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ADIS DRUG EVALUATION

Micafungin: A Review in the Prophylaxis and Treatment of Invasive *Candida* Infections in Paediatric Patients

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Abstract Intravenous micafungin (Mycamine®; Funguard®), an echinocandin, is approved in the EU for the treatment of invasive candidiasis in children (including neonates) and adolescents (<16 years of age) and as prophylaxis against *Candida* infections in patients undergoing haematopoietic stem cell transplantation (HSCT) or who are expected to have neutropenia for ≥10 days. This narrative review focuses on the use of micafungin in paediatric indications approved in the EU, which may vary from those approved elsewhere in the world. Micafungin has a broad spectrum of in vitro activity against clinically relevant isolates of *Candida* spp. (including fluconazole-resistant *Candida glabrata* isolates), a low propensity for emergence of resistant isolates and a convenient once-daily regimen. In paediatric substudies and a small multinational, phase 3 trial in neonates with proven invasive candidiasis, intravenous micafungin was effective and generally well tolerated in the treatment of candidaemia and other types of invasive candidiasis and as prophylaxis against fungal infections in patients undergoing HSCT. Hence, micafungin remains an important option for the prophylaxis and treatment of invasive *Candida* infections in paediatric and adult patients.

Micafungin: clinical considerations in prophylaxis and treatment of invasive *Candida* infections

Micafungin, a 1,3-β-D-glucan synthase inhibitor, exhibits a broad spectrum of activity against clinically relevant *Candida* spp. and other fungal pathogens

High clinical cure rates in the treatment of candidaemia and other types of invasive candidiasis in paediatric patients (aged <16 years), including neonates (aged 2 days to <4 months)

Provides effective prophylaxis against invasive fungal infections in paediatric patients, including in neonates

Generally well tolerated; paediatric patients (especially those aged <1 year) appear to be more likely to develop drug-related liver function test abnormalities than adult patients

1 Introduction

Globally, *Candida* infections remain a major cause of morbidity and mortality in immunocompromised and critically ill patients, especially in patients with significant comorbidities who are hospitalized for prolonged periods,

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very young (aged <1 year) and elderly (aged >70 years) patients, and those with haematological malignancies and/or neutropenia [1, 2]. However, despite the addition of several broad-spectrum antifungal agents over the last couple of decades [such as azoles (e.g. fluconazole, voriconazole, itraconazole) and echinocandins (anidulafungin, caspofungin, micafungin)], the frequency of invasive candidiasis and associated mortality have not been significantly altered [1, 2]. Moreover, the increasing use of fluconazole has played a key role in the shift in the primary causative pathogen of invasive candidiasis from *Candida albicans* to non-*C. albicans* isolates, with *Candida glabrata* and *Candida parapsilosis* becoming the key pathogens in northern and southern Europe, respectively [1]. Given the shift in causative pathogens and the increase in drug-resistant pathogens (especially fluconazole-resistant *C. glabrata* isolates), judicious antifungal stewardship is imperative in the management of these serious, potentially life-threatening infections [1, 2].

Intravenous micafungin (Mycamine®; Funguard®) is approved in many countries worldwide, including in the EU, USA and Japan, for the prophylaxis and treatment of invasive *Candida* infections. Its use in paediatric and/or adult patients has been reviewed previously in *Pediatric Drugs* [3] and *Drugs* [4, 5]. This narrative review, written from an EU perspective, summarizes the pharmacological properties of micafungin and discusses its clinical use in children (including neonates) and adolescents (aged <16 years) for the prophylaxis and treatment of invasive *Candida* infections.

2 Pharmacodynamic Properties of Micafungin

Micafungin is a noncompetitive, concentration-dependent inhibitor of the enzyme 1,3-β-D-glucan synthase and, consequently, inhibits the synthesis of 1,3-β-D-glucan (an integral component of the fungal cell wall, but not present in mammalian cells) [3–5]. Inhibition of 1,3-β-D-glucan synthesis, leads to increased susceptibility of fungal cells to osmotic pressures and ultimately results in cell lysis [3–5].

Given micafungin is approved for the prophylaxis and treatment of invasive *Candida* infections, this section focuses on its in vitro activity against *Candida* spp. European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptibility breakpoints against *C. albicans*, *C. glabrata* and *C. parapsilosis* are ≤0.016, ≤0.03 and ≤0.002 μg/mL, respectively [6]. Minimum inhibitory concentrations (MICs) for *Candida tropicalis* are 1–2 twofold dilution steps higher than for *C. albicans* and *C. glabrata*, and those for *Candida krusei* and *Candida guilliermondii* are ≈3 and ≈8 twofold dilution steps higher than those for *C. glabrata*. This means that there is insufficient evidence to indicate whether the wild-type isolates of *C. tropicalis*, *C. krusei*, *C. guilliermondii* and other *Candida* spp. can be considered susceptible to micafungin [6]. The epidemiological cutoff value (ECV) is being increasingly used to harmonize national differences in clinical breakpoints, with ECV values considered the most sensitive measure for assessing the emergence of strains with reduced susceptibility versus the wild-type strain [7, 8].

Micafungin exhibited very good in vitro activity against a broad spectrum of clinical isolates of *Candida* spp. causing invasive candidiasis, based on worldwide surveillance studies of isolates collected from 2001–2006 [9] and in 2013 [10] (Table 1). MIC values at which 90% of isolates were inhibited (MIC_{90}) showed minimal or no change for *Candida* spp. isolates collected between 2001–2006 and those collected more recently in 2013 (Table 1). For *Candida* spp. isolates collected in 2013, 97–100% had an MIC that did not exceed the ECV for micafungin, with similar rates observed with anidulafungin and caspofungin (Table 1) [10]. For 2001–2006 isolates, 100, 92.5–100 and 90.2–100% of individual *Candida* spp. isolates were susceptible to micafungin, caspofungin and anidulafungin, respectively, at an MIC of ≤2 μg/mL [9]. Like all echinocandins, micafungin exhibits less in vitro activity against *C. parapsilosis* and *C. guilliermondii* isolates, than against other *Candida* spp. (Table 1).

Candida biofilm-related vascular catheter infections, a typical characteristic of which is antifungal resistance, significantly impact on patient management and care, increasing the length of hospital stay and costs of treatment (reviewed by Ghannoum et al. [11]). Like liposomal amphotericin B formulations and other echinocandins, micafungin exhibits very good in vitro and in vivo activity against *Candida* biofilms, including those resistant to other antifungal drugs [12–15]. Conversely, conventional amphotericin B deoxycholate (CAB) and triazoles (e.g. voriconazole and fluconazole) showed no activity against *Candida* biofilm infections [12, 14].

In in vitro studies, micafungin exhibited time-dependent, concentration-independent, fungicidal activity and produced a post-antifungal effect against several clinical and laboratory strains of *Candida* spp. (as reviewed previously [3–5]).

There appeared to be a low potential for the emergence of resistance to echinocandins, including micafungin, amongst clinical *Candida* spp. isolates collected since 2001 in large global surveillance studies (including the two studies [9, 10] summarized in Table 1) [8–10, 16, 17]. Nonetheless, *Candida* spp. isolates with reduced susceptibility to echinocandins have emerged, with mutations conferring reduced susceptibility to echinocandins mapped to the *FSK1* and/or *FSK2* genes encoding 1,3-β-D-glucan synthase [8, 17–21]. In a recent single-centre, retrospective study of 293 episodes (313 isolates) of *C. glabrata*

Table 1 Comparative in vitro activity of echinocandins against clinical isolates of *Candida* spp. collected in two large, global surveillance studies

Candida spp.	Isolates collected 2001–2006 [9]				Isolates collected 2013 [10]						
	No. of isolates	MIC_{90} (μg/mL)[a]			No. of isolates	MIC_{90} (μg/mL)[a]			% of isolates susceptible[a] (CLSI/ECV)		
		MFG	CAS	ANI		MFG	CAS	ANI	MFG	CAS	ANI
C. albicans	2869	0.03	0.06	0.06	712	0.03	0.03	0.06	100/100	100/100	100/100
C. glabrata	747	0.015	0.06	0.12	251	0.03	0.06	0.12	98.8/97.6	98/98	96/96
C. guilliermondii	61	1	1	2	16	1	1	4	100/100	100/100	97.5/100
C. krusei	136	0.12	0.25	0.06	49	0.12	0.25	0.06	100/100	100/100	100/100
C. lusitaniae	58	0.25	0.5	0.5	24	0.25	0.5	0.5	100/100	100/100	87.5/100
C. parapsilosis	759	2	1	2	215	2	0.5	2	100/100	100/100	95.3/100
C. tropicalis	625	0.06	0.06	0.06	155	0.06	0.03	0.03	98.7/97.4	98.7/98.7	98.7/98.7

ANI anidulafungin, *CAS* caspofungin, *CLSI* Clinical and Laboratory Standards Institute, *ECV* epidemiological cutoff value, *MFG* micafungin, MIC_{90} minimum inhibitory concentration required to inhibit 90% of isolates

[a] As assessed by CLSI microbroth dilution assays; susceptibility based on CLSI breakpoints or the ECV

bloodstream infections, 14.1% of 78 fluconazole-resistant *C. glabrata* isolates were resistant to at least one echinocandin [21]. Prior echinocandin therapy was the sole predictor for the presence of an *FKS* mutation (odds ratio 19.647; 95% CI 7.19–58.1) in a stepwise multivariate analysis. Of ten patients infected with *C. glabrata FKS* mutant isolates, most (80%) failed to respond or had an inadequate response to echinocandin therapy [21].

The inter-relationships between pharmacodynamic and pharmacokinetic parameters are an important consideration in predicting antifungal activity. Based on a population pharmacokinetic model utilizing data from phase 3 trials in patients with invasive candidiasis, univariate analyses indicated that there was a significant ($p = 0.05$) relationship between the area under the plasma concentration-time curve (AUC)/MIC ratio and the mycological response to micafungin [22]. A lower target MIC/AUC ratio was identified for *C. parapsilosis* than for other *Candida* spp. based on univariate analyses, suggesting that species-specific clinical breakpoints should be considered. In multivariate analyses, predictors of a favourable response to micafungin therapy were the AUC/MIC ratio, Acute Physiology and Chronic Health Evaluation (APACHE) score and a history of corticosteroid use [22]. In animal models, an AUC/MIC ratio of ≈2400 was required for *C. albicans* and ≈1300 for *C. glabrata*, with these ratios achievable at the recommended therapeutic dosages of micafungin (Sect. 6) [6].

3 Pharmacokinetic Properties of Micafungin

The pharmacokinetics of intravenous micafungin in paediatric and adult patients has been extensively reviewed [3–5]; for the most part, discussion in this section focuses on data from paediatric patients.

Intravenous micafungin exhibits linear, dose-proportional pharmacokinetics with once daily doses of 12.5–200 mg and 3–8 mg/kg in adults and 0.5–4 mg/kg in paediatric patients [6]. With repeated administration, there is no evidence of systemic accumulation and steady state is generally attained in 4–5 days [6]. The pharmacokinetic parameters of recommended dosages of micafungin in paediatric patients with invasive candidiasis or deep mycosis are summarized in Table 2 [23–25]. In a single-dose study in premature infants weighing >1000 g (aged 3–8 weeks; mean gestational age 26.4 weeks), micafungin (0.75–3.0 mg/kg) exhibited linear pharmacokinetics, although the drug had a shorter average elimination half-life (8 h) and faster clearance (≈39 mL/h/kg) than that observed in studies in older children (Table 2) and adults [26]. With recommended dosages of micafungin, steady-state mean maximum plasma concentrations (Table 2) exceeded specified EUCAST breakpoints against *Candida* spp. (Sect. 2). Based on pharmacokinetic modelling data, respective dosage regimens of micafungin 1 and 2 mg/kg/day for the prophylaxis and treatment of invasive candidiasis in children aged 4 months to <17 years appeared appropriate, with cutoffs of 40 and 50 kg for bodyweight-based dosing [27]. These dosage regimens differ from those outlined in the European Medicines Agency summary of product characteristics (SPC; Sect. 6) [6].

Micafungin is extensively (>99%) bound to plasma protein (primarily to albumin), with binding independent of drug plasma concentrations across a range of 10–100 μg/mL [6]. Micafungin is rapidly and extensively distributed into tissues [6], with a volume of distribution at steady state of ≈18 to 19 L [6]. In adults, micafungin shows very good penetration into epithelial lining fluid, alveolar macrophages, the vitreous of the eye, peritoneum and ascites, but

Table 2 Mean steady-state (at 4 [24], 7 [23] or ≥14 [25] days) pharmacokinetic parameters of intravenous micafungin in paediatric patients (with febrile neutropenia [24], invasive candidiasis [25] or undergoing HSCT [23])

Study	Age (years) (no. of patients)	Micafungin regimen (od)	C_{max} (μg/mL)	AUC_{24} (μg·h/mL)	V_{ss} (mL/kg)	$t_{½}$ (h)	CL (mL/h/kg)
Albano et al. [23]	6–11 (6)	1 mg/kg	6.7	77.9	9184	14.7	13.2
	12–16 (9)	1 mg/kg	5.6	65.4	14,387	13.1	13.0
	0.3 to <2 (11)	1.5 mg/kg	8.1	77.3	2554	11.5	19.7
	2–5 (11)	1.5 mg/kg	8.6	76.0	4691	11.1	20.4
	6–11 (3)	1.5 mg/kg	8.7	113.6	6713	15.2	13.3
Seibel et al. [24]	2–17 (16)	0.5 mg/kg	6.4	27.9	320	12.3	19.4
	2–17 (11)	1.0 mg/kg	16.2	52.4	390	17.3	20.6
	2–17 (10)	1.5 mg/kg	16.3	100.6	280	12.9	16.5
	2–12 (8)	2 mg/kg	21.4	94.3	420	12.2	24.3
	2–12 (5)	3 mg/kg	30.4	190.5	290	13.2	17.0
	2–12 (7)	4 mg/kg	43.5	301.9	260	13.5	14.2
Undre et al. [25]	<5 (7)	2 mg/kg or 100 mg[a]	4.7	53.8		10.1	42.7
	≥5 (5)	2 mg/kg or 100 mg[a]	11.0	81.7		13.8	28.5

AUC_{24} area under the plasma concentration-time curve from 0 to 24 h, *CL* clearance, *C_{max}* maximum plasma concentration, HSCT haematopoietic stem cell transplantation, *od* once daily, *$t_{½}$* terminal elimination half-life, *Vss* volume of distribution at steady state

[a] Patients with a bodyweight of ≤40 kg received 2 mg/kg and those with a bodyweight of >40 kg received 100 mg

limited dose-dependent penetration into cerebrospinal fluid and pancreatic fluid [3–5].

Unchanged micafungin is the principal compound in the systemic circulation [6]. Micafungin is metabolized to several compounds [6] (mainly in the liver [3–5]). Of these metabolites, low concentrations of M-1, M-2 and M-5 have been detected in the plasma, none of which contribute to the efficacy of micafungin [6]. Although micafungin is a substrate for cytochrome P450 (CYP) 3A4 in vitro, hydroxylation by CYP3A4 is not a major metabolic pathway in vivo. In healthy adult volunteers, micafungin was primarily eliminated in the faeces, with faecal and renal excretion accounting for 71 and 11.6% of the radioactivity recovered over the 28-day period post dose [6].

The mean terminal elimination half-life of micafungin is ≈10 to 17 h and remains consistent across doses up to 8 mg/kg, and after multiple and single doses [6]. In paediatric patients, mean clearance values for micafungin were influenced by bodyweight, with mean values of weight-adjusted clearance ≈1.35-fold higher in younger children (4 months to 5 years) and 1.14-fold higher in those aged 6–11 years than in older children (aged 12–16 years). Mean clearance values in older children were similar to those in adults. Mean weight-adjusted clearance of micafungin in children <4 months of age was ≈2.6-fold higher than in older children (aged 12–16 years) and 2.3-fold greater than in adults [6].

There are no clinically relevant effects on the pharmacokinetics of micafungin based on gender, ethnicity (Caucasian, Black or Oriental), renal impairment or mild to moderate hepatic impairment [6]. There are insufficient data to support a dosing recommendation in patients with severe hepatic impairment and its use is not recommended in these patients [6].

Micafungin has a low potential for interactions with drugs metabolized via CYP3A mediated pathways [6]. Coadministration of micafungin and CAB was associated with a 30% increase in exposure to CAB. Hence, micafungin and CAB should only be used concomitantly when the benefits clearly outweigh the risks, with close monitoring of CAB-related toxicities [6].

4 Therapeutic Efficacy of Micafungin

4.1 In Invasive Candidiasis

The efficacy of micafungin for the treatment of invasive candidiasis was investigated in a paediatric substudy (median age ≤1 year) [28] conducted as part of a double-blind, multinational, phase 3, noninferiority trial in adults and adolescents (aged ≥16 years) [29] and in a double-blind, multinational, phase 3, noninferiority trial (NCT00815516) in infants (aged <4 months) [abstract plus poster presentation] [30]. These two phase 3 studies form the focus of discussion, with one [28] of these trials having been extensively reviewed previously [3, 4]. Results from these trials are supported by a noncomparative, multinational study in adults and children (aged <16 years; 15.9% of the

126 patients) with new or refractory candidaemia [31]; as no separate data are reported for paediatric patients, this study is not discussed further. Supporting evidence also comes from a prospective, multicentre, observational study in 108 adults and children (33% of whom were aged <18 years; of these 36 children, 13 were in neonatal intensive care units and 50% were extremely low birthweight neonates) with proven or suspected invasive candidiasis [32]. In this observational study, 76% of children had a favourable outcome (i.e. complete or partial response) at the end of therapy (EOT), with a survival rate of 97% [32].

In NCT00815516, infants (aged >2 to 120 days; ≈80% were aged ≤4 weeks) with proven invasive candidiasis were randomized to intravenous micafungin 10 mg/kg/day ($n = 20$) or CAB 1 mg/kg/day ($n = 10$) for ≥21 days, with stratification by gestational age (<27 and ≥27 weeks) and geographic location (North America, Europe, Latin America/Mexico and other regions) [30]. Mean treatment durations in the micafungin and CAB groups were 18.6 and 15.5 days. The study planned to enrol 225 infants to determine the noninferiority of micafungin to CAB treatment; however, as only 30 infants (25 of whom were aged ≤4 weeks) were randomized and received study drug, it was not possible to assess noninferiority as had been planned. The lack of recruitment and consequent early termination of the study reflected numerous factors, including several sites being unable to meet study requirements, insufficient patient population, local ethics committee/country restrictions on studies in paediatric patients and the decreased incidence of neonatal invasive candidiasis due to antifungal prophylaxis. The primary endpoint was fungal-free survival (FFS) 1 week after the last dose of study drug, with FFS defined as an infant alive and fungal free with no requirement for alternative antifungal therapy for continued therapy. At baseline, 40% of infants in the micafungin group and 20% in the CAB group had invasive candidiasis, with respective rates of candidaemia of 60 and 70%. The most common pathogens identified at baseline were *C. albicans* (40 and 50% of infants in the micafungin and CAB groups) and *C. parapsilosis* (45 and 20%); infants could have more than one *Candida* spp. identified. In the micafungin and CAB groups, FFS rates 1 week post therapy were 60% (95% CI 36–81) and 70% (95% CI 35–93), with mycological eradication rates of 55 and 80% [30].

In the paediatric substudy [28], eligible children had clinical signs of candidaemia or other types of invasive candidiasis caused by *Candida* spp. (*C. albicans* and non-*C. albicans*) and at least one *Candida* spp.-positive culture from blood or another sterile site within 4 days of study enrolment. Key exclusion criteria included systemic antifungal treatment for >3 days during the previous week (antifungal prophylaxis received by patients with neutropenia was permitted) and the presence of any type of significant liver disease. Children received a 60-min intravenous infusion of micafungin 2 mg/kg/day (100 mg/day in those weighing >40 kg) or liposomal amphotericin B (3 mg/kg/day), with the dosage adjusted after the initial 5-day fixed-dose period based on efficacy and tolerability. The respective median duration of treatment in each group was 15 and 14.5 days. The primary efficacy endpoint was the response rate, based on overall treatment success (i.e. achieving both a clinical and mycological cure) at the EOT. The modified intent-to-treat (mITT) population ($n = 98$) included patients with a confirmed diagnosis of candidaemia (≈93% of patients) or other invasive candidiasis who had received at least one dose of study drug. Most infections (≈92%) were caused by *Candida* spp., with 38 and 26% of infections in the micafungin and liposomal amphotericin B groups caused by *C. albicans* [28].

High treatment success rates were observed at the EOT in the micafungin and liposomal amphotericin B groups in primary mITT analyses (73 vs. 76%; $n = 48$ and 50), with respective treatment success rates in the per-protocol population of 85 and 88% ($n = 41$ and 42) [28]. Moreover, treatment success rates at the EOT generally exceeded 60% in both treatment groups, irrespective of baseline stratification factors (Fig. 1).

In patients with *C. albicans* infections at baseline, overall rates of mycological persistence at the EOT in the micafungin and liposomal amphotericin B groups were 11 and 0% ($n = 18$ and 13 evaluable patients), with respective rates in those with non-*C. albicans* infections of 18 and 22% ($n = 28$ and 32) [28]. During the 12-week post therapy phase, confirmed recurrence of fungal infection occurred in three micafungin recipients (two with candidaemia and one with acute disseminated candidiasis) and no liposomal amphotericin B recipients [28].

4.2 For Prophylaxis Against *Candida* Infections

The use of micafungin as prophylaxis against *Candida* infections was investigated in a large ($n = 882$ in the mITT population), double-blind, multinational, phase 3 noninferiority (vs. fluconazole) trial in adult and paediatric patients undergoing an allogeneic haematopoietic stem cell transplant (HSCT) for any reason or an autologous HSCT for haematological malignancy [33], with discussion focusing on data from paediatric patients (aged ≥6 months to <16 years; 9–10% of the population). These data are supported by a noncomparative, multicentre, Korean study in children and adolescents (aged ≤20 years; median age 9.7 years) with haematological and non-haematological disease undergoing allogeneic HSCT [34], which is not discussed further.

At the time of enrolment in the phase 3 trial, patients had to be free of deeply invasive fungal and liver disease, and to have had no treatment with any other systemic

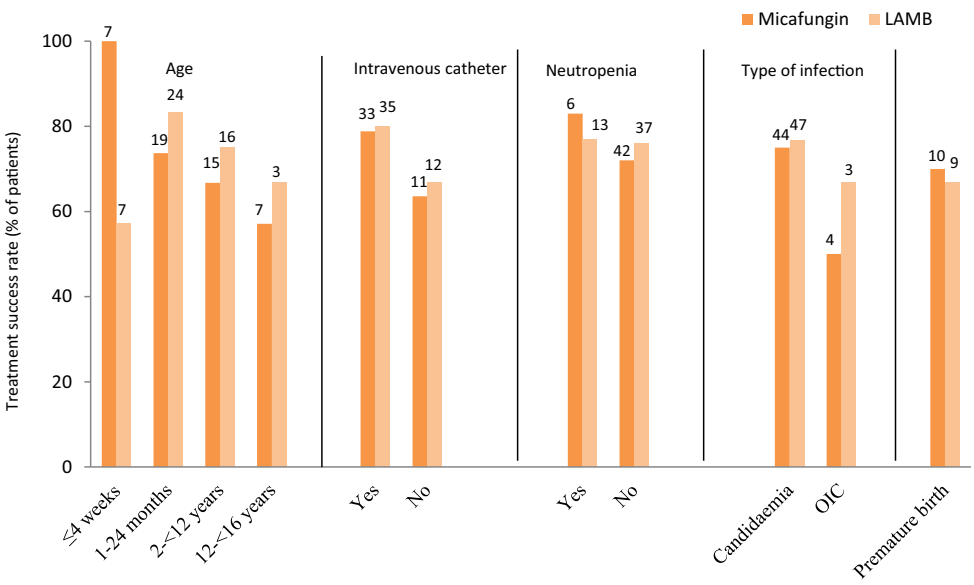

Fig. 1 Efficacy of micafungin at the end of therapy in children (median age ≤1 year) with invasive candidiasis in a paediatric substudy [28] of a multinational phase 3 trial [29], according to baseline stratification factors (modified intent-to-treat analyses). Evaluable patient numbers appear above the bars. Adapted from Scott [4]. *LAMB* liposomal amphotericin B, *OIC* other invasive candidiasis

antifungal drug within 72 h of the first dose of study drug [33]. Participants received a once-daily, 60-min intravenous infusion of micafungin 50 mg (1 mg/kg in those weighing <50 kg) or fluconazole 400 mg (8 mg/kg in those weighing <50 kg), with treatment given during the neutropenic phase of HSCT. In the overall population, the mean duration of treatment in the micafungin and fluconazole group was 19.2 and 18.7 days. The primary endpoint was treatment success (i.e. the absence of proven, probable or suspected systemic fungal infection until EOT and absence of proven or probable systemic fungal infection during the 4-week post-treatment phase) [33].

Micafungin provided superior prophylaxis to fluconazole in the overall mITT population in terms of treatment success rates (80.5 vs. 73.5%; 95% CI 0.9–12; $p = 0.03$; $n = 425$ and 457), with similar benefits seen across subgroups based on transplant type, gender, age, the presence or absence of graft-versus-host disease, and whether fungal colonization was present or absent at baseline [33]. In a subanalysis of paediatric patients, treatment success rates in the micafungin ($n = 39$) and fluconazole ($n = 45$) groups were 69.2 and 53.3% [33]. One (3%) micafungin recipient experienced a proven or probable breakthrough infection (a case of zygomycosis). In the fluconazole group, three children experienced a probable or proven fungal infection (two had proven aspergillosis and one had candidaemia caused by *C. parapsilosis*) [33].

5 Tolerability of Micafungin

Given the significant morbidity associated with their underlying conditions, intravenous micafungin treatment was generally well tolerated by paediatric patients (including neonates) with complex and life-threatening fungal infections and as prophylaxis in patients undergoing HSCT in clinical trials discussed in Sect. 4. For the most part, discussion focuses on a pooled safety analysis of paediatric clinical trials ($n = 296$) [35], with these data supplemented by a pooled analysis of accumulated clinical trial safety data ($n = 3028$; included paediatric pooled safety population) [36].

In the pooled analysis of paediatric studies, the median duration of treatment was 15 days and the median dosage of micafungin (including neonates aged <4 weeks) was 1.7 mg/kg/day, with a median dosage in neonates ($n = 18$) of 2.0 mg/kg/day [35]. There was no difference in the tolerability profile of micafungin based on age stratification in paediatric patients (<4 weeks, 4 weeks to 1 year, 1–4 years, 5–12 years and >12 years). Most patients (93.2%) experienced at least one treatment-emergent adverse event (TEAE), the most common of which were vomiting (31.8%), pyrexia (22.3%), diarrhoea (21.6%), nausea (21.3%) and hypokalaemia (20.9%). Of the TEAEs, 26.7% were considered to be at least possibly related to micafungin [i.e. treatment-related adverse events (TRAEs)], the most common (incidence 2–3%) of which included hypokalaemia, increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels, hyperbilirubinaemia and hypertension. Of these, 4.7% of patients experienced serious adverse events that were considered TRAEs, with TRAEs leading to treatment discontinuation in 7 of these 14 patients (i.e. 2.4% of the overall paediatric population). Albeit data are limited, there were no apparent trends relating to treatment dose or duration and the occurrence of adverse events in paediatric patients [35]. The larger accumulated safety analysis in adult and paediatric patients also indicated that there was no association

between higher doses of micafungin or treatment duration and the incidence of TRAEs [36].

In the accumulated safety analysis (paediatric and adult patients), hepatic TRAEs occurred in 8.6% of micafungin recipients, with the most common being increased alkaline phosphatase (2.7%), increased AST (2.3%), increased ALT (2%), abnormal liver function tests (1.5%) and hyperbilirubinaemia (1%) [36]. There were generally no significant differences in the incidence of hepatic TRAEs based on age [paediatric patients (aged <16 years), younger adults (aged 16–64 years) and elderly adults (≥65 years)]. Serious hepatic TRAEs occurred in 0.7% (21 of 3028) of patients, with 0.5% (15 of 3028 patients) discontinuing treatment because of these events [36]. More severe hepatic dysfunction, hepatitis or hepatic failure, including fatal cases, have been reported in some patients receiving micafungin [6]. The likelihood of developing micafungin-associated liver function test abnormalities was higher in paediatric patients than in adults and higher in infants aged <1 year than in older paediatric patients [6, 36]. In infants <1 year of age, micafungin-associated increases in AST, ALT or alkaline phosphatase levels occurred twice as frequently as they did in older paediatric patients [6]. This most likely reflects the higher proportion of serious underlying disorders in younger paediatric patients than in older paediatric patients or adults [6].

An observational, multicentre, pharmacoepidemiology, cohort study (MYCOS) in hospitalized adult and paediatric patients indicated that during short-term follow-up (i.e. ≤30 days post treatment) micafungin treatment ($n = 2970$) was not associated with an increased risk of liver injury compared with a propensity score-matched, cohort treated with other parenteral antifungal medications ($n = 6726$) [13 vs. 12% of patients experienced a treatment-emergent acute liver injury; hazard ratio (HR) 0.99; 95% CI 0.86–1.14] [37]. There was a trend for a reduced risk of the occurrence of acute renal injury in the micafungin versus the comparator group (63 vs. 65%; HR 0.93; 95% CI 0.87–0.99). Comparator parenteral antifungal agents included caspofungin, anidulafungin, fluconazole, itraconazole, voriconazole, CAB and lipid amphotericin B formulations. An ongoing long-term safety follow-up phase (≤13 years; completion 2017) will evaluate the risk of death from hepatocellular carcinoma (HCC) [37].

6 Dosage and Administration of Micafungin

In the EU, intravenous micafungin (administered over ≈1 h) is indicated in children (including neonates) and adolescents (<16 years of age) for the treatment of invasive candidiasis and as prophylaxis for *Candida* infection in patients undergoing HSCT or patients who are expected to have neutropenia (absolute neutrophil count <500 cells/μL) for ≥10 days (featured patient populations) [6]. It is also approved in adults and adolescents (≥16 years of age) in these indications and for the treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate [6].

For the treatment of invasive candidiasis, the recommended dosage of micafungin in children (aged ≥4 months) and adolescents (<16 years of age) is 100 mg/day in those weighing >40 kg and 2 mg/kg/day in those weighing ≤40 kg, with the dosage increased to 200 mg/day or 4 mg/kg/day, respectively, in patients with an inadequate response (e.g. persistence of cultures or if the patient's clinical condition does not improve) [6]. In children aged <4 months (including neonates), the recommended dosage of micafungin is 4–10 mg/kg/day, with the 4 mg/kg dose in this population approximating drug exposures in adults receiving 100 mg/day. If CNS infection is suspected, a higher dosage (e.g. 10 mg/kg/day) should be used due to the dose-dependent penetration of micafungin into the CNS, the safety and efficacy of the micafungin 4 and 10 mg/kg doses for the treatment of invasive fungal infections with CNS involvement have not been adequately established in controlled clinical trials. The minimum duration of treatment for invasive fungal infections should be 14 days, with treatment continued for ≥1 week after two sequential negative blood cultures have been obtained and after resolution of clinical signs and symptoms of infection [6].

For prophylaxis of *Candida* infections, the recommended dosage in children (aged ≥4 months) and adolescents (<16 years of age) is 50 mg/day in those weighing >40 kg and 1 mg/kg/day in those weighing ≤40 kg [6]. In children aged <4 months (including neonates), the recommended dosage for prophylaxis is 2 mg/kg/day. Micafungin should be administered for ≥1 week after neutrophil recovery. Clinical experience with micafungin as prophylaxis in patients <2 years of age is limited [6].

Foci of altered hepatocytes and HCC developed in rats treated with micafungin for ≥3 months, with the assumed threshold for tumour development in rats approximately in the range of clinical exposure [6]. The relevance of this finding for the therapeutic use of micafungin in patients cannot be excluded. Thus, as with many antimicrobial drugs, liver function should be carefully monitored during micafungin therapy, with treatment undertaken on a careful benefit/risk basis, particularly in those with severe liver impairment or chronic liver diseases known to represent preneoplastic conditions, or receiving a concomitant therapy including hepatotoxic and/or genotoxic properties. In patients with clinically relevant and persistent elevations of AST/ALT during micafungin treatment, early discontinuation of treatment is recommended to minimize the risk of

adaptive regeneration and potentially subsequent liver tumour formation [6].

Local prescribing information should be consulted for detailed information including contraindications, drug interactions and use in special populations.

7 Place of Micafungin in the Prophylaxis and Treatment of Invasive *Candida* Infections in Paediatric Patients

The prophylaxis and treatment of *Candida* infections remains challenging, with appropriate antifungal stewardship pivotal in optimizing the use of anti-infective agents (both antimicrobial and antifungal therapy) and ensuring that the most appropriate drug and treatment regimen is used for each individual patient [2]. The judicious use of anti-infective agents plays a key role in limiting selection pressures that drive fungal overgrowth and the potential emergence of resistant pathogens, and is also important in reducing the mortality and costs associated with treating nosocomial infections such as invasive candidiasis. Other important factors for optimizing clinical outcomes and minimizing selection pressures for resistance during antifungal therapy include the timeliness of initiating therapy, appropriate selection of antifungal drug for the causative pathogen (with consideration given to the frequency of a specific pathogen and resistance patterns for the geographical region and/or institution) and the use of a clinically relevant regimen (appropriate dosage and duration of treatment) [2]. The lack of rapid, sensitive and specific diagnostic tools for identifying causative fungal pathogens has been an added barrier to delivery of timely, targeted antifungal therapy and thereby, impacted on judicious antifungal stewardship [2, 38]. The recent development of rapid proteomic and molecular diagnostic tools should improve the management of invasive *Candida* infections and ability to optimize antifungal therapy [2].

Recent 2012 guidelines of ESCMID [39] strongly recommend micafungin, caspofungin and liposomal amphotericin B for the treatment of invasive candidiasis in children, with no one agent recommended over another. Micafungin is the only echinocandin that is specifically approved in the EU for the treatment of *Candida* infections in neonates [6]. ESCMID guidelines moderately recommend the use of micafungin in infants with invasive candidiasis and/or haematogenous *Candida* meningoencephalitis (HCME), with a higher dosage required in those with HCME given that micafungin shows limited penetration into the CNS (Sect. 3) [39]. As there are insufficient safety and efficacy data in the respective populations, caution is advised regarding the use of caspofungin in neonates and infants aged $\leq$1 year [40] (ESCMID guidelines specify marginal support for treatment of invasive candidiasis and/or HCME in infants [39]) and the use of anidulafungin is not recommended in paediatric patients (aged <18 years) [41].

For prophylaxis against *Candida* infections in paediatric patients, ESCMID guidelines strongly recommend the use of micafungin and fluconazole for allogeneic and autologous HSCT, and acute myeloid leukaemia and recurrent leukaemia, with voriconazole strongly recommended for allogeneic HSCT [39]. Fluconazole is also strongly recommended for prophylaxis in neonates in neonatal intensive care units; the approval of micafungin as prophylaxis against *Candida* infections in neonates is too recent for it to have been considered in 2012 ESCMID guidelines [39]. Currently, micafungin is the only echinocandin approved for use as prophylaxis against *Candida* infections in the EU [6, 40, 41].

The SPC for micafungin indicates that it should only be used if other agents are not suitable [6], which reflects the increased incidence of HCC identified in preclinical studies (Sect. 6) [39]. Of note, no safety signal relating to this potential risk has been identified during extensive, worldwide clinical use of micafungin for the treatment and prevention of invasive *Candida* infections. In addition, a class effect regarding the potential risk of HCC cannot be excluded, as similar preclinical studies have not been conducted with caspofungin or anidulafungin [39]. Long-term safety data from the MYCOS study relating to the potential risk of developing HCC during parenteral antifungal treatment (including with micafungin) are awaited with interest. During short-term follow-up in this study, there was no difference in the 30-day risk of acute liver injury between micafungin-treated patients and a propensity score-matched cohort receiving other parenteral antifungal therapy (Sect. 5).

Micafungin exhibited very good in vitro activity against a broad spectrum of *Candida* spp. isolates causing invasive infections based on global surveillance studies, with a low potential for the emergence of resistance (Sect. 2). Like all echinocandins, micafungin exhibited less in vitro activity against *C. parapsilosis* and *C. guilliermondii* than against other *Candida* spp. isolates. Micafungin also exhibited very good in vitro and in vivo activity against *Candida* biofilms, including those resistant to other antifungal drugs (Sect. 2). *Candida* biofilm infections are associated with the development of invasive candidiasis and often develop on medically implanted devices, such as indwelling catheters, with consequent impacts on patient care and healthcare costs [11].

Recommended dosages of intravenous micafungin were efficacious in the treatment of invasive candidiasis in paediatric patients (median age $\leq$1 year) participating in a substudy of a multinational trial in adults (Sect. 4.1), in which micafungin was noninferior to liposomal

amphotericin B [29]. High treatment success rates at the EOT were observed in the primary mITT analysis in paediatric patients, irrespective of baseline stratification factors (e.g. age, neutropenic status, presence or absence of indwelling catheter, type of primary infection). These data are supported by evidence from a phase 3 study in neonates (aged >2 to 120 days) with proven invasive candidiasis, which was designed to determine the noninferiority of micafungin 10 mg/kg/day to CAB (Sect. 4.1). Due to mitigating factors, insufficient patients were enrolled to permit noninferiority testing and the study was terminated early (see Sect. 4.1 for further discussion). As prophylaxis against fungal infections, micafungin was superior to fluconazole in a large multinational trial in paediatric (aged 0.5 to <16 years) and adult patients undergoing HSCT, irrespective of baseline stratification type (e.g. transplant type, whether fungal colonization was present or absent) [Sect. 4.2].

Given the significant comorbidities associated with their underlying conditions, micafungin was generally well tolerated in clinical trials in paediatric patients (including neonates) with invasive candidiasis and as prophylaxis against invasive *Candida* infections (Sect. 5). Approximately a quarter of TEAEs occurring in paediatric patients receiving micafungin were considered to be TRAEs, all of which occurred with an incidence of ≤3%, and relatively few patients discontinued treatment because of these events. Micafungin has been associated with abnormalities in liver function tests, as well as cases of more severe hepatic dysfunction, hepatitis and hepatic failure, with children more likely than adults to experience liver function abnormalities. Infants aged <1 year are more likely than older children to develop liver function abnormalities, most likely reflecting the higher proportion of serious underlying disorders in infants than in older children or adults (Sect. 5).

In conclusion, intravenous micafungin was effective and generally well tolerated in the treatment of candidaemia and other types of invasive candidiasis and as prophylaxis against fungal infections in those undergoing HSCT in paediatric substudies (including in neonates) and a small multinational, phase 3 trial in neonates with proven invasive candidiasis. Micafungin exhibits a broad spectrum of in vitro activity against clinically relevant isolates of *Candida* spp. (including fluconazole-resistant *C. glabrata* isolates), low propensity for emergence of resistant isolates and a convenient once-daily regimen. Hence, micafungin remains an important option in children (including neonates) and adolescents (<16 years of age) for the treatment of invasive candidiasis and as prophylaxis for *Candida* infection in patients undergoing HSCT or who are expected to have neutropenia for ≥10 days.

Data Selection Micafungin: 171 records identified	
Duplicates removed	16
Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication)	36
Excluded during initial selection (e.g. preclinical study; review; case report; not randomized trial)	21
Excluded by author (e.g. not randomized trials; review; duplicate data; small patient number; phase I/II trials)	57
Cited efficacy/tolerability articles	10
Cited articles not efficacy/tolerability	31
Search Strategy: EMBASE, MEDLINE and PubMed from 2009 to present. The previous Adis Drug Evaluation published in 2009 was hand-searched for relevant data. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Micafungin, Mycamine, Micamin, FK-463, candidiasis, candidaemia, candidemia, *Candida* infection. Records were limited to those in English language. Searches last updated 15 December 2016	

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Compliance with Ethical Standards

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