.

Testicular toxicity was observed in animal studies. Micafungin may have the potential to affect male fertility in humans.

Effect on laboratory tests

There is no information on the effect of micafungin on laboratory tests.

Interactions with other medicinal products

Patients receiving sirolimus in combination with Mycamine should be monitored for sirolimus toxicity and the sirolimus dosage should be reduced if necessary (see INTERACTIONS WITH OTHER MEDICINES).

INTERACTIONS WITH OTHER MEDICINES

Micafungin has a low potential for interactions with medicines metabolised via CYP3A mediated pathways as shown below.

Effects of other medicines on micafungin

A total of 14 drug-drug interaction studies were conducted in healthy volunteers to evaluate the potential for interaction between micafungin and mycophenolate mofetil, cyclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, rifampicin, itraconazole, voriconazole and amphotericin B. In these studies, no interaction that altered the pharmacokinetics of micafungin was observed. Therefore, no Mycamine dose adjustments are necessary when these medicines are administered concomitantly.

Effects of micafungin on other medicines

There was no effect of a single dose or multiple doses of micafungin on mycophenolate mofetil, cyclosporin, tacrolimus, prednisolone, fluconazole and voriconazole 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. Therefore, patients receiving sirolimus, nifedipine or itraconazole in combination with Mycamine should be monitored for toxicity and the dosage of sirolimus, nifedipine or itraconazole reduced if necessary.

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, adverse reactions may occur, which may influence the ability to drive and use machines (see ADVERSE EFFECTS).

ADVERSE EFFECTS

Overall Mycamine Safety Experience in Clinical Trials

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

In all clinical trials with Mycamine, 2497/2748 (91%) adult patients and 439/479 (92%) paediatric patients experienced at least one treatment-emergent adverse reaction.

Table 4. Selected[*] Treatment-Emergent Adverse Reactions in Adult Patients on Mycamine with Candidemia and Other *Candida* Infections (occurred in ≥ 5%)

System Organ Class[¥] (Preferred Term)[†]	Mycamine 100 mg n (%)	Mycamine 150 mg n (%)	Caspofungin[‡] n (%)
Number of Patients	200	202	193
Gastrointestinal Disorders	**81 (41)**	**89 (44)**	**76 (39)**
Diarrhea	15 (8)	26 (13)	14 (7)
Nausea	19 (10)	15 (7)	20 (10)
Vomiting	18 (9)	15 (7)	16 (8)
Metabolism and Nutrition Disorders	**77 (39)**	**83 (41)**	**73 (38)**
Hypoglycemia	12 (6)	14 (7)	9 (5)
Hypernatremia	8 (4)	13 (6)	8 (4)
Hyperkalemia	10 (5)	8 (4)	5 (3)
General Disorders/Administration Site Conditions	**59 (30)**	**56 (28)**	**51 (26)**
Pyrexia	14 (7)	22 (11)	15 (8)
Investigations	**36 (18)**	**49 (24)**	**37 (19)**
Blood Alkaline Phosphatase Increased	11 (6)	16 (8)	8 (4)
Cardiac Disorders	**35 (18)**	**48 (24)**	**36 (19)**
Atrial Fibrillation	5 (3)	10 (5)	0

Patient base: all randomized patients who received at least 1 dose of trial drug.
[*] During IV treatment + 3 days.
[¥] MedDRA v5.0.
[†] Within a system organ class patients may experience more than 1 adverse reaction.
[‡] 70 mg loading dose on day 1 followed by 50 mg/day thereafter (caspofungin).

Table 5. Selected[*] Treatment-Emergent Adverse Reactions in Adult Patients on Mycamine with Esophageal Candidiasis (occurred in ≥ 5%)

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

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

* During treatment + 3 days.
¥ MedDRA v5.0.
† Within a system organ class patients may experience more than 1 adverse reaction.

Table 6. Selected Adverse Reactions in Adult Patients on Mycamine During Prophylaxis of *Candida* Infection in Hematopoietic Stem Cell Transplant Recipients (occurred in ≥ 15%)

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

Patient base: all randomized adult patients who received at least 1 dose of trial drug
¥ MedDRA v12.0.
† Within a system organ class patients may experience more than 1 adverse reaction.

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

- *Blood and lymphatic system disorders*: coagulopathy, pancytopenia, thrombotic thrombocytopenic purpura
- *Cardiac disorders*: cardiac arrest, myocardial infarction
- *General disorders and administration site conditions*: infusion reaction, injection site thrombosis
- *Hepatobiliary disorders*: hepatocellular damage, hepatomegaly, jaundice, hepatic failure
- *Immune disorders*: hypersensitivity, anaphylactic reaction
- *Nervous system disorders*: convulsions, encephalopathy, intracranial hemorrhage
- *Psychiatric disorders*: delirium
- *Skin and subcutaneous tissue disorders*: urticaria

Clinical Trials Experience in Paediatric Patients

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

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

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

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

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

The selected treatment-emergent adverse reactions, those occurring in 15% or more of the patients and more frequently in a Mycamine group, for all Mycamine paediatric studies and for the two comparative studies (candidemia and prophylaxis) described above are shown in Table 7.

Table 7. Selected Treatment-Emergent Adverse Reactions in All Paediatric Patients, in Patients with Candidemia and Other *Candida* Infections (C/IC), and in Hematopoietic Stem-Cell Recipients During Prophylaxis of *Candida* Infections

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

System Organ Class[¥] (Preferred Term)[†]	All Micafungin-treated Patients n = 479 n (%)	C/IC		Prophylaxis	
		Mycamine n = 56 n (%)	AmBisome n = 56 n (%)	Mycamine n = 43 n (%)	Fluconazole n = 48 n (%)
Abdominal pain	76 (16)	2 (4)	2 (4)	15 (35)	12 (25)
Abdominal distension	29 (6)	1 (2)	1 (2)	8 (19)	6 (13)
General disorders and administration site conditions	256 (53)	14 (25)	14 (25)	41 (95)	46 (96)
Pyrexia	103 (22)	5 (9)	9 (16)	26 (61)	31 (65)
Infusion related reaction	24 (5)	0	3 (5)	7 (16)	4 (8)
Skin and subcutaneous tissue disorders	197 (41)	11 (20)	8 (14)	33 (77)	38 (79)
Pruritus	54 (11)	0	1 (2)	14 (33)	15 (31)
Rash	55 (12)	1 (2)	1 (2)	13 (30)	13 (27)
Urticaria	24 (5)	0	1 (2)	8 (19)	4 (8)
Respiratory, thoracic and mediastinal disorders	194 (41)	9 (16)	13 (23)	30 (70)	33 (69)
Epistaxis	45 (9)	0	0	4 (9)	8 (17)
Blood and lymphatic system disorders	161 (34)	17 (30)	13 (23)	40 (93)	44 (92)
Thrombocytopenia	70 (15)	5 (9)	3 (5)	31 (72)	37 (77)
Neutropenia	61 (13)	3 (5)	4 (7)	33 (77)	34 (71)
Anemia	63 (13)	10 (18)	6 (11)	22 (51)	24 (50)
Febrile neutropenia	23 (5)	0	0	7 (16)	7 (15)
Investigations	191 (40)	12 (21)	8 (14)	24 (56)	25 (52)
Alanine aminotransferase increased	45 (10)	0	0	7 (16)	1 (2)
Urine output decreased	18 (4)	0	0	10 (23)	8 (17)
Cardiac disorders	97 (20)	7 (13)	3 (5)	10 (23)	17 (35)
Tachycardia	47 (10)	2 (4)	1 (2)	7 (16)	12 (25)
Renal and urinary disorders	78 (16)	4 (7)	4 (7)	16 (37)	15 (31)
Hematuria	18 (4)	0	0	10 (23)	7 (15)
Psychiatric disorders	80 (17)	3 (5)	1 (2)	20 (47)	9 (19)
Anxiety	35 (7)	0	0	10 (23)	3 (6)

Patient base: all randomized patients who received at least one dose of trial drug.
[¥] MedDRA v12.0.
[†] Within a system organ class, patients may experience more than 1 adverse reaction.

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

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

Post-marketing Adverse Reactions

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

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

DOSAGE AND ADMINISTRATION

Consideration should be given to official/national guidance on the appropriate use of antifungal agents. Treatment with Mycamine should be initiated by a physician experienced in the management of fungal infections.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Mycamine should be administered once daily by intravenous infusion. The dosage depends on the indication and body weight of the patient as shown in Table 8 below.

Table 8. Dosage for adults, adolescents ≥ 16 years of age, and the elderly

	Recommended Reconstituted Dose Once Daily in Adult Patients	
Indication	**Body weight > 40 kg**	**Body weight ≤ 40 kg**
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Treatment of oesophageal candidiasis	150 mg/day	3 mg/kg/day
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

***** If the patient's response is inadequate, e.g. persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients weighing ≤ 40 kg.

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

Treatment duration

Invasive candidiasis: The treatment duration of *Candida* infection should be a minimum of 14 days. The antifungal treatment should continue for at least one week after two sequential negative blood cultures have been obtained and after resolution of clinical signs and symptoms of infection.

Oesophageal candidiasis: For the treatment of oesophageal candidiasis, Mycamine should be administered for at least one week after resolution of clinical signs and symptoms.

Prophylaxis of Candida infections: For prophylaxis of *Candida* infection, Mycamine should be administered for at least one week after neutrophil recovery.

Table 9. Dosage for paediatric patients 4 months and older

	Paediatric Dose Given Once Daily	
Indication	**30 kg or less**	**Greater than 30 kg**
Treatment of invasive candidiasis	2 mg/kg (maximum daily dose 100 mg)	
Treatment of oesophageal candidiasis	3 mg/kg	2.5 mg/kg (maximum daily dose 150 mg)
Prophylaxis of *Candida* infection	1 mg/kg (maximum daily dose 50 mg)	

Patients with hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment (see PHARMACOLOGY, Pharmacokinetic characteristics in special populations). There are currently insufficient data available for the use of Mycamine in patients with severe hepatic impairment and its use is not recommended in these patients.

Patients with renal impairment

No dosage adjustment is required in patients with renal impairment (creatinine clearance < 30mL/min) (see PHARMACOLOGY, Pharmacokinetic characteristics in special populations).

Instructions for reconstitution and dilution

Mycamine must not be mixed or co-infused with any other medicinal products except those mentioned below. Mycamine has been shown to precipitate when mixed directly with a number of other commonly used medications.

Using aseptic techniques at room temperature, Mycamine should be reconstituted and diluted as follows:

1. Remove the plastic cap from the vial and disinfect the stopper with alcohol.
2. Five mL of sodium chloride 9 mg/mL (0.9%) solution for infusion or glucose 50 mg/mL (5%) solution for infusion (taken from a 100 mL bag/bottle) should be aseptically and

slowly injected into each vial along the side of the inner wall. Although the concentrate will foam, every effort should be made to minimise the amount of foam generated. A sufficient number of vials of Mycamine should be reconstituted to obtain the required dose as shown in Table 10 below.

3. The vial should be rotated gently. DO NOT SHAKE. The powder will dissolve completely. The concentrate should be used immediately for further dilution. Each vial is for single use only; any unused reconstituted concentrate should be discarded immediately.
4. All of the reconstituted concentrate should be withdrawn from each vial and returned into the infusion bag/bottle from which it was originally taken. The diluted infusion solution should be used immediately.
5. The infusion bag/bottle should be gently inverted to disperse the diluted solution but NOT agitated in order to avoid foaming. Do not use if the solution is cloudy or has precipitated.
6. The infusion bag/bottle containing the diluted infusion solution should be inserted into a closable opaque bag for protection from light.

Table 10. Preparation of the Mycamine solution for infusion

Dose	Vials of Mycamine to be used	Volume of sodium chloride 0.9% or glucose 5% to be added per vial	Volume (concentration) of reconstituted powder	Final concentration of standard infusion (made up to 100 mL)
50 mg	1 x 50 mg	5 mL	approx. 5 mL (10 mg/mL)	0.5 mg/mL
100 mg	2 x 50 mg	5 mL	approx. 10 mL (10 mg/mL)	1.0 mg/mL
150 mg	3 x 50 mg	5 mL	approx. 15 mL (10 mg/mL)	1.5 mg/mL
200 mg	4 x 50 mg	5 mL	approx. 20 mL (10 mg/mL)	2.0 mg/mL

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

Administration

An existing intravenous line should be flushed with sodium chloride 0.9% solution prior to infusion of Mycamine. Administer the reconstituted and diluted Mycamine solution intravenously over approximately one hour. More rapid infusions may result in more frequent histamine mediated reactions.

Paediatric Patients
Mycamine should be infused over one hour. To minimize the risk of infusion reactions, concentrations of greater than 1.5 mg/mL should be administered via central catheter.

OVERDOSAGE

There is no experience with overdoses of micafungin. In case of overdose, general supportive measures and symptomatic treatment should be administered. Micafungin is highly protein bound and is therefore not dialysable.

Repeated daily doses of up to 8 mg/kg (median 50.0 mg per day, maximum 896 mg per day) in adult patients have been administered in clinical trials with no reported dose-limiting toxicity.

PRESENTATION AND STORAGE CONDITIONS

Mycamine 50 mg is a white coloured powder for solution for infusion containing 50 mg micafungin, corresponding to 50.86 mg micafungin sodium.

Mycamine is presented in a 10 mL glass vial with a rubber stopper and flip-off cap. The vials are shrink-wrapped with a UV-protective film.

Mycamine is supplied in packs containing 1 or 10 single-use vials.

Storage conditions

Unopened vial: Store below 30°C. Protect from light.

Reconstituted concentrate in vial: Chemical and physical in-use stability has been demonstrated for up to 24 hours at 30°C when reconstituted with sodium chloride 0.9% or glucose 5% solution.

Diluted infusion solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C when diluted with sodium chloride 0.9% solution or glucose 5% solution and protected from light.

Mycamine contains no preservatives. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

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