

Comparing echinocandins: a review

Professor Irene Krämer, PharmD, PhD



Currently there are three echinocandins, caspofungin, anidulafungin and micafungin, licensed in the European Union for the treatment of invasive fungal infections. This review compares the pharmacological properties, clinical efficacy, safety profiles and practical aspects of the echinocandins available.

Treatment options currently licensed for the treatment of systemic fungal infections include the polyenes, the triazoles and the echinocandins (ECH). For some years caspofungin (Cancidas, approval 2001) [1] was the only ECH licensed in the European Union (EU). In 2007 and 2008 the European Commission granted a marketing authorisation valid throughout the EU for anidulafungin (Ecalta) [2] and micafungin (Mycamine) [3], respectively. Micafungin has already been licensed in Japan in 2002 and in the US in 2005. Today in hospitals Pharmacy and Therapeutics committees have to evaluate whether the recently approved ECHs mean considerable advantages and whether they should be added to the formulary. This mini-review discusses whether the newly approved ECHs are of superior efficacy or do have a better safety profile or cost-benefit-relationship than caspofungin. Product characteristics useful for the evaluation are presented here.

Spectrum of activity

The ECHs are semi-synthetic, high-molecular lipoproteins which vary in their N-linked acyl lipid side chain. Selective antifungal activity of ECHs is due to the inhibition of the enzyme beta-glucan synthase, which is essential for the formation of the fungal cell wall. ECHs show fungicidal activity against *Candida* spp., and fungistatic or fungicidal activity against *Aspergillus* spp. They lack activity against *Cryptococcus*, *Zygomycetes*, *Fusarium* spp. and *Trichosporon* spp. The *in vitro* activity of the different ECH representatives varies for different *Candida* spp. (in general the highest MIC is for *C. parapsilosis*) [4]. However, the *in vitro*

variability in activity seems not to be relevant for the clinical outcome or the development of tolerance. Synergistic activity (to be explained by different mechanisms of action) against *Aspergillus* spp. was reported for the combinations of caspofungin/anidulafungin with itraconazole/voriconazole in 50% of the cases. The various ECHs showed comparable activity in different animal models. In order to assess efficacy and safety of each agent in specific indications and patient groups, clinical trials are necessary not with respect to the spectrum of action, but primarily because of pharmacokinetic variations [5].

Dosage and indications

The currently EU approved indications and the recommended dosages and dosage adjustments of the ECH representatives are given in Table 1.

None of the ECHs require dosage adjustments in renal dysfunction and removal by haemodialysis can be ignored. However, there are differences between

the ECHs with regard to the use and dosage adjustments in hepatic insufficiency (see Table 1). Careful monitoring of liver function is recommended in patients treated with micafungin [3]. Patients with increased hepatic enzymes during anidulafungin therapy should be monitored for evidence of worsening hepatic function [2]. Close monitoring of liver enzymes should be considered if caspofungin and cyclosporin (CsA) are used concomitantly [1]. According to a retrospective postmarketing study in 40 patients with concomitant caspofungin/CsA use, a significant risk of clinically relevant hepatotoxicity was not evident [6]. Furthermore, in patients with invasive candidiasis both caspofungin regimens standard dose (50 mg/d after 70 mg on day 1) and high dose (150 mg/d) were well tolerated (increased aspartate transaminase level 4% and 2%, respectively) [7].

Invasive candidiasis is the predominant fungal infection in immunocompetent

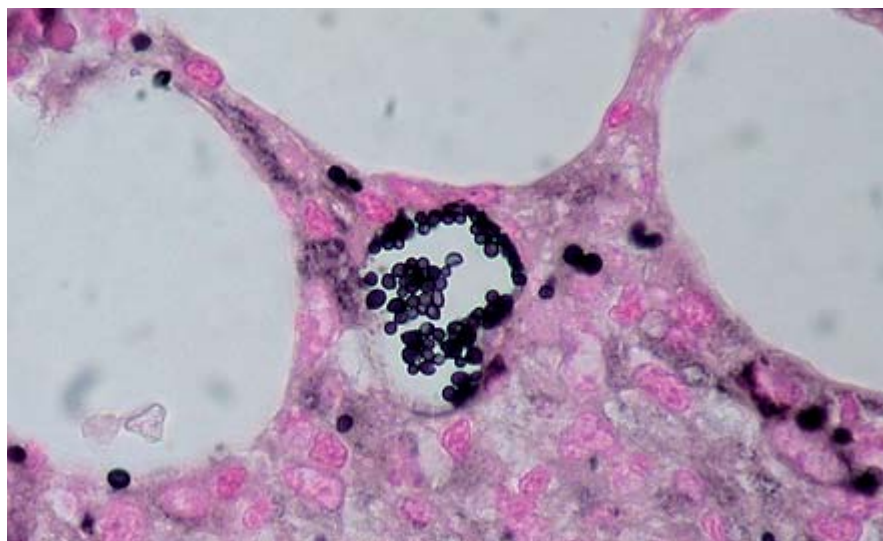


Table 1: European Union approved indications, dosages and dosage adjustments of echinocandins

		Caspofungin Cancidas	Anidulafungin Ecalta	Micafungin Mycamine
Licensed Indication	Adults	Treatment of invasive candidiasis	Treatment of invasive candidiasis in non-neutropenic patients	Treatment of invasive candidiasis
		Treatment of invasive aspergillosis, refractory or intolerant to amphotericin B, itraconazole		Treatment of oesophageal candidiasis in patients for whom IV therapy is appropriate
		Empirical therapy for presumed fungal infections in febrile neutropenic patients		Prophylaxis of candida infection in patients undergoing allogeneic HSCT or patients who are expected to have neutropenia >10 days
	Paediatric	Treatment of invasive candidiasis		Treatment of invasive candidiasis
		Treatment of invasive aspergillosis, refractory or intolerant to amphotericin B, itraconazole		Prophylaxis of candida infection in patients undergoing allogeneic HSCT or patients who are expected to have neutropenia >10 days
		Empirical therapy for presumed fungal infections in febrile neutropenic patients		
Dosage	Adults	70 mg loading dose day 1 50 mg or 70 mg (patients with body weight >80 kg) daily thereafter	200 mg loading dose day 1 100 mg daily thereafter	Body weight >40 kg: 100 mg (max. 200 mg) daily or 150 mg daily in oesophageal candidiasis or 50 mg daily in prophylaxis
	Paediatric	1-17 y: 70 mg/m ² , max. 70 mg day 1, 50 mg/m ² or 70 mg/m ² , max. 70 mg daily thereafter 50 mg/m ² daily 3-11 months 25 mg/m ² daily up to 3 months		Neonates – 16 y Body weight <40 kg: 2 mg/kg (max. 4 mg/kg) daily, or 1 mg/kg daily in prophylaxis
Dosage adjustments	Renal insufficiency	None	None	None
	Hepatic insufficiency	Mild: none Moderate: 70 mg Loading dose day 1, 35 mg daily thereafter Severe: no data available	Mild-severe: none	Mild-moderate: none Severe: no data available

HSCT: hematopoietic stem cell transplantation

and immunocompromised critically ill patients. All available ECHs were studied in phase III clinical trials for this indication and found to be at least as effective as other antifungal agents [8-11] (see Table 2). Anidulafungin is not approved for the treatment of invasive candidiasis in neutropenic patients. The pivotal study comprised too low a percentage of neutropenic patients to prove efficacy in this patient group [11]. For caspofungin an additional non-randomised study was performed with daily 50 or 100 mg caspofungin in 48 patients

with serious, less common forms of invasive candidiasis, e.g. endocarditis, osteomyelitis [12]. The overall response rate was 81%. Generally clinical trial results show that ECHs are efficacious and safe in the management of invasive candidiasis. Therefore, ECHs are first choice in the treatment of invasive candidiasis in intensive care unit patients [13, 14].

Caspofungin is also the preferred first-line treatment in empirical antifungal treatment in non-neutropenic patients and neu-

tropenic high-risk patients (total duration of neutropenia >10 days, persistent fever for 72-96 h) with prior azole prophylaxis [13]. In patients whose aspergillosis is refractory to voriconazole, a change to another drug class or to a combination of agents is to be considered [15]. Therapeutic options include liposomal amphotericin B or an echinocandin, such as caspofungin [15]. Micafungin and anidulafungin are known to have activity against *Aspergillus* species, but are not approved for this indication and the data available are very limited [16]. The use of higher doses of

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Table 2: Randomised multicentre clinical trials with echinocandins in patients with candidaemia or invasive candidiasis

	Pappas et al. 2007 [8]			Reboli et al. 2007 [11]		Mora-Duarte et al. 2002 [9]		Kuse et al. 2007 [10]	
	Mica-fungin 100 mg	Mica-fungin 150 mg	Caspo-fungin 70 mg/50 mg	Anidu-lafungin 200 mg/100 mg	Fluco-nazole 800 mg/400 mg	Caspo-fungin 70 mg/50 mg	Ampho. B deoxy-chelate 0.6-1 mg/kg	Mica-fungin 100mg	Liposomal Ampho B 3 mg/kg
Study Design	Randomised, controlled			Phase III Double-blind, randomised, controlled		Phase III Double-blind, randomised, controlled		Phase III Double-blind, randomised, controlled	
Number of patients enrolled	191	199	188	132	129	114	125	264	267
Mean Apache II score	14.9	14.7	13.8	15.0	14.4	14.8	15.4	15.4	15.8
Neutrophil count <500/ μ l	11.5%	8.5%	5.9%	2%	3%	12.8%	8.7%	13%	10%
Candidaemia/ invasive candidiasis	85% 15%	84% 15%	86% 14%	91% 6%	87% 9%	83% 13%	79% 17%	84% 16%	86% 14%
<i>C. Albicans</i>	48%	51%	44%	64%	59%	36%	54%	42%	44%
<i>C. glabrata</i>	15%	17%	18%	16%	25%	13%	9%	11%	7%
<i>C. krusei</i>	4%	4%	2%	excluded	excluded	4%	1%	3%	4%
Success of therapy (MITT) at the end of IV therapy	76%	71%	72%	76%	60%	73%	62%	74%	70%
<i>C. glabrata</i> infection	86%	88%	67%	75%	60%	77%	80%	83% per protocol	80% per protocol
Adverse drug events	22%	23%	24%	24%	26%	42%	75%	43%	51%

MITT: modified intention to treat analyses, patients with at least one dose of study medication; per protocol: patients with at least 5 days of study medication

Table 3: Posology and method of administration of echinocandins

	Caspofungin Cancidas	Anidulafungin Ecalta	Micafungin Mycamine
Posology	Powder for concentrate for solution for infusion	Powder and solvent for concentrate for solution for infusion	Powder for solution for infusion
Active substance	Caspofungin acetate (soluble)	Anidulafungin (not soluble)	Micafungin sodium (soluble)
Excipients	Sucrose Mannitol Glacial acetic acid Sodium hydroxide (to adjust pH)	Fructose Mannitol Polysorbate 80 Tartaric acid Hydrochloric acid (to adjust pH) Sodium hydroxide (to adjust pH)	Lactose monohydrate Citric acid (to adjust pH) Sodium hydroxide (to adjust pH)
Solvent	10.5 mL water for injection	30 mL ethanol 20% (w/w)	5 mL 0.9% sodium chloride solution or 5% glucose solution
Diluent	0.9% sodium chloride solution, lactated Ringer's solution (not 5% glucose solution)	0.9% sodium chloride solution or 5% glucose solution	0.9% sodium chloride solution or 5% glucose solution
Total infusion volume	260 mL for 50/70 mg 100 mL for 35 mg	280 mL for 100 mg 560 mL for 200 mg	105 mL to 110 mL per dose
Infusion rate	60 min per dose	3,3 mL/min not to be exceeded, 90 min per 100 mg	60 min per dose

casposfungin (70 mg/day) for use in salvage combination therapy of invasive aspergillosis was reported [17]. Combinations of an echinocandin with amphi-

thericin should be restricted to controlled clinical trials and may be considered for refractory disease and severely ill patients [16].

Posology and method of administration

ECHs offer the benefit of once daily administration. However, they are only

Table 4: Key differentiators of echinocandins

	Benefits	Limitations
Anidulafungin Ecalta	Licensed for use in severe hepatic insufficiency (in non-neutropenic adults patients with invasive candidiasis)	Licensed only for treatment of non-neutropenic adult patients in invasive candidiasis Maximum infusion rate 1.1 mg/min, Ethanol contained as excipient
Caspofungin Cancidas	Broad spectrum of licensed indications Extensively studied efficacy and safety profile	Not licensed for use in severe hepatic insufficiency Precautious use in neonates and infants below 12 months
Micafungin Mycamine	Broad spectrum of licensed indications Licensed for use in neonates (if other antifungals are not appropriate)	Risk of development of liver tumours: usage only if other antifungals are not appropriate Not licensed for use in severe hepatic insufficiency

available in an IV formulation. Cancidas is not stable in diluents containing glucose and is given according to the patient's weight (see Table 3).

In order to reduce infusion-related reactions infusion time should not go below 60 minutes for caspofungin and micafungin. Anidulafungin should not be infused above 1.1 mg/min in order to reduce histamine-related reactions. The resulting infusion time is 90 minutes for 100 mg and 3 hours for the 200 mg loading dose.

According to the label Micafungin is the only ECH representative not requiring a loading dose.

Adverse drug reactions and interactions

As mammalian cells lack the enzymes of glucan synthesis, the activity of ECHs is restricted to fungal pathogens and adverse drug reactions are rare compared to polyenes or azoles. In comparison to amphotericin B based therapies, especially, the safety profile of ECHs is impressive. Side effects most frequently reported are fever, chills, increased serum alkaline phosphatase, nausea, vomiting, diarrhoea, phlebitis, and histamine-mediated reactions (percentage ranges about 3% to 10% of patients). Elevated AST/ALT levels are reported for caspofungin and micafungin recipients. In the comparative trial of micafungin and caspofungin abnormal liver function test results occurred with similar incidence across the groups. Micafungin treatment was associated with significant impairment of liver function in healthy volunteers and patients. The

EMA SmPC [3] carries a special warning regarding the risk of liver toxicity of micafungin, because after a treatment period of three months or longer, rats developed foci of altered hepatocytes and hepatocellular tumours. As the risk of hepatocarcinogenicity in humans can not be excluded, micafungin treatment should be conducted on a careful risk/benefit analysis particularly in patients having severe liver function impairment or chronic liver diseases or receiving a concomitant therapy including hepatotoxic and/or genotoxic drugs. In order to investigate further some of the safety concerns, additional pharmacovigilance (close monitoring, observational study) and risk minimisation activities are required by the marketing authorisation administration.

The ECHs are associated with relatively few drug-drug-interactions. Tacrolimus blood levels may be influenced by co-administration of caspofungin and requires standard monitoring and dosage adjustments. Although caspofungin is a poor substrate for cytochrome P450 enzymes, an increase in the dosage of caspofungin should be considered when the drug is coadministered with certain inducers of the CYP, enzymes, e.g. efavirenz, phenytoin, rifampicin. The interactions seem to occur due to inhibition or induction of the hepatic transport proteins [1]. Micafungin slightly increases the AUC of sirolimus, nifedipine and itraconazole. The co-administered agent may require dosage reduction. No hepatic metabolism is observed for anidulafungin.

Conclusion

Although the currently available ECHs have many similarities there are criteria to be considered when selecting one of the ECHs for antifungal therapy (see Table 4):

- Clinical status of the patient, e.g. type of infection, neutropenia status, organ dysfunction
- Tolerability profile, e.g. liver insufficiency
- Ease of administration, e.g. infusion time, dosage adjustment
- Pharmacoeconomic considerations, e.g. acquisition costs

Caspofungin remains the mainstay among the ECHs with a broad spectrum of licensed indications, its excellent efficacy and safety profile and the largest patient experience database. The potential use of the recently approved micafungin is limited by the warning of the marketing authorisation administration with regard to liver toxicity. The potential use of anidulafungin is restricted by the single approved indication.

Author

Professor Irene Krämer, PharmD, PhD
Director of the Pharmacy Department
Johannes Gutenberg University Hospital
1 Langenbeckstrasse
D-55131 Mainz, Germany
kraemer@apotheke.klinik.uni-mainz.de

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