

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mycamine 50 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg micafungin (as sodium).

After reconstitution each ml contains 10 mg micafungin (as sodium).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White compact powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mycamine is indicated for:

Adults, adolescents ≥ 16 years of age and elderly:

- 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.

Children (including neonates) and adolescents < 16 years of age:

- Treatment of invasive candidiasis.
- 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.

The decision to use Mycamine should take into account a potential risk for the development of liver tumours (see section 4.4). Mycamine should therefore only be used if other antifungals are not appropriate.

4.2 Posology and method of 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.

Posology

The dose regimen of Mycamine depends on the body weight of the patient as given in the following tables:

Use in adults, adolescents ≥ 16 years of age and elderly

<u>Indication</u>	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 <i>Candida</i> 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 ≤ 40 kg.

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.

Use in children ≥ 4 months of age up to adolescents < 16 years of age

<u>Indication</u>	Body weight > 40 kg	Body weight ≤ 40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Prophylaxis of <i>Candida</i> 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.

Use in children (including neonates) < 4 months

<u>Indication</u>	
Treatment of invasive candidiasis	4 -10 mg/kg/day*
Prophylaxis of <i>Candida</i> infection	2 mg/kg/day

*Micafungin dosed at 4 mg/kg in children less than 4 months approximates drug exposures achieved in adults receiving 100 mg/day for the treatment of invasive candidiasis. If central nervous system (CNS) infection is suspected, a higher dosage (e.g. 10 mg/kg) should be used due to the dose-dependent penetration of micafungin into the CNS (see section 5.2). The safety and efficacy in children (including neonates) less than 4 months of age of doses of

4 and 10 mg/kg for the treatment of invasive candidiasis with CNS involvement has not been adequately established in controlled clinical studies.

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.

Prophylaxis of *Candida* infections: For prophylaxis of *Candida* infection, Mycamine should be administered for at least one week after neutrophil recovery. Experience with Mycamine in patients less than 2 years of age is limited.

Gender/race

No dose adjustment is necessary based on gender or race (see section 5.2).

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (see section 5.2). 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 (see section 4.4 and 5.2).

Patients with renal impairment

No dose adjustment is necessary in patients with renal impairment (see section 5.2).

Method of administration

After reconstitution and dilution, the solution should be administered by intravenous infusion over approximately 1 hour. More rapid infusions may result in more frequent histamine mediated reactions. For reconstitution instructions see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to other echinocandins or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 can not 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. Paediatric patients < 1 year of age might be more prone to liver injury (see section 4.8).

Anaphylactic reactions

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

Skin reactions

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 micafungin discontinued if lesions progress.

Haemolysis

Rare 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 micafungin therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing micafungin 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.

Interactions with other medicinal products

Co-administration of micafungin and amphotericin B desoxycholate should only be used when the benefits clearly outweigh the risks, with close monitoring of amphotericin B desoxycholate toxicities (see section 4.5).

Patients receiving sirolimus, nifedipine or itraconazole in combination with Mycamine should be monitored for sirolimus, nifedipine or itraconazole toxicity and the sirolimus, nifedipine or itraconazole dosage should be reduced if necessary (see section 4.5).

Paediatric population

The incidence of some adverse reactions was higher in paediatric patients than in adult patients (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

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

Drug interaction studies in healthy human subjects were conducted to evaluate the potential for interaction between micafungin and mycophenolate mofetil, ciclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, rifampicin, itraconazole, voriconazole and amphotericin B. In these studies, no evidence of altered pharmacokinetics of micafungin was observed. No micafungin dose adjustments are necessary when these medicines are administered concomitantly. Exposure (AUC) of itraconazole, sirolimus and nifedipine was slightly increased in the presence of micafungin (22%, 21% and 18% respectively).

Co-administration of micafungin and amphotericin B desoxycholate was associated with a 30% increase in amphotericin B desoxycholate exposure. Since this may be of clinical significance this co-administration should only be used when the benefits clearly outweigh the risks, with close monitoring of amphotericin B desoxycholate toxicities (see section 4.4).

Patients receiving sirolimus, nifedipine or itraconazole in combination with Mycamine should be monitored for sirolimus, nifedipine or itraconazole toxicity and the sirolimus, nifedipine or itraconazole dosage should be reduced if necessary (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

There are no data from the use of micafungin in pregnant women. In animal studies micafungin crossed the placental barrier and reproductive toxicity was seen (see section 5.3). The potential risk for humans is unknown.

Mycamine should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is not known whether micafungin is excreted in human breast milk. Animal studies have shown excretion of micafungin in 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.

Fertility

Testicular toxicity was observed in animal studies (see section 5.3). Micafungin may have the potential to affect male fertility in humans.

4.7 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 section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety profile of micafungin is based on 3028 patients treated with micafungin in clinical studies: 2.002 patients with *Candida* infections (including candidaemia, invasive candidiasis and oesophageal candidiasis), 375 with invasive aspergillosis (primarily refractory infections) and 651 for prophylaxis of systemic fungal infections.

The patients treated with micafungin in clinical studies represent a critically ill patient population that requires multiple medicinal products including antineoplastic chemotherapy, potent systemic immunosuppressants and broad spectrum antibiotics. These patients had a wide variety of complex underlying conditions such as haematological malignancies and HIV-infection or were transplant recipients and/or treated in intensive care. Patients treated prophylactically with micafungin were those undergoing haematopoietic stem cell transplantation (HSCT) who were at high risk for fungal infections.

Overall 32.2% of the patients experienced adverse drug reactions. The most frequently reported adverse reactions were nausea (2.8%), blood alkaline phosphatase increased (2.7%), phlebitis (2.5%, primarily in HIV infected patients with peripheral lines), vomiting (2.5%), and aspartate aminotransferase increased (2.3%). No clinically significant differences were seen when the safety data were analysed by gender or race.

Tabulated list of adverse reactions

In the following table adverse reactions are listed by system organ class and MedDRA preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Not known (frequency cannot be estimated from available data)
Blood and lymphatic system disorders	leukopenia, neutropenia, anaemia	pancytopenia, thrombocytopenia, eosinophilia, hypoalbuminaemia	haemolytic anaemia, haemolysis (see section 4.4)	disseminated intravascular coagulation
Immune system disorders		anaphylactic / anaphylactoid reaction (see section 4.4), hypersensitivity		
Endocrine disorders		hyperhidrosis		
Metabolism and nutritional disorders	hypokalaemia, hypomagnesaemia, hypocalcaemia	hyponatraemia, hyperkalaemia, hypophosphataemia, anorexia		
Psychiatric disorders		insomnia, anxiety, confusion		
Nervous system disorders	headache	somnolence, tremor, dizziness, dysgeusia		

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Not known (frequency cannot be estimated from available data)
Cardiac disorders		tachycardia, palpitations, bradycardia		
Vascular disorders	phlebitis	hypotension, hypertension, flushing		shock
Respiratory, thoracic and mediastinal disorders		dyspnoea		
Gastrointestinal disorders	nausea, vomiting, diarrhoea, abdominal pain	dyspepsia, constipation		
Hepatobiliary disorders	blood alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased (including hyperbilirubinaemia), liver function test abnormal	hepatic failure (see section 4.4), gamma-glutamyltransferase increased, jaundice, cholestasis, hepatomegaly, hepatitis		hepatocellular damage including fatal cases (see section 4.4)
Skin and subcutaneous tissue disorders	rash	urticaria, pruritus, erythema		toxic skin eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see section 4.4)
Renal and urinary disorders		blood creatinine increased, blood urea increased, renal failure aggravated		renal impairment (see section 4.4), acute renal failure
General disorders and administration site conditions	pyrexia, rigors	injection site thrombosis, infusion site inflammation, injection site pain, peripheral oedema		
Investigations		blood lactate dehydrogenase increased		

Description of selected adverse reactions

Possible allergic-like symptoms

Symptoms such as rash and rigors have been reported in clinical studies. The majority were of mild to moderate intensity and not treatment limiting. Serious reactions (e.g. anaphylactoid reaction 0.2%, 6/3028) were uncommonly reported during therapy with micafungin and only in patients with serious underlying conditions (e.g. advanced AIDS, malignancies) requiring multiple co-medications.

Hepatic adverse reactions

The overall incidence of hepatic adverse reactions in the patients treated with micafungin in clinical studies was 8.6% (260/3028). The majority of hepatic adverse reactions were mild and moderate. Most frequent reactions were increase in AP (2.7%), AST (2.3%), ALT (2.0%), blood bilirubin (1.6%) and liver function test abnormal (1.5%). Few patients (1.1%; 0.4% serious) discontinued treatment due to a hepatic event. Cases of serious hepatic dysfunction occurred uncommonly (see section 4.4).

Injection-site reactions

None of the injection-site adverse reactions were treatment limiting.

Paediatric population

The incidence of some adverse reactions (listed in the table below) was higher in paediatric patients than in adult patients. Additionally, paediatric patients < 1 year of age experienced about two times more often an increase in ALT, AST and AP than older paediatric patients (see section 4.4). The most likely reason for these differences were different underlying conditions compared with adults or older paediatric patients observed in clinical studies. At the time of entering the study, the proportion of paediatric patients with neutropenia was several-fold higher than in adult patients (40.2% and 7.3% of children and adults, respectively), as well as allogeneic HSCT (29.4% and 13.4%, respectively) and haematological malignancy (29.1% and 8.7%, respectively).

Blood and lymphatic system disorders

Cardiac disorders

common tachycardia

Vascular disorders

common hypertension, hypotension

Hepatobiliary disorders

common hyperbilirubinaemia, hepatomegaly

Renal and urinary disorders

common acute renal failure, blood urea increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Repeated daily doses up to 8 mg/kg (maximum total dose 896 mg) in adult patients have been administered in clinical trials with no reported dose-limiting toxicity. In one spontaneous case, it was reported a dosage of 16 mg/kg/day was administered in a newborn patient. No adverse reactions associated with this high dose were noted.

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 not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, other antimycotics for systemic use, ATC code: J02AX05

Mode of action

Micafungin non-competitively inhibits the synthesis of 1,3- β -D-glucan, an essential component of the fungal cell wall. 1,3- β -D-glucan is not present in mammalian cells.

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

PK/PD relationship

In animals models of candidiasis, a correlation was observed between exposure of micafungin divided by MIC (AUC/MIC) and efficacy defined as the ratio required to prevent progressive fungal growth. A ratio of ~2400 and ~1300 was required for *C. albicans* and *C. glabrata*, respectively, in these models. At the recommended therapeutic dosage of Mycamine, these ratios are achievable for the wild-type distribution of *Candida spp.*

Mechanism(s) of resistance

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.

Breakpoints

EUCAST breakpoints

<i>Candida</i> species	MIC breakpoint (mg/L)	
	$\leq S$ (Susceptible)	$> R$ (Resistant)
<i>Candida albicans</i>	0.016	0.016
<i>Candida glabrata</i>	0.03	0.03
<i>Candida parapsilosis</i>	0.002	2
<i>Candida tropicalis</i> ¹	Insufficient evidence	
<i>Candida krusei</i> ¹	Insufficient evidence	
<i>Candida guilliermondii</i> ¹	Insufficient evidence	
Other <i>Candida</i> spp.	Insufficient evidence	

¹ 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 3 two-fold dilution steps higher than those for *C. albicans* and, similarly, those for *C. guilliermondii* are approximately 8 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.

Information from clinical studies

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; 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). 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.

Overall Treatment Success in the 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 <i>Candida</i> Species					
<i>Candida albicans</i>	102	91 (89.2)	98	89 (90.8)	
Non- <i>albicans</i> species ¶: all	151	133 (88.1)	140	123 (87.9)	
<i>C. tropicalis</i>	59	54 (91.5)	51	49 (96.1)	
<i>C. parapsilosis</i>	48	41 (85.4)	44	35 (79.5)	
<i>C. glabrata</i>	23	19 (82.6)	17	14 (82.4)	
<i>C. krusei</i>	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. The nature and incidence of adverse events were similar between treatment groups.

Prophylaxis: 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/ μ L). 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).

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.

5.2 Pharmacokinetic properties

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 (V_{ss}) 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 ¹⁴C-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.

Special populations

Paediatric patients: In paediatric patients AUC values were dose proportional over the dose range of 0.5-4 mg/kg. Clearance was influenced by weight, with mean values of weight-adjusted clearance 1.35 times higher in the younger children (4 months to 5 years) and 1.14 times higher in paediatric patients aged 6 to 11 years. Older children (12-16 years) had mean clearance values similar to those determined in adult patients. Mean weight-adjusted clearance in children less than 4 months of age is approximately 2.6-fold greater than older children (12-16 years) and 2.3-fold greater than in adults.

PK/PD bridging study demonstrated dose-dependent penetration of micafungin into CNS with the minimum AUC of 170 µg*hr/L required to achieve maximum eradication of fungal burden in the CNS tissues. Population PK modeling demonstrated that a dose of 10 mg/kg in children less than 4 month of age would be sufficient to achieve the target exposure for the treatment of CNS *Candida* infections.

Elderly: When administered as a single 1-hour infusion of 50 mg the pharmacokinetics of micafungin in the elderly (aged 66-78 years) were similar to those in young (20-24 years) subjects. No dose adjustment is necessary for the elderly.

Patients with hepatic impairment: In a study performed in patients with moderate hepatic impairment (Child-Pugh score 7-9), (n=8), the pharmacokinetics of micafungin did not significantly differ from those in healthy subjects (n=8). Therefore, no dose adjustment is necessary for patients with mild to moderate hepatic impairment. In a study performed in patients with severe hepatic impairment (Child-Pugh score 10-12) (n=8), lower plasma concentrations of micafungin and higher plasma concentrations of the hydroxide metabolite (M-5) were seen compared to healthy subjects (n=8). These data are insufficient to support a dosing recommendation in patients with severe hepatic impairment.

Patients with renal impairment: Severe renal impairment (Glomerular Filtration Rate [GFR] < 30 ml/min) did not significantly affect the pharmacokinetics of micafungin. No dose adjustment is necessary for patients with renal impairment.

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

5.3 Preclinical safety data

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 plasma exposure at the assumed threshold for tumour development in rats (i.e. the dose where no FAH and liver tumours were detected) was in the same range as the clinical exposure. The relevance of the hepatocarcinogenic potential of micafungin for the human therapeutic use is not known.

The toxicology of micafungin following repeated intravenous dosing in rats and/or dogs showed adverse responses in liver, urinary tract, red blood cells, and male reproductive organs. The exposure levels at which these effects did not occur (NOAEL) were in the same range as the clinical exposure or lower. Consequently, the occurrence of these adverse responses may be expected in human clinical use of micafungin.

In standard safety pharmacology tests, cardiovascular and histamine releasing effects of micafungin were evident and appeared to be time above threshold dependent. Prolongation of infusion time reducing the plasma concentration peak appeared to reduce these effects.

In repeated dose toxicity studies in rat signs of hepatotoxicity consisted of increased liver enzymes and degenerative changes of hepatocytes which were accompanied by signs of compensatory regeneration. In dog, liver effects consisted of increased weight and centrilobular hypertrophy, no degenerative changes of hepatocytes were observed.

In rats, vacuolation of the renal pelvic epithelium as well as vacuolation and thickening (hyperplasia) of the bladder epithelium were observed in 26-week repeat dose studies. In a second 26-week study hyperplasia of transitional cells in the urinary bladder occurred with a much lower incidence. These findings showed reversibility over a follow-up period of 18 months. The duration of micafungin dosing in these rat studies (6 months) exceeds the usual duration of micafungin dosing in patients (see section 5.1).

Micafungin haemolysed rabbit blood *in vitro*. In rats, signs of haemolytic anaemia were observed after repeated bolus injection of micafungin. In repeat dose studies in dogs, haemolytic anaemia was not observed.

In reproductive and developmental toxicity studies, reduced birth weight of the pups was noted. One abortion occurred in rabbits at 32 mg/kg/day. Male rats treated intravenously for 9 weeks showed vacuolation of the epididymal ductal epithelial cells, increased epididymis weights and reduced number of sperm cells (by 15%), however, in studies of 13 and 26 weeks duration these changes did not occur. In adult dogs, atrophy of seminiferous tubules with vacuolation of the seminiferous epithelium and decreased sperm in the epididymides were noted after prolonged treatment (39 weeks) but not after 13 weeks of treatment. In juvenile dogs, 39 weeks treatment did not induce lesions in the testis and epididymides in a dose dependent manner at the end of treatment but after a treatment free period of 13 weeks a dose dependent increase in these lesions were noted in the treated recovery groups. No impairment of male or female fertility was observed in the fertility and early embryonic development study in rats.

Micafungin was not mutagenic or clastogenic when evaluated in a standard battery of *in vitro* and *in vivo* tests, including an *in vitro* study on unscheduled DNA synthesis using rat hepatocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Citric acid anhydrous (to adjust the pH)
Sodium hydroxide (to adjust the pH)

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 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion.

Diluted infusion solution:

Chemical and physical in-use stability has been demonstrated for 96 hours at 25°C when protected from light when diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion.

Mycamine contains no preservatives. From a microbiological point of view, the reconstituted and diluted solutions 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, unless the reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened vials: 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

10 ml Type I glass vial with an isobutylene-isoprene (PTFE-laminated) rubber stopper and a flip-off cap. The vial is wrapped with an UV-protective film.

Supplied in packs of 1 vial.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Mycamine must not be mixed or co-infused with other medicinal products except those mentioned below. Using aseptic techniques at room temperature, Mycamine is reconstituted and diluted as follows:

1. The plastic cap must be removed from the vial and the stopper disinfected 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 bottle/bag) 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 must be reconstituted to obtain the required dose in mg (see table below).
3. The vial should be rotated gently. DO NOT SHAKE. The powder will dissolve completely. The concentrate should be used immediately. The vial is for single use only. Therefore, please discard unused reconstituted concentrate immediately.
4. All of the reconstituted concentrate should be withdrawn from each vial and returned into the infusion bottle/bag from which it was originally taken. The diluted infusion solution should be used immediately. Chemical and physical in-use stability has been demonstrated for 96 hours at 25°C when protected from light and diluted as described above.
5. The infusion bottle/bag 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 bottle/bag containing the diluted infusion solution should be inserted into a closable opaque bag for protection from light.

Preparation of the solution for infusion

Dose (mg)	Mycamine vial to be used (mg/vial)	Volume of sodium chloride (0.9%) or glucose (5%) to be added per vial	Volume (concentration) of reconstituted powder	Standard infusion (added up to 100 ml) Final concentration
50	1 x 50	5 ml	approx. 5 ml (10 mg/ml)	0.5 mg/ml
100	1 x 100	5 ml	approx. 5 ml (20 mg/ml)	1.0 mg/ml
150	1 x 100 + 1 x 50	5 ml	approx. 10 ml	1.5 mg/ml
200	2 x 100	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. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/448/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 April 2008
Date of latest renewal: 20 December 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.

1. NAME OF THE MEDICINAL PRODUCT

Mycamine 100 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg micafungin (as sodium).

After reconstitution each ml contains 20 mg micafungin (as sodium).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White compact powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mycamine is indicated for:

Adults, adolescents ≥ 16 years of age and elderly:

- 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.

Children (including neonates) and adolescents < 16 years of age:

- Treatment of invasive candidiasis.
- 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.

The decision to use Mycamine should take into account a potential risk for the development of liver tumours (see section 4.4). Mycamine should therefore only be used if other antifungals are not appropriate.

4.2 Posology and method of 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.

Posology

The dose regimen of Mycamine depends on the body weight of the patient as given in the following tables:

Use in adults, adolescents ≥ 16 years of age and elderly

<u>Indication</u>	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 <i>Candida</i> 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 ≤ 40 kg.

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.

Use in children ≥ 4 months of age up to adolescents < 16 years of age

<u>Indication</u>	Body weight > 40 kg	Body weight ≤ 40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Prophylaxis of <i>Candida</i> 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.

Use in children (including neonates) < 4 months of age

<u>Indication</u>	
Treatment of invasive candidiasis	4 -10 mg/kg/day*
Prophylaxis of <i>Candida</i> infection	2 mg/kg/day

*Micafungin dosed at 4 mg/kg in children less than 4 months approximates drug exposures achieved in adults receiving 100 mg/day for the treatment of invasive candidiasis. If central nervous system (CNS) infection is suspected, a higher dosage (e.g. 10 mg/kg) should be used due to the dose-dependent penetration of micafungin into the CNS (see section 5.2).

The safety and efficacy in children (including neonates) less than 4 months of age of doses of 4 and 10 mg/kg for the treatment of invasive candidiasis with CNS involvement has not been adequately established in controlled clinical studies.

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.

Prophylaxis of *Candida* infections: For prophylaxis of *Candida* infection, Mycamine should be administered for at least one week after neutrophil recovery. Experience with Mycamine in patients less than 2 years of age is limited.

Gender/race

No dose adjustment is necessary based on gender or race (see section 5.2).

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (see section 5.2). 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 (see section 4.4 and 5.2).

Patients with renal impairment

No dose adjustment is necessary in patients with renal impairment (see section 5.2).

Method of administration

After reconstitution and dilution, the solution should be administered by intravenous infusion over approximately 1 hour. More rapid infusions may result in more frequent histamine mediated reactions. For reconstitution instructions see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, to other echinocandins or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 can not 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. Paediatric patients < 1 year of age might be more prone to liver injury (see section 4.8).

Anaphylactic reactions

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

Skin reactions

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 micafungin discontinued if lesions progress.

Haemolysis

Rare 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 micafungin therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing micafungin 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.

Interactions with other medicinal products

Co-administration of micafungin and amphotericin B desoxycholate should only be used when the benefits clearly outweigh the risks, with close monitoring of amphotericin B desoxycholate toxicities (see section 4.5).

Patients receiving sirolimus, nifedipine or itraconazole in combination with Mycamine should be monitored for sirolimus, nifedipine or itraconazole toxicity and the sirolimus, nifedipine or itraconazole dosage should be reduced if necessary (see section 4.5).

Paediatric population

The incidence of some adverse reactions was higher in paediatric patients than in adult patients (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

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

Drug interaction studies in healthy human subjects were conducted to evaluate the potential for interaction between micafungin and mycophenolate mofetil, ciclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, ritonavir, rifampicin, itraconazole, voriconazole and amphotericin B. In these studies, no evidence of altered pharmacokinetics of micafungin was observed. No micafungin dose adjustments are necessary when these medicines are administered concomitantly. Exposure (AUC) of itraconazole, sirolimus and nifedipine was slightly increased in the presence of micafungin (22%, 21% and 18% respectively).

Co-administration of micafungin and amphotericin B desoxycholate was associated with a 30% increase in amphotericin B desoxycholate exposure. Since this may be of clinical significance this co-administration should only be used when the benefits clearly outweigh the risks, with close monitoring of amphotericin B desoxycholate toxicities (see section 4.4).

Patients receiving sirolimus, nifedipine or itraconazole in combination with Mycamine should be monitored for sirolimus, nifedipine or itraconazole toxicity and the sirolimus, nifedipine or itraconazole dosage should be reduced if necessary (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

There are no data from the use of micafungin in pregnant women. In animal studies micafungin crossed the placental barrier and reproductive toxicity was seen (see section 5.3). The potential risk for humans is unknown.

Mycamine should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is not known whether micafungin is excreted in human breast milk. Animal studies have shown excretion of micafungin in 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.

Fertility

Testicular toxicity was observed in animal studies (see section 5.3). Micafungin may have the potential to affect male fertility in humans.

4.7 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 section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety profile of micafungin is based on 3028 patients treated with micafungin in clinical studies: 2.002 patients with *Candida* infections (including candidaemia, invasive candidiasis and oesophageal candidiasis), 375 with invasive aspergillosis (primarily refractory infections) and 651 for prophylaxis of systemic fungal infections.

The patients treated with micafungin in clinical studies represent a critically ill patient population that requires multiple medicinal products including antineoplastic chemotherapy, potent systemic immunosuppressants and broad spectrum antibiotics. These patients had a wide variety of complex underlying conditions such as haematological malignancies and HIV-infection or were transplant recipients and/or treated in intensive care. Patients treated prophylactically with micafungin were those undergoing haematopoietic stem cell transplantation (HSCT) who were at high risk for fungal infections.

Overall 32.2% of the patients experienced adverse drug reactions. The most frequently reported adverse reactions were nausea (2.8%), blood alkaline phosphatase increased (2.7%), phlebitis (2.5%, primarily in HIV infected patients with peripheral lines), vomiting (2.5%), and aspartate aminotransferase increased (2.3%). No clinically significant differences were seen when the safety data were analysed by gender or race.

Tabulated list of adverse reactions

In the following table adverse reactions are listed by system organ class and MedDRA preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Not known (frequency cannot be estimated from available data)
Blood and lymphatic system disorders	leukopenia, neutropenia, anaemia	pancytopenia, thrombocytopenia, eosinophilia, hypoalbuminaemia	haemolytic anaemia, haemolysis (see section 4.4)	disseminated intravascular coagulation
Immune system disorders		anaphylactic / anaphylactoid reaction (see section 4.4), hypersensitivity		
Endocrine disorders		hyperhidrosis		
Metabolism and nutritional disorders	hypokalaemia, hypomagnesaemia, hypocalcaemia	hyponatraemia, hyperkalaemia, hypophosphataemia, anorexia		
Psychiatric disorders		insomnia, anxiety, confusion		
Nervous system disorders	headache	somnolence, tremor, dizziness, dysgeusia		

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Not known (frequency cannot be estimated from available data)
Cardiac disorders		tachycardia, palpitations, bradycardia		
Vascular disorders	phlebitis	hypotension, hypertension, flushing		shock
Respiratory, thoracic and mediastinal disorders		dyspnoea		
Gastrointestinal disorders	nausea, vomiting, diarrhoea, abdominal pain	dyspepsia, constipation		
Hepatobiliary disorders	blood alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased (including hyperbilirubinaemia), liver function test abnormal	hepatic failure (see section 4.4), gamma-glutamyltransferase increased, jaundice, cholestasis, hepatomegaly, hepatitis		hepatocellular damage including fatal cases (see section 4.4)
Skin and subcutaneous tissue disorders	rash	urticaria, pruritus, erythema		toxic skin eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see section 4.4)
Renal and urinary disorders		blood creatinine increased, blood urea increased, renal failure aggravated		renal impairment (see section 4.4), acute renal failure
General disorders and administration site conditions	pyrexia, rigors	injection site thrombosis, infusion site inflammation, injection site pain, peripheral oedema		
Investigations		blood lactate dehydrogenase increased		

Description of selected adverse reactions

Possible allergic-like symptoms

Symptoms such as rash and rigors have been reported in clinical studies. The majority were of mild to moderate intensity and not treatment limiting. Serious reactions (e.g. anaphylactoid reaction 0.2%, 6/3028) were uncommonly reported during therapy with micafungin and only in patients with serious underlying conditions (e.g. advanced AIDS, malignancies) requiring multiple co-medications.

Hepatic adverse reactions

The overall incidence of hepatic adverse reactions in the patients treated with micafungin in clinical studies was 8.6% (260/3028). The majority of hepatic adverse reactions were mild and moderate. Most frequent reactions were increase in AP (2.7%), AST (2.3%), ALT (2.0%), blood bilirubin (1.6%) and liver function test abnormal (1.5%). Few patients (1.1%; 0.4% serious) discontinued treatment due to a hepatic event. Cases of serious hepatic dysfunction occurred uncommonly (see section 4.4).

Injection-site reactions

None of the injection-site adverse reactions were treatment limiting.

Paediatric population

The incidence of some adverse reactions (listed in the table below) was higher in paediatric patients than in adult patients. Additionally, paediatric patients < 1 year of age experienced about two times more often an increase in ALT, AST and AP than older paediatric patients (see section 4.4). The most likely reason for these differences were different underlying conditions compared with adults or older paediatric patients observed in clinical studies. At the time of entering the study, the proportion of paediatric patients with neutropenia was several-fold higher than in adult patients (40.2% and 7.3% of children and adults, respectively), as well as allogeneic HSCT (29.4% and 13.4%, respectively) and haematological malignancy (29.1% and 8.7%, respectively).

Blood and lymphatic system disorders

Cardiac disorders

common tachycardia

Vascular disorders

common hypertension, hypotension

Hepatobiliary disorders

common hyperbilirubinaemia, hepatomegaly

Renal and urinary disorders

common acute renal failure, blood urea increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Repeated daily doses up to 8 mg/kg (maximum total dose 896 mg) in adult patients have been administered in clinical trials with no reported dose-limiting toxicity. In one spontaneous case, it was reported a dosage of 16 mg/kg/day was administered in a newborn patient. No adverse reactions associated with this high dose were noted.

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 not dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, other antimycotics for systemic use, ATC code: J02AX05

Mode of action

Micafungin non-competitively inhibits the synthesis of 1,3- β -D-glucan, an essential component of the fungal cell wall. 1,3- β -D-glucan is not present in mammalian cells.

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

PK/PD relationship

In animals models of candidiasis, a correlation was observed between exposure of micafungin divided by MIC (AUC/MIC) and efficacy defined as the ratio required to prevent progressive fungal growth. A ratio of ~2400 and ~1300 was required for *C. albicans* and *C. glabrata*, respectively, in these models. At the recommended therapeutic dosage of Mycamine, these ratios are achievable for the wild-type distribution of *Candida spp.*.

Mechanism(s) of resistance

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.

Breakpoints

EUCAST breakpoints

<i>Candida species</i>	MIC breakpoint (mg/L)	
	$\leq S$ (Susceptible)	$> R$ (Resistant)
<i>Candida albicans</i>	0.016	0.016
<i>Candida glabrata</i>	0.03	0.03
<i>Candida parapsilosis</i>	0.002	2
<i>Candida tropicalis</i> ¹	Insufficient evidence	
<i>Candida krusei</i> ¹	Insufficient evidence	
<i>Candida guilliermondii</i> ¹	Insufficient evidence	
Other <i>Candida spp.</i>	Insufficient evidence	

¹ 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 3 two-fold dilution steps higher than those for *C. albicans* and, similarly, those for *C. guilliermondii* are approximately 8 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.

Information from clinical studies

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; 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). 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.

Overall Treatment Success in the 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 <i>Candida</i> Species					
<i>Candida albicans</i>	102	91 (89.2)	98	89 (90.8)	
Non- <i>albicans</i> species ¶: all	151	133 (88.1)	140	123 (87.9)	
<i>C. tropicalis</i>	59	54 (91.5)	51	49 (96.1)	
<i>C. parapsilosis</i>	48	41 (85.4)	44	35 (79.5)	
<i>C. glabrata</i>	23	19 (82.6)	17	14 (82.4)	
<i>C. krusei</i>	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. The nature and incidence of adverse events were similar between treatment groups.

Prophylaxis: 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/ μ L). 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).

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.

5.2 Pharmacokinetic properties

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 (V_{ss}) 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 ¹⁴C-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.

Special populations

Paediatric patients: In paediatric patients AUC values were dose proportional over the dose range of 0.5-4 mg/kg. Clearance was influenced by weight, with mean values of weight-adjusted clearance 1.35 times higher in the younger children (4 months to 5 years) and 1.14 times higher in paediatric patients aged 6 to 11 years. Older children (12-16 years) had mean clearance values similar to those determined in adult patients. Mean weight-adjusted clearance in children less than 4 months of age is approximately 2.6-fold greater than older children (12-16 years) and 2.3-fold greater than in adults.

PK/PD bridging study demonstrated dose-dependent penetration of micafungin into CNS with the minimum AUC of 170 µg*hr/L required to achieve maximum eradication of fungal burden in the CNS tissues. Population PK modeling demonstrated that a dose of 10 mg/kg in children less than 4 month of age would be sufficient to achieve the target exposure for the treatment of CNS *Candida* infections.

Elderly: When administered as a single 1-hour infusion of 50 mg the pharmacokinetics of micafungin in the elderly (aged 66-78 years) were similar to those in young (20-24 years) subjects. No dose adjustment is necessary for the elderly.

Patients with hepatic impairment: In a study performed in patients with moderate hepatic impairment (Child-Pugh score 7-9), (n=8), the pharmacokinetics of micafungin did not significantly differ from those in healthy subjects (n=8). Therefore, no dose adjustment is necessary for patients with mild to moderate hepatic impairment. In a study performed in patients with severe hepatic impairment (Child-Pugh score 10-12) (n=8), lower plasma concentrations of micafungin and higher plasma concentrations of the hydroxide metabolite (M-5) were seen compared to healthy subjects (n=8). These data are insufficient to support a dosing recommendation in patients with severe hepatic impairment..

Patients with renal impairment: Severe renal impairment (Glomerular Filtration Rate [GFR] < 30 ml/min) did not significantly affect the pharmacokinetics of micafungin. No dose adjustment is necessary for patients with renal impairment.

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

5.3 Preclinical safety data

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 plasma exposure at the assumed threshold for tumour development in rats (i.e. the dose where no FAH and liver tumours were detected) was in the same range as the clinical exposure. The relevance of the hepatocarcinogenic potential of micafungin for the human therapeutic use is not known.

The toxicology of micafungin following repeated intravenous dosing in rats and/or dogs showed adverse responses in liver, urinary tract, red blood cells, and male reproductive organs. The exposure levels at which these effects did not occur (NOAEL) were in the same range as the clinical exposure or lower. Consequently, the occurrence of these adverse responses may be expected in human clinical use of micafungin.

In standard safety pharmacology tests, cardiovascular and histamine releasing effects of micafungin were evident and appeared to be time above threshold dependent. Prolongation of infusion time reducing the plasma concentration peak appeared to reduce these effects.

In repeated dose toxicity studies in rat signs of hepatotoxicity consisted of increased liver enzymes and degenerative changes of hepatocytes which were accompanied by signs of compensatory regeneration. In dog, liver effects consisted of increased weight and centrilobular hypertrophy, no degenerative changes of hepatocytes were observed.

In rats, vacuolation of the renal pelvic epithelium as well as vacuolation and thickening (hyperplasia) of the bladder epithelium were observed in 26-week repeat dose studies. In a second 26-week study hyperplasia of transitional cells in the urinary bladder occurred with a much lower incidence. These findings showed reversibility over a follow-up period of 18 months. The duration of micafungin dosing in these rat studies (6 months) exceeds the usual duration of micafungin dosing in patients (see section 5.1).

Micafungin haemolysed rabbit blood *in vitro*. In rats, signs of haemolytic anaemia were observed after repeated bolus injection of micafungin. In repeat dose studies in dogs, haemolytic anaemia was not observed.

In reproductive and developmental toxicity studies, reduced birth weight of the pups was noted. One abortion occurred in rabbits at 32 mg/kg/day. Male rats treated intravenously for 9 weeks showed vacuolation of the epididymal ductal epithelial cells, increased epididymis weights and reduced number of sperm cells (by 15%), however, in studies of 13 and 26 weeks duration these changes did not occur. In adult dogs, atrophy of seminiferous tubules with vacuolation of the seminiferous epithelium and decreased sperm in the epididymides were noted after prolonged treatment (39 weeks) but not after 13 weeks of treatment. In juvenile dogs, 39 weeks treatment did not induce lesions in the testis and epididymides in a dose dependent manner at the end of treatment but after a treatment free period of 13 weeks a dose dependent increase in these lesions were noted in the treated recovery groups. No impairment of male or female fertility was observed in the fertility and early embryonic development study in rats.

Micafungin was not mutagenic or clastogenic when evaluated in a standard battery of *in vitro* and *in vivo* tests, including an *in vitro* study on unscheduled DNA synthesis using rat hepatocytes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Citric acid anhydrous (to adjust the pH)

Sodium hydroxide (to adjust the pH)

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 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion.

Diluted infusion solution:

Chemical and physical in-use stability has been demonstrated for 96 hours at 25°C when protected from light when diluted with sodium chloride 9 mg/ml (0.9%) solution for infusion or glucose 50 mg/ml (5%) solution for infusion.

Mycamine contains no preservatives. From a microbiological point of view, the reconstituted and diluted solutions 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, unless the reconstitution and dilution have taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened vials: 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

10 ml Type I glass vial with an isobutylene-isoprene (PTFE-laminated) rubber stopper and a flip-off cap. The vial is wrapped with an UV-protective film.

Supplied in packs of 1 vial.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Mycamine must not be mixed or co-infused with other medicinal products except those mentioned below. Using aseptic techniques at room temperature, Mycamine is reconstituted and diluted as follows:

1. The plastic cap must be removed from the vial and the stopper disinfected 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 bottle/bag) 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 must be reconstituted to obtain the required dose in mg (see table below).
3. The vial should be rotated gently. DO NOT SHAKE. The powder will dissolve completely. The concentrate should be used immediately. The vial is for single use only. Therefore, please discard unused reconstituted concentrate immediately.
4. All of the reconstituted concentrate should be withdrawn from each vial and returned into the infusion bottle/bag from which it was originally taken. The diluted infusion solution should be used immediately. Chemical and physical in-use stability has been demonstrated for 96 hours at 25°C when protected from light and diluted as described above.
5. The infusion bottle/bag 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 bottle/bag containing the diluted infusion solution should be inserted into a closable opaque bag for protection from light.

Preparation of the solution for infusion

Dose (mg)	Mycamine vial to be used (mg/vial)	Volume of sodium chloride (0.9%) or glucose (5%) to be added per vial	Volume (concentration) of reconstituted powder	Standard infusion (added up to 100 ml) Final concentration
50	1 x 50	5 ml	approx. 5 ml (10 mg/ml)	0.5 mg/ml
100	1 x 100	5 ml	approx. 5 ml (20 mg/ml)	1.0 mg/ml
150	1 x 100 + 1 x 50	5 ml	approx. 10 ml	1.5 mg/ml
200	2 x 100	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. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden

Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/448/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 April 2008

Date of latest renewal: 20 December 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Astellas Ireland Co. Ltd
Killorglin
Co. Kerry
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- Additional risk minimisation measures**

The MAH shall ensure that prior to prescribing of the product prescribers will receive the prescriber checklist and the Administration and monitoring guide.

The MAH shall ensure that all healthcare professionals involved in treatment and monitoring of patients will receive the Administration and monitoring guide.

The MAH should agree the final content, format and distribution modalities of the Prescriber checklist and the Administration and monitoring guide with the National Competent Authority in each Member State and ensure that the materials contain the key elements as described below.

Prescriber checklist

- 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

- Mycamine is contra-indicated if the patient has a history of hypersensitivity to micafungin, other echinocandins or excipients.
- Mycamine should not be used during pregnancy unless clearly necessary.
- Caution must be demonstrated if the patient:
 - has severe liver function impairment
 - has chronic liver diseases known to represent preneoplastic conditions (e.g. advanced liver fibrosis, cirrhosis, viral hepatitis, neonatal liver disease or congenital enzyme defects)
 - is receiving a concomitant therapy including hepatotoxic and/or genotoxic properties
 - is receiving concomitant therapy with amphotericin B desoxycholate
 - has history of haemolysis, haemolytic anaemia or renal impairment.
- Patients receiving sirolimus, nifedipine or itraconazole in combination with Mycamine should be monitored for sirolimus, nifedipine or itraconazole toxicity and the sirolimus, nifedipine or itraconazole dosage should be reduced if necessary.
- Patients should be carefully monitored for liver damage and for worsening of renal function.
- 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.

Administration and monitoring guide

- Provide details of how Mycamine is reconstituted, diluted and administered in accordance with the Summary of Product Characteristics, section 6.6.
- Patients should be monitored during micafungin treatment for anaphylactic/anaphylactoid reactions, worsening of liver function, worsening of renal function, haemolysis, exfoliative cutaneous reactions, and concomitant drug therapy toxicity and adequate measures (discontinuation or evaluation for the risk/benefit of continuing micafungin therapy and treatment of adverse reactions) should be undertaken when such conditions occur.
- 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.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Mycamine 50 mg powder for solution for infusion
Micafungin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains: 50 mg micafungin (as sodium).
After reconstitution each ml contains 10 mg of micafungin (as sodium).

3. LIST OF EXCIPIENTS

Lactose monohydrate, citric acid anhydrous and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/448/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**VIAL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Mycamine 50 mg powder for solution for infusion

Micafungin

Intravenous use.

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

Mycamine 100 mg powder for solution for infusion
Micafungin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains: 100 mg micafungin (as sodium).
After reconstitution each ml contains 20 mg of micafungin (as sodium).

3. LIST OF EXCIPIENTS

Lactose monohydrate, citric acid anhydrous and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/448/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**VIAL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Mycamine 100 mg powder for solution for infusion
Micafungin
Intravenous use.

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Mycamine 50 mg powder for solution for infusion Mycamine 100 mg powder for solution for infusion Micafungin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mycamine is and what it is used for
2. What you need to know before you use Mycamine
3. How to use Mycamine
4. Possible side effects
5. How to store Mycamine
6. Contents of the pack and other information

1. What Mycamine is and what it is used for

Mycamine contains the active substance micafungin. Mycamine is called an antifungal medicine because it is used to treat infections caused by fungal cells.

Mycamine is used to treat fungal infections caused by fungal or yeast cells called Candida. Mycamine is effective in treating systemic infections (those that have penetrated within the body). It interferes with the production of a part of the fungal cell wall. An intact cell wall is necessary for the fungus to continue living and growing. Mycamine causes defects in the fungal cell wall, making the fungus unable to live and grow.

Your doctor has prescribed Mycamine for you in the following circumstances when there are no other suitable antifungal treatments available (see section 2):

- To treat adults, adolescents and children who have a serious fungal infection called invasive candidiasis (infection that has penetrated the body).
- To treat adults and adolescents ≥ 16 years of age who have a fungal infection in the gullet (oesophagus) where treatment into a vein (intravenous) is appropriate.
- To treat adults, adolescents and children who are at risk of developing a Candida fungal infection that may penetrate the body.

2. What you need to know before you use Mycamine

Do not use Mycamine

- if you are allergic to micafungin, other echinocandins (Ecalta or Cancidas) or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

In rats, long-term treatment with micafungin led to liver damage and subsequent liver tumours. The potential risk of developing liver tumours in humans is not known, and your doctor will assess the benefits and risks of Mycamine treatment before starting your medicine. Please tell your doctor if you have severe liver problems (e.g. liver failure or hepatitis) or have had abnormal liver function tests. During treatment your liver functions will be monitored more closely.

Talk to your doctor or pharmacist before using Mycamine

- if you have haemolytic anaemia (anaemia due to breakdown of red blood cells) or haemolysis (breakdown of red blood cells).
- if you have kidney problems (e.g. kidney failure and abnormal kidney function test). If this happens, your doctor may decide to monitor your kidney function more closely.

Other medicines and Mycamine

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is especially important to inform your doctor if you are using amphotericin B desoxycholate or itraconazole (antifungal antibiotics), sirolimus (an immunosuppressant) or nifedipine (a calcium antagonist). Your doctor may decide to adjust the dose of these medicines.

Mycamine with food and drink

As Mycamine is given intravenously (into a vein), no restrictions on food or drink are required.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Mycamine should not be used during pregnancy unless clearly necessary. If you use Mycamine you should not breast-feed.

Driving and using machines

There is no information on the effect of Mycamine on the ability to drive or use machines. Please inform your doctor if you experience any effects that may cause you to have problems with driving or using other machinery.

3. How to use Mycamine

Mycamine must be prepared and given to you by a doctor or another healthcare professional.

Mycamine should be administered once daily by slow intravenous (into a vein) infusion. Your doctor will determine how much Mycamine you will receive each day.

Use in adults, adolescents ≥ 16 years of age and elderly

- The usual dose to treat an invasive Candida infection is 100 mg per day for patients weighing 40 kg or more and 2 mg/kg per day for patients weighing 40 kg or less.
- The dose to treat a Candida infection of the oesophagus is 150 mg for patients weighing more than 40 kg and 3 mg/kg per day for patients weighing 40 kg or less.
- The usual dose to prevent invasive Candida infections is 50 mg per day for patients weighing more than 40 kg and 1 mg/kg per day for patients weighing 40 kg or less.

Use in children > 4 months of age and adolescents < 16 years of age

- The usual dose to treat an invasive Candida infection is 100 mg per day for patients weighing 40 kg or more and 2 mg/kg per day for patients weighing 40 kg or less.
- The usual dose to prevent invasive Candida infections is 50 mg per day for patients weighing more than 40 kg and 1 mg/kg per day for patients weighing 40 kg or less.

Use in children and newborns < 4 months of age

- The usual dose to treat an invasive Candida infection is 4-10 mg/kg per day.
- The usual dose to prevent invasive Candida infections is 2 mg/kg per day.

If you receive more Mycamine than you should

Your doctor monitors your response and condition to determine what dose of Mycamine is needed. However, if you are concerned that you may have been given too much Mycamine, speak to your doctor or another healthcare professional immediately.

If you miss a dose of Mycamine

Your doctor monitors your response and condition to determine what Mycamine treatment is needed. However, if you are concerned that you may have missed a dose, speak to your doctor or another healthcare professional immediately.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience an allergic attack, or a severe skin reaction (e.g. blistering and peeling of the skin), you must inform your doctor or nurse immediately

Mycamine may cause the following other side effects:

Common (may affect up to 1 in 10 people)

- abnormal blood tests (decreased white blood cells [leucopenia; neutropenia]); decreased red blood cells (anaemia)
- decreased potassium in the blood (hypokalaemia); decreased magnesium in the blood (hypomagnesaemia); decreased calcium in the blood (hypocalcaemia)
- headache
- inflammation of the vein wall (at injection-site)
- nausea (feeling sick); vomiting (being sick); diarrhoea; abdominal pain
- abnormal liver function tests (increased alkaline phosphatase; increased aspartate aminotransferase, increased alanine aminotransferase)
- increased bile pigment in the blood (hyperbilirubinaemia)
- rash
- fever
- rigors (shivering)

Uncommon (may affect up to 1 in 100 people)

- abnormal blood tests (decreased blood cells [pancytopenia]); decreased blood platelets (thrombocytopenia); increases in a certain type of white blood cells called eosinophils; decreased albumin in the blood (hypoalbuminaemia)
- hypersensitivity
- increased sweating
- decreased sodium in the blood (hyponatraemia); increased potassium in the blood (hyperkalaemia); decreased phosphates in the blood (hypophosphataemia); anorexia (eating disorder)
- insomnia (difficulty in sleeping); anxiety; confusion
- feeling lethargic (somnolence); trembling; dizziness; disturbed taste
- increased heart rate; stronger heartbeat; irregular heartbeat
- high or low blood pressure; skin flushing
- shortness of breath
- indigestion; constipation
- liver failure; increased liver enzymes (gamma-glutamyltransferase); jaundice (yellowing of the skin or whites of the eyes caused by liver or blood problems); reduced bile reaching the intestine (cholestasis); enlarged liver; liver inflammation
- itchy rash (urticaria); itching; skin flushing (erythema)
- abnormal kidney function tests (increased blood creatinine; increased urea in the blood); aggravated kidney failure
- increase in an enzyme called lactate dehydrogenase
- clotting in vein at injection-site; inflammation at injection-site; pain at injection-site; collection of fluid in your body

Rare (may affect up to 1 in 1,000 people)

- anaemia due to breakdown of red blood cells (haemolytic anaemia), breakdown of red blood cells (haemolysis)

Not known (frequency cannot be estimated from the available data)

- disorder of blood clotting system
- shock
- damage to liver cells including death
- kidney problems; acute kidney failure

Additional side effects in children and adolescents

The following reactions have been reported more often in paediatric patients than in adult patients:

Common (may affect up to 1 in 10 people)

- decreased blood platelets (thrombocytopenia)
- increased heart rate (tachycardia)
- high or low blood pressure
- increased bile pigment in the blood (hyperbilirubinaemia); enlarged liver
- acute kidney failure; increased urea in the blood

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Mycamine

Keep this medicine out of the sight and reach of children.

Do not use Mycamine after the expiry date which is stated on the vial and on the carton. The expiry date refers to the last day of that month.

The unopened vial does not require any special storage conditions.

The reconstituted concentrate and the diluted infusion solution should be used immediately, because it does not contain any preservatives to prevent bacterial contamination. Only a trained healthcare professional who has read the complete directions properly can prepare this medicine for use.

Do not use the diluted infusion solution if it is cloudy or precipitated.

In order to protect the infusion bottle / bag containing the diluted infusion solution from light it should be inserted into a closable opaque bag.

The vial is for single use only. Therefore, please discard unused reconstituted concentrate immediately.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Mycamine contains

- The active substance is micafungin (as sodium).
1 vial contains 50 mg or 100 mg micafungin (as sodium).
- The other ingredients are lactose monohydrate, citric acid anhydrous and sodium hydroxide.

What Mycamine looks like and contents of the pack

Mycamine 50 mg or 100 mg powder for solution for infusion is a white compact freeze-dried powder.
Mycamine is supplied in a box containing 1 vial.

Marketing Authorisation Holder

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
Netherlands

Manufacturer

Astellas Ireland Co., Ltd.
Killorglin, County Kerry
Ireland

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu/>.

The following information is intended for medical or healthcare professionals only:

Mycamine must not be mixed or co-infused with other medicinal products except those mentioned below. Using aseptic techniques at room temperature, Mycamine is reconstituted and diluted as follows:

1. The plastic cap must be removed from the vial and the stopper disinfected 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 bottle/bag) 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 must be reconstituted to obtain the required dose in mg (see table below).
3. The vial should be rotated gently. DO NOT SHAKE. The powder will dissolve completely. The concentrate should be used immediately. The vial is for single use only. Therefore, please discard unused reconstituted concentrate immediately.
4. All of the reconstituted concentrate should be withdrawn from each vial and returned into the infusion bottle/bag from which it was originally taken. The diluted infusion solution should be used immediately. Chemical and physical in-use stability have been demonstrated for 96 hours at 25°C when protected from light and diluted as described above.
5. The infusion bottle/bag 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 bottle/bag containing the diluted infusion solution should be inserted into a closable opaque bag for protection from light.

Preparation of the solution for infusion

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