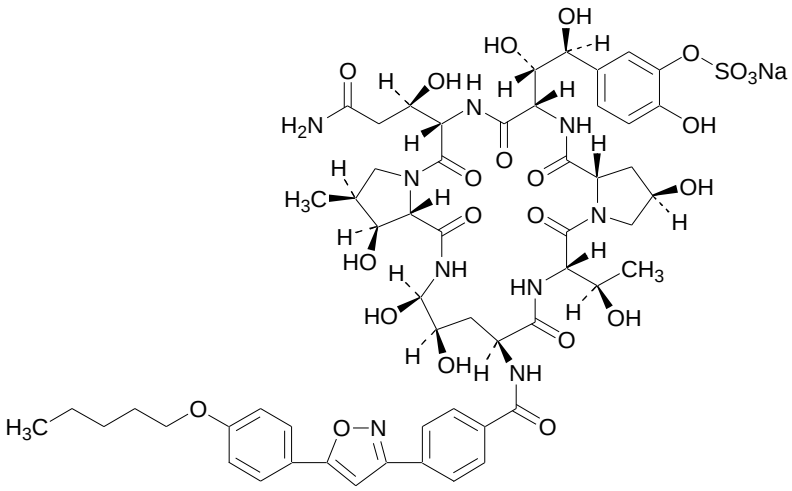
DATA SHEET
MYCAMINE® 50 mg and 100 mg POWDER FOR INJECTION

1. NAME OF THE MEDICINE

MYCAMINE® 50 mg powder for injection
MYCAMINE® 100 mg powder for injection

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MYCAMINE is a sterile, white, powder for injection 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 must be diluted with either sodium chloride 0.9% or glucose 5% solution prior to use (see DOSAGE AND ADMINISTRATION).

3. PHARMACEUTICAL FORM

MYCAMINE 50 mg is a white-coloured powder for injection, containing 50.86 mg micafungin sodium, corresponding to 50 mg micafungin.

MYCAMINE 100 mg is a white-coloured powder for injection, containing 101.73 mg micafungin sodium, corresponding to 100 mg micafungin.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

MYCAMINE is indicated for:

- Treatment of invasive candidiasis in children and adults
- Treatment of oesophageal candidiasis in adults, adolescents ≥ 16 years of age and the elderly patients for whom intravenous therapy is appropriate
- Prophylaxis of Candida infection in children and adult 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

4.2 Dose and method of administration

MYCAMINE should be administered once daily by intravenous infusion. The dosage depends on the indication and the body-weight of the patient as shown in Tables 1 and 2 below.

Table 1. Dosage for adults, adolescents ≥ 16 years of age, and the elderly

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.

Treatment duration

Invasive candidiasis: The treatment duration for *Candida* infection should be a minimum of 14 days. The antifungal treatment should continue for at least 1 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 1 week after resolution of clinical signs and symptoms.

Prophylaxis of Candida infections: For prophylaxis of *Candida* infection, MYCAMINE should be administered for at least 1 week after neutrophil recovery.

Table 2. Dosage for children (including neonates) and adolescents < 16 years of age

Indication	Body-weight > 40 kg	Body-weight ≤ 40 kg
Treatment of invasive candidiasis	100 mg/day*	2 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.

Treatment duration

Invasive candidiasis: The treatment duration for *Candida* infection should be a minimum of 14 days and should continue for at least 1 week after two sequential negative blood cultures have been obtained and after resolution of clinical signs and symptoms of infection.

Prophylaxis of Candida infections: For prophylaxis of *Candida* infection, MYCAMINE should be administered for at least 1 week after neutrophil recovery. Experience in patients less than two years of age is limited.

Patients with hepatic impairment

No dosage adjustment is required in patients with mild to severe hepatic impairment (see PHARMACOLOGY, Pharmacokinetic characteristics in special populations).

Patients with renal impairment

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

Administration

An existing intravenous line should be flushed with sodium chloride 0.9% solution prior to infusion. Administer the reconstituted and diluted MYCAMINE solution intravenously over approximately 1 hour.

4.3 Contraindications

MYCAMINE is contraindicated in patients with hypersensitivity to any component of this medication or to other echinocandins (see QUALITATIVE AND QUANTITATIVE COMPOSITION).

4.4 Special warnings and precautions for use

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 and Subcutaneous Tissue Disorders

Exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. If patients develop a rash, they should be monitored closely and MYCAMINE discontinued if lesions progress.

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.

Hepatic effects

Liver function should be carefully monitored during MYCAMINE treatment. Early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended. MYCAMINE 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.

Paediatric use

No dosage adjustment is necessary for children (see PHARMACOLOGY, Pharmacokinetic characteristics in special populations). However, the incidence of some adverse reactions was higher in paediatric patients than in adult patients (see ADVERSE EVENTS).

Use in the elderly

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

Effect on laboratory tests

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

4.5 Interaction with other medicines and other forms of interaction

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.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

Micafungin had no effect on the fertility of male and female rats at doses up to 32 mg/kg/day IV (four times the anticipated maximum clinical exposure, based on AUC). However, male rats treated for 9 weeks at 10–32 mg/kg/day IV micafungin (resulting in 1–4-fold the anticipated maximum clinical exposure, based on AUC) showed vacuolation of the epididymal ductal epithelial cells. A dose of 32 mg/kg/day also resulted in higher epididymis weights and reduced numbers of sperm cells. In a 39-week IV study in dogs, seminiferous tubular atrophy

and decreased sperm in the epididymis were also observed at 10 and 32 mg/kg/day IV micafungin (resulting in 1–5-fold the anticipated maximum clinical exposure, based on AUC).

Testicular toxicity was observed in two animal species. Although the clinical relevance is unknown, micafungin may have the potential to affect male fertility in humans.

Use in pregnancy (Category B3[1])

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 (twice 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 and its metabolites were excreted in the milk of lactating rats. In a pre- and postnatal development study in rats, doses of 32 mg/kg/day IV micafungin (resulting in 2–3-fold the anticipated maximum clinical exposure, based on AUC) were associated with reduced pup birth-weights and a possible delay in the time of eyelid opening and balanopreputia cleavage.

It is not known whether micafungin is excreted in human breast-milk. Therefore caution should be exercised when MYCAMINE is administered during breastfeeding.

4.7 Effects on ability to drive and use machines

Micafungin has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable Effects

Overall Mycamine Safety Experience in Clinical Trials

The overall safety of MYCAMINE was assessed in 3083 patients and 501 volunteers in 41 clinical studies, including the invasive candidiasis, oesophageal candidiasis and prophylaxis

[1] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

studies, who received single or multiple doses of MYCAMINE, ranging from 12.5 mg to ≥ 150 mg/day. Treatment emergent adverse events which occurred in ≥ 5% of all patients who received MYCAMINE in these trials are shown in Table 3.

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

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

- *Blood and lymphatic system disorders*: coagulopathy, febrile neutropenia, haemolysis, haemolytic anaemia, pancytopenia, thrombotic thrombocytopenic purpura
- *Cardiac disorders*: arrhythmia, atrial fibrillation, cardiac arrest, cyanosis, hypotension, myocardial infarction, tachycardia
- *Gastrointestinal disorders*: abdominal pain upper, dyspepsia
- *General disorders and administration site conditions*: injection site thrombosis
- *Hepatobiliary disorders*: hepatocellular damage, hepatomegaly, jaundice, hepatic failure
- *Infections and infestations*: infection, pneumonia, sepsis
- *Metabolism and nutrition disorders*: acidosis, anorexia, hyponatraemia
- *Musculoskeletal, connective tissue and bone disorders*: arthralgia
- *Nervous system disorders*: convulsions, encephalopathy, intracranial haemorrhage
- *Psychiatric disorders*: delirium
- *Renal and urinary disorders*: anuria, haemoglobinuria, oliguria, renal failure acute, renal tubular necrosis
- *Respiratory, thoracic and mediastinal disorders*: apnoea, dyspnoea, hypoxia, pulmonary embolism
- *Skin and subcutaneous tissue disorders*: erythema multiforme, skin necrosis, urticaria
- *Vascular disorders*: deep venous thrombosis, hypertension

Table 3. *Adverse Events in Patients Who Received Mycamine in Clinical Trials

Adverse Events † **(MedDRA System Organ Class and Preferred Term)**	**Mycamine** **n (%)**
Number of Patients	**3083**
All Systems, Any Adverse Event	**2810 (91.1)**
Gastrointestinal Disorders	**1764 (57.2)**
Diarrhoea NOS	718 (23.3)
Nausea	679 (22)
Vomiting NOS	669 (21.7)
Constipation	341 (11.1)
Abdominal Pain	300 (9.7)
Dyspepsia	176 (5.7)
General Disorders / Administration Site Conditions	**1407 (45.6)**
Pyrexia	618 (20)
Mucosal Inflammation NOS	438 (14.2)
Rigors	281 (9.1)
Oedema Peripheral	209 (6.8)
Fatigue	198 (6.4)
Metabolism and Nutrition Disorders	**1316 (42.7)**
Hypokalaemia	556 (18)
Hypomagnesaemia	409 (13.3)
Hypocalcaemia	201 (6.5)
Anorexia	190 (6.2)
Hyperglycaemia NOS	173 (5.6)
Fluid Overload	155 (5)
Infections and Infestations	**1227 (39.8)**
Bacteraemia	185 (6)
Sepsis NOS	156 (5.1)
Respiratory, Thoracic and Mediastinal Disorders	**1108 (35.9)**
Cough	251 (8.1)
Dyspnoea NOS	182 (5.9)
Epistaxis	172 (5.6)
Blood and Lymphatic System Disorders	**1047 (34)**
Thrombocytopenia	474 (15.4)
Neutropenia	436 (14.1)
Anaemia NOS	302 (9.8)
Febrile Neutropenia	187 (6.1)
Investigations	**989 (32.1)**
Aspartate Aminotransferase Increased	172 (5.6)
Blood Alkaline Phosphatase NOS Increased	168 (5.4)
Alanine Aminotransferase Increased	165 (5.4)
Skin and Subcutaneous Tissue Disorders	**940 (30.5)**
Rash NOS	269 (8.7)

Pruritus NOS	187 (6.1)
Nervous System Disorders	**889 (28.8)**
Headache NOS	489 (15.9)
Psychiatric Disorders	**727 (23.6)**
Insomnia	303 (9.8)
Anxiety	198 (6.4)
Vascular Disorders	**867 (28.1)**
Hypotension NOS	279 (9.1)
Hypertension NOS	214 (6.9)
Phlebitis NOS	172 (5.6)
Musculoskeletal and Connective Tissue Disorders	**579 (18.8)**
Back Pain	166 (5.4)
Cardiac Disorders	**563 (18.3)**
Tachycardia NOS	231 (7.5)

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

Post-marketing Adverse Reactions

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

Paediatric patients

The incidence of some adverse events (AEs) in the clinical study database (thrombocytopenia, tachycardia, hypertension, hypotension, hyperbilirubinaemia, hepatomegaly, renal failure acute, blood urea increased) was higher in children than in adult patients. Additionally, paediatric patients < 1 year of age experienced about twice as often an increase in ALT, AST and AP than older paediatric patients. No clinically meaningful differences in the safety profile could be discerned by paediatric age strata of < 4 weeks, 4 weeks to < 1 year, 1 to 4 years, 5 to 8 years, 9 to 12 years and 13 to < 16 years.

4.9 Overdose

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

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 4 mg/kg (median 1.2 mg/kg per day, maximum 4.6 mg/kg per day), and maximum doses of 8.6 mg/kg in paediatric patients and 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. A newborn patient received a high initial dose of 7.8 mg/kg/day in a clinical trial, which following its detection after 7 days was decreased to 2.0 mg/kg/day. No ill effects associated with this high dose were noted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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 inhibits actively growing hyphae of *Aspergillus* species.

In vitro activity

Susceptibility testing was performed with modifications according to the Clinical and Laboratory Standards Institute (CLSI) methods M27-A2 (*Candida* species) and M38-A (*Aspergillus* species).

Micafungin displayed inhibitory activity against clinically relevant *Candida* species. The Minimum Inhibitory Concentration (MIC) rank order was: *C. albicans* (including azole resistant strains) < *C. tropicalis, C. glabrata* < *C. krusei* << *C. parapsilosis, C. guilliermondii.*

Micafungin displayed inhibitory activity against clinically relevant *Aspergillus* species *(A. fumigatus, A. niger, A. flavus, A. nidulans, A. terreus and A. versicolor).*

Micafungin has virtually no activity against *Cryptococcus neoformans, Trichosporon cutaneum, Trichosporon asahii, Fusarium solani, Pseudallescheria boydii, Absidia corymbifera, Cunninghamella elegans, Rhizopus oryzae, or Rhizopus microsporus.*

In vivo activity

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

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 gene coding for a major subunit of glucan synthase.

Clinical efficacy and Safety

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 subpopulations (including neonates and premature infants). Efficacy findings were consistent, independent of the infective *Candida* species, primary site of infection and neutropenic status (see Table 4). 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 4. Summary of overall treatment success (per protocol set)

	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). Most patients in this study had HIV infection. 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. The

odds of endoscopic cure was approximately 2.6 times higher in HIV patients with a baseline CD4 count ≥100 than in HIV patients with a baseline CD4 count <100. 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 childrenn (N = 84). Table 5 summarises the main efficacy findings.

Table 5. 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 one *versus* seven patients, and proven or probable breakthrough *Candida* infections were observed in four *versus* two patients in the micafungin and fluconazole groups, respectively. Other breakthrough infections were caused by *Fusarium* (one and two patients, respectively) and *Zygomycetes* (1 and 0 patients, respectively). The nature and incidence of adverse reactions were similar between treatment groups.

5.2 Pharmacokinetic Properties

Absorption

The pharmacokinetics of micafungin have been evaluated in healthy subjects, haematopoietic stem cell transplant recipients and patients with invasive and oesophageal candidiasis up to a maximum dose of 8 mg/kg. There is no evidence of systemic accumulation with repeated administration and increases in systemic exposure (AUC and C_{max}) are proportional to increases in dose. Steady-state is generally reached by Day 4.

Distribution

Following intravenous administration, concentrations of micafungin show a bi-exponential decline as the drug is rapidly distributed into tissues. Micafungin is highly protein-bound (> 99%), primarily to albumin and to a lesser extent to alpha-1-acid glycoprotein. Binding to albumin is independent of micafungin concentration (10 to 100 µg/mL). Micafungin does not displace albumin-bound bilirubin at clinically relevant concentrations.

In an *in vitro* study in which ^{14}C-micafungin was added to whole human blood, the blood to plasma ratio was approximately 0.85 and was independent of concentration over the range of 0.1 to 10 µg/mL micafungin. Micafungin was not extensively taken up by blood cells.

The volume of distribution of micafungin at terminal phase was 0.24 to 0.41 L/kg of body-weight.

Metabolism

Unchanged micafungin is the principal circulating compound in the systemic circulation. Metabolism takes place in the liver where micafungin is metabolised to M1 (catechol form) by arylsulfatase, with further metabolism to M2 (methoxy form) by catechol-O-methyltransferase. M5 is formed by hydroxylation at the side chain (ω-1 position) of micafungin catalysed by cytochrome P450 (CYP) isoenzymes. Exposure to these metabolites is generally low and they are not expected to contribute to the overall efficacy of micafungin. Although micafungin is a substrate for CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for metabolism *in vivo*.

Excretion

The mean terminal half-life of micafungin is approximately 10 to 17 hours and stays consistent across doses up to 8 mg/kg after single and repeated administration in patients and healthy volunteers. Faecal excretion is the major route of elimination. 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.

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 100 mg 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 to severe 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: No clinically meaningful differences based on age in the pharmacokinetic profile of micafungin that would require a dosing adjustment were observed in children 2 to 17 years of age compared with adults. However, clearance in premature infants was approximately 2- to 6-fold greater than in adults in one study.

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.

5.3 Pre-clinical Safety Data

Genotoxicity

Micafungin was not genotoxic nor clastogenic in a standard battery of 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

No standard carcinogenicity studies have been conducted with micafungin.

Hepatic carcinomas and adenomas were observed in 3- to 6-month repeat-dose IV toxicity studies in rats at 32 mg/kg/day (resulting in four times the maximum anticipated clinical exposure, based on AUC) with 12 to 20 month recovery periods. In shorter term studies, altered hepatocellular foci, which were likely precursors to the hepatic tumours, were observed. Exposure at the no observed adverse effect level for altered hepatocellular foci resulted in exposures similar to the maximum anticipated clinically, based on AUC.

It is not known whether the hepatic neoplasms observed in treated rats also occur in other species, or if there is a dose threshold for this effect. The relevance of the hepatocarcinogenic potential of micafungin in humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

MYCAMINE contains the following excipients: lactose, anhydrous citric acid, and sodium hydroxide.

6.2 Incompatibilities

This medicinal product must not be mixed or co-infused with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened Vial: 3 years

Reconstituted concentrate in vial: Chemical and physical in-use stability has been demonstrated for up to 48 hours at 25°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 96 hours at 25°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.

6.4 Special Precautions for Storage

Unopened vial:

Store below 25°C.

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and Contents of Container

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 one or ten single-use vials.

6.6 Special Precautions for Disposal and other Handling

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 6 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. The product is for single use in one patient only. Discard any residue.
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 6. 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	1 x 100 mg	5 mL	approx. 5 mL (20 mg/mL)	1.0 mg/mL
150 mg	1 x 50 mg + 1 x 100 mg	5 mL	approx. 10 mL	1.5 mg/mL
200 mg	2 x 100 mg	5 mL	approx. 10 mL	2.0 mg/mL

After reconstitution and dilution, the solution should be administered by intravenous infusion over approximately 1 hour.

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

Seqirus (NZ) Ltd
PO Box 62 590,
Greenlane, Auckland, 1546
New Zealand

9. DATE OF FIRST APPROVAL

15 May 2014

10. DATE OF REVISION OF THE TEXT

22 May 2019

Summary of Changes

Section changed	Summary of new information
N/A	Change to SmPC format