SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Micafungin 100 mg powder for concentrate 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 concentrate for solution for infusion.
White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Consideration should be given to official/national guidance on the appropriate use of antifungal agents.

4.2 Posology and method of administration

Treatment with Micafungin should be initiated by a physician experienced in the management of fungal infections.

Posology

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.

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

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

Indication

	Body weight	Body weight ≤
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Treatment of oesophageal candidiasis	150 mg/day	3 mg/kg/day
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

* If the patient's response is inadequate, e.g. persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients ≤ 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: Micafungin should be administered for at least one week after resolution of clinical signs and symptoms.

Prophylaxis of *Candida* infections: Micafungin 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

Indication		
	Body weight > 40 kg	Body weight ≤ 40
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Prophylaxis of *Candida* infection	50 mg/day	1 mg/kg/day

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

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

Indication	
Treatment of invasive candidiasis	4 -10 mg/kg/day*
Prophylaxis of Candida 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).

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: Micafungin should be administered for at least one week after neutrophil recovery. Experience with Micafungin in patients less than 2 years of age is limited.

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 micafungin in patients with severe hepatic impairment and its use is not recommended in these patients (see sections 4.4 and 5.2).

Renal impairment

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

Paediatric population

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. Currently available data are described in section 4.8, 5.1, 5.2.

Method of administration

For intravenous use.

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 clinical relevance of this finding is not known. 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 population < 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 micafungin 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).

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially “sodium-free”.

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 micafungin 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 Fertility, 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.

Micafungin should not be used during pregnancy unless clearly necessary.

Breastfeeding

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 Micafungin should be made taking into account the benefit of breast-feeding to the child and the benefit of Micafungin 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

Micafungin has no or negligible influence on the ability to drive or use machines. However, patients should be informed that dizziness has been reported during treatment with micafungin (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Based on clinical trial experience, 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%).

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

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)
Immune system disorders		anaphylactic / anaphylactoid reaction (see section 4.4), hypersensitivity		anaphylactic and anaphylactoid shock (see section 4.4)
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		
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)

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)
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	
common	thrombocytopenia
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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Mechanism 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 Micafungin, 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

Candida species	MIC breakpoint (mg/L)	
	≤S (Susceptible)	>R (Resistant)
Candida albicans	0.016	0.016
Candida glabrata	0.03	0.03
Candida parapsilosis	0.002	2
Candida tropicalis [1]	Insufficient evidence	
Candida krusei [1]	Insufficient evidence	
Candida guilliermondii [1]	Insufficient evidence	
Other *Candida 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	190	170	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	175	158	
Paediatric Patients					

	Micafungin		Liposomal Amphotericin B		% Difference [95% CI]
	N	**n (%)**	**N**	**n (%)**	
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 [illegible])	7	7 (100)	5	4 (80)	
2 to 15 years old	22	14 (63.6)	19	14 (73.7)	
Adults and Children Combined, Overall Treatment Success by *Candida* Species					
Candida albicans	102	91 (89.2)	98	89 (90.8)	
Non-*albicans* species ¶: all	151	133	140	123	
C. tropicalis	59	54 (91.5)	51	49 (96.1)	
C. parapsilosis	48	41 (85.4)	44	35 (79.5)	
C. glabrata	23	19 (82.6)	17	14 (82.4)	
C. krusei	9	8 (88.9)	7	6 (85.7)	

† Micafungin rate minus the liposomal amphotericin B rate, and 2-sided 95% confidence interval for the difference in overall success rate based on large sample normal approximation.

‡ Adjusted for neutropenic status; primary endpoint.

§ The paediatric population was not sized to test for non-inferiority.

¶ Clinical efficacy was also observed (< 5 patients) in the following *Candida* species: *C. guilliermondii*, *C. famata*, *C. lusitaniae*, *C. utilis*, *C. inconspicua* and *C. dubliniensis*.

Oesophageal Candidiasis: In a randomised, double-blind study of micafungin versus fluconazole in the first-line treatment of oesophageal candidiasis, 518 patients received at least a single dose of study drug. The median treatment duration was 14 days and the median average daily dose was 150 mg for micafungin (N=260) and 200 mg for fluconazole (N=258). An endoscopic grade of 0 (endoscopic cure) at the end of treatment was observed for 87.7% (228/260) and 88.0% (227/258) of patients in the micafungin and fluconazole groups, respectively (95% CI for difference: [-5.9%, 5.3%]). The lower limit of the 95% CI was above the predefined non-inferiority margin of -10%, proving non-inferiority. 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/µL). 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

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

Distribution

Following intravenous administration concentrations of micafungin show a biexponential decline. The drug is rapidly distributed into tissues.

In systemic circulation, micafungin is highly bound to plasma protein (> 99%), primarily to albumin. Binding to albumin is independent of micafungin concentration (10-100 µg/ml).

The volume of distribution at steady state (Vss) was approximately 18-19 litres.

Biotransformation

Unchanged micafungin is the principal circulating compound in systemic circulation. Micafungin has been shown to be metabolised to several compounds; of these M-1 (catechol form), M-2 (methoxy form of M-1) and M-5 (hydroxylation at the side chain) of micafungin have been detected in systemic circulation. Exposure to these metabolites is low and metabolites do not contribute to the overall efficacy of micafungin.

Even though micafungin is a substrate for CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for micafungin metabolism *in vivo*.

Elimination

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

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.

Micafungin 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 clear glass vial with a chlorobutyl rubber stopper and an aluminium cap seal/polypropylene cap. The vial is wrapped with an UV-protective film.

Pack size: packs of 1 vial and 5 vials.

6.6 Special precautions for disposal

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

Micafungin must not be mixed or co-infused with other medicinal products except those mentioned below. Using aseptic techniques at room temperature, Micafungin 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 Micafungin 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, unused reconstituted concentrate must be discarded 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. The solution must not be used if it 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)	**Micafungin 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

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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