EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Rationale for EUCAST clinical breakpoints

Agent	**Micafungin against *Candida* spp.**

Current version	**2.0**	**4th February, 2020**
Previous version	1.0	5th February 2013

Foreword

EUCAST
The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002. The current remit of EUCAST is to harmonise clinical breakpoints for existing drugs in Europe, to determine clinical breakpoints for new drugs, to set epidemiological (microbiological) breakpoints, to revise breakpoints as required, to harmonise methodology for antimicrobial susceptibility testing, to develop a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms and to liaise with European governmental agencies and European networks involved with antimicrobial resistance and resistance surveillance.

Information on EUCAST and EUCAST breakpoints is available on the EUCAST website at http://www.EUCAST.org.

EUCAST rationale documents
EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

Availability of EUCAST document
All EUCAST documents are freely available from the EUCAST website at http://www.EUCAST.org.

Citation of EUCAST documents
This rationale document should be cited as: “European Committee on Antimicrobial Susceptibility Testing. Micafungin and *Candida* spp.: Rationale for the clinical breakpoints, version 2.0, 2020. http://www.eucast.org.

1. Introduction

Micafungin is an echinocandin antifungal agent active against the majority of *Candida* species.

Micafungin is licensed for treatment of invasive candidiasis, and prophylaxis of *Candida* infection for 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 (adults and children (including neonates)). Micafungin is also licensed for treatment of oesophageal candidiasis in adult patients for whom intravenous therapy is appropriate.

The *in vitro* activity of micafungin against species of *Candida* is not uniform. *C. albicans, C. tropicalis* and *C. glabrata* tend to exhibit low micafungin MIC values. In contrast, *C. parapsilosis* and *C. guilliermondii* have higher MICs resulting from naturally occurring amino-acid substitutions within a hot spot region of the Fks1p target protein. Analogous substitutions in other *Candida* species results in higher MICs and potentially clinical resistance to micafungin therapy. Therefore, and as the breakpoints are species specific, species identification is important and every attempt should be made to identify *Candida* to species level.

Laboratory animal model studies have demonstrated cross resistance between the three currently available echinocandins (anidulafungin, caspofungin and micafungin) for isolates with hot spot mutations in the target gene. However, there may be subtle differences depending on the specific genotype (for example, Arendrup et al. Antimicrobial Agents Chemother 2012; 56: 2435-42).

The European Committee on Antimicrobial susceptibility Testing – subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST) has determined breakpoints for micafungin for *Candida* species.

In version 2.0 of this rationale document, the clinical breakpoints have been revised for *C. parapsilosis* due to the revised definition of the “I” category and an ATU (area of technical uncertainty) has been introduced for *C. albicans* with MICs of 0.03 mg/L to avoid misclassifications of wild-type isolates.

2. Dosage	
Most common dose	100 mg/day (weight ≥40 kg); 2 mg/kg/day in patients weighing <40 kg
Maximum dose schedule	200 mg/day (weight ≥40 kg); 4 mg/kg/day in patients weighing <40 kg
Available formulations	iv

3a. MIC distributions (numbers) and epidemiological cut-off (ECOFF) values (mg/l)

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
*Candida albicans***	0	290	360	243	39	5	1	0	0	2	0	0	0	0	0	0	0	0	0	0.016
*Candida glabrata***	0	90	182	100	35	3	4	0	1	1	2	0	0	0	0	0	0	0	0	0.03
Candida guilliermondii	0	0	0	0	0	0	1	5	7	8	1	0	0	0	0	0	0	0	0	ND
Candida krusei	0	1	0	4	26	185	215	37	9	0	4	0	0	0	0	0	0	0	0	0.25
Candida parapsilosis	0	0	0	3	1	0	1	35	113	332	244	14	0	0	0	0	0	0	0	2
*Candida tropicalis***	0	48	51	247	200	59	14	2	0	2	0	0	0	0	0	0	0	0	0	0.06

** Data from truncated datasets as follows also supported the ECOFFs:
For *C. albicans* 107/107 (100%) MICs were ≤ 0.03 mg/l (one data set), 520/560 (92.9%) were ≤0,016 (one data set) and 87/89 (97.8%) were ≤0.08 mg/l (one data set).
For *C. glabrata* 100/100 (100%) MICs were ≤ 0.03 mg/l (one data set) and 173/177 (97.7%) MICs were ≤0.016 mg/l.
For *C. tropicalis* 98/98 (100%) MICs were ≤ 0.03 mg/l (one data set).

MIC values were determined with the EUCAST EDEF 7.2 methodology.

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple (7) data sources and time periods. The distributions are used to define the epidemiological cut-offs (ECOFF) and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. When there is insufficient evidence no epidemiological cut-off has been determined (ND).

3b. MIC distributions (%) and epidemiological cut-off (ECOFF) values (mg/l)

	N	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
*Candida albicans***	940	0	31	38	26	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0.016
*Candida glabrata***	418	0	22	44	24	8	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0.03
Candida guilliermondii	22	0	0	0	0	0	0	5	23	32	36	5	0	0	0	0	0	0	0	0	ND
Candida krusei	481	0	0	0	1	5	38	45	8	2	0	1	0	0	0	0	0	0	0	0	0.25
Candida parapsilosis	743	0	0	0	0	0	0	0	5	15	45	33	2	0	0	0	0	0	0	0	2
*Candida tropicalis***	623	0	8	8	40	32	9	2	0	0	0	0	0	0	0	0	0	0	0	0	0.06

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4. Breakpoints prior to harmonisation (mg/l) S≤ / R>

	European breakpoints	CLSI
General breakpoint		
	NA	2/- (tentative breakpoints in CLSI document M27-S3, 2012)
Species specific breakpoints:		
	NA	*C. albicans*: ≤0.25/ >0.5* *C. glabrata*: ≤ 0.06/ >0.12* *C. tropicalis*: ≤0.25/ >0.5* *C. krusei*: ≤0.25/ >0.5* *C. parapsilosis*: ≤2/ >4* *C. guilliermondii*: ≤2/ >4*

NA = Not available
* Pfaller et al Drug Resistance Updates 2011; 14: 164–76. CLSI document M27-S4, 2013.

5. Pharmacokinetics

	Adults[1]	Adults[2]	Children <5 years[3]	Children >5 years[3]
Dosage (mg)	100 mg/day		2 mg/kg	2 mg/kg
Cmax (mg/l)			4.66	11.01
Cmin (mg/l)				
Total body clearance	9-18 ml/h/kg*	1.165 (0.83-1.23) l/h*	42.72 ml/h/kg	28.52 ml/h/kg
T ½ (h),	10-17 (range)		10.13 (mean)	13.81 (mean)
AUC24h (mg.h/l)	115	81.3 – 121.06	72.19	90.43
Fraction unbound (%)	<1%		<1%	<1%
Volume of distribution at steady state (l)	18-19	10.43 (central compartment)		
Comments	• * Clearance increases with body weight in patients >66 kg[2,4]			
References	• [1] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000734/WC500031075.pdf • [2] Gumbo et al Diagn Microbiol Infect 2008; 60: 329–31 • [3] Undre et al. Pediatr Infect Dis J. 2012; 31: 630-2 • [4] Hall et al. 2011. Antimicrobial Agents Chemother 55: 5107-12			

6. Pharmacodynamics				
Total AUC/MIC for stasis	2420* (*C. albicans*) 1283** (*C. glabrata*)			
Total AUC/MIC for 2 log reduction				
Total AUC/MIC from clinical data***	>3000 (*Candida* spp) >5000 (Non-*C. parapsilosis*) ≥285 (*C. parapsilosis*)			
Comments	• *The total AUC/MIC required for stasis in a neutropenic murine model of disseminated candidiasis with *C. albicans* (Slater et al) is 2420. Higher drug exposures are required for fungicidal activity. • **The total AUC/MIC required for stasis in a neutropenic murine model of disseminated candidiasis with *C. glabrata* (Howard et al) is 1283. Higher drug exposures are required for fungicidal activity. • ***Pk/Pd breakpoints were determined based on CLSI MICs which are usually 1 two-fold dilutions higher than EUCAST MICs Pfaller et al Diagn Microbiol Infect Dis. 2014 Jun;79(2):198-204) • Pharmacodynamic data and preclinical-to-clinical bridging studies suggest that isolates with *Fks1* mutations and MIC elevation cannot be adequately treated with micafungin (Slater et al, Arendrup et al).			
References	• Slater et al Antimicrobial Agents Chemother 2011; 55:3075–83 • Howard et al Antimicrobial Agents Chemother 2011; 55:4880–7 • Arendrup et al Antimicrobial Agents Chemother 2012; 56:2435-42 • Andes et al Antimicrob Agents Chemother. 2011 May;55(5):2113-21			

7. Monte Carlo simulations and PK/PD breakpoints*

Monte Carlo simulations and *C. albicans*

MIC (mg/l)	% Success (i.e. % population with total AUC/MIC ≥2420)
0.016	89.2
0.03	51.0
0.06	2.5
0.125	0

Monte Carlo simulations and *C. glabrata*

MIC (mg/l)	% Success (i.e. % population with total AUC/MIC ≥1283)
0.016	96.3
0.03	88.0
0.06	45.0
0.125	1.1

*The Monte Carlo simulations were performed using ADAPT 5. The pharmacodynamic targets for *C. albicans* and *C. glabrata* were defined from the publications of Slater et al (Antimicrobial Agents Chemother 2011; 55: 3075–3083) and Howard et al (Antimicrobial Agents Chemother 2011; 55: 4880–4887) respectively. For both pathogens, the drug exposure required for stasis (i.e. the drug exposure that is required to prevent progressive fungal growth) was determined and used in the subsequent simulations. A standard micafungin regimen of 100 mg/day was used. The population pharmacokinetic model for adults receiving micafungin developed by Gumbo et al (Diagn Microbiol Infec. 2008; 60: 329–331) was used. Pharmacodynamic models for other *Candida* species with EUCAST MIC methodology have not been performed.
Similar estimates have been obtained using clinical data and the CLSI MIC method as summarised below (7. Clinical data, last paragraph) (Andes et al, Antimicrobial Agents Chemother 2011; 55: 2113–2121).

8. Clinical data

Invasive candidiasis:
Micafungin (100 mg) was compared with liposomal amphotericin for the treatment of candidaemia and invasive candidiasis in adults. The study design was a double-blind, randomised, multinational non-inferiority trial. The primary endpoint was treatment success, defined as both a clinical and a mycological response at the end of treatment. Out of 264 individuals who received micafungin, 202 were included in the per-protocol analyses (and a similar number in the liposomal amphotericin arm). Treatment success was similar with micafungin and liposomal amphotericin (89.6 and 89.5% in the micafungin and liposomal amphotericin arms, respectively). Efficacy was independent of the *Candida* species, primary site of infection, presence of neutropenia, APACHE II score, and whether a catheter was removed or replaced during the study (Kuse et al, Lancet 2007; 369: 1519–27).

Micafungin at two dosages (100 and 150 mg/day) was compared with caspofungin (70 mg followed by 50 mg) for the treatment of candidaemia and invasive candidiasis in adults. The study design was a double-blind, randomised, multi-national non-inferiority trial. The primary end point was treatment success, defined as clinical and mycological success at the end of blinded intravenous therapy. In the modified intention to treat population 191, 199 and 188 patients were assigned to micafungin 100 mg/day, micafungin 150 mg/day and caspofungin treatment, respectively. Treatment success was similar for the different treatments (76.4%, 71.4% and 72.3% of patients in the micafungin 100 mg/day, 150 mg/day and caspofungin groups, respectively). The median time to culture negativity was two days in the micafungin 100 mg/day group and the caspofungin group, compared with three days in the micafungin 150 mg/day groups. There were no significant differences in mortality, relapsing and emergent infections (invasive infection that developed during the treatment or follow–up periods), or adverse events between the study arms. (Pappas et al, Clin. Inf. Dis. 2007; 45: 883–93.) Micafungin was compared with liposomal amphotericin for the treatment of candidaemia and invasive candidiasis in children <16 years old. The study design was a double-blind, randomised, multi-national trial. The primary endpoint was treatment success, defined as both a clinical and a mycological response at the end of treatment. In the modified intention to treat population, 48 patients received micafungin (2 mg/kg) and 50 patients liposomal amphotericin B (3 mg/kg). Treatment success was similar for the two treatments (72.9% and 76.0% for micafungin and liposomal amphotericin, respectively) (Queiroz-Telles et al, Pediatr Infect Dis J 2008; 27: 820–6).

Breakthrough infections in patients with invasive candidiasis receiving micafungin have been reported. Twelve breakthrough cases in 649 patients receiving at least 3 doses of micafungin were found (1.8%). Six out of 12 involved *C. parapsilosis,* all of which had wild-type target gene sequence, 5/12 involved *C. glabrata* (4/5 with a hot spot target gene mutation), 2/12 involved *C. tropicalis* (1/2 with a hot spot target gene mutation), and 4/12 involved one each of *C. albicans, C. dubliniensis, C. krusei* or an unspecified yeast, respectively (1/2 available isolates with a hot spot target gene mutation). Five cases involved two species. The main conclusion was that *C. parapsilosis,* which harbours a naturally occurring alteration in the target gene, was over-represented in breakthrough cases but these cases were not associated with acquired resistance. The majority of other cases involved isolates with acquired resistance and hot spot Fksp alterations. (Pfeiffer et al, J Clin Microbiol; 2010; 48: 2373-80).

In a retrospective observational cohort study, including 307 unique patients with *C. parapsilosis* candidaemia of whom 126 (41%) received fluconazole and 181 (59%) received an echinocandin, mortality was equal (fluconazole 9.5% vs echinocandin 9.9%, (OR 1.05, 95% CI 0.49–2.26)) (Chiotos et al, J Antimicrob Chemother; 2016; 71: 3536-3539).

Oesophageal candidiasis:
Micafungin (150 mg) was compared with fluconazole (200 mg) for the treatment of oesophageal candidiasis in patients >16 years of age. The study design was a double-blind, randomised, non-inferiority trial. The primary end-point was endoscopic cure and clinical cure at end of therapy and at two and four weeks later. A total of 523 patients were included. Treatment success was similar for the different treatments: endoscopic cure rate was 87.7% for patients treated with micafungin compared with 88.0% for patients treated with fluconazole. Clinical success rates were 94.2% and 94.6%, overall therapeutic success rates were 87.3% and 87.2%, and the overall incidence of

relapse (through to week four) was 15.2% and 11.3% for the micafungin and fluconazole groups, respectively. The majority of cases (98%) involved *C. albicans* (De Wet et al, Aliment Pharmacol Ther 2005; 21: 899–907).

Prophylaxis:
Micafungin (50 mg) has been compared with itraconazole (5 mg/kg) for the prophylaxis of invasive fungal infections in haematological stem cell transplant recipients. The study design was a randomised, multicentre, open-label non-inferiority trial. The primary endpoint was lack of proven, probable or suspected invasive fungal infection during the 42 days of treatment and through to the end of 4 weeks after therapy. Of 287 patients, 283 were evaluable for efficacy (136 for micafungin and 147 for itraconazole in the intent-to-treat population). Treatment success in the two groups was not statistically different, 92.6% and 94.6% in patients treated with micafungin and itraconazole, respectively. The rates of proven or probable (but not suspected) invasive fungal infection were numerically higher with micafungin (4.4%) than with itraconazole (1.4%) (Huang, Biol Blood Marrow Transplant 2012; 18:1509-16).

Micafungin (50 mg or 1 mg/kg if weight <50 kg) has also been compared with fluconazole (400 mg or 8 mg/kg if weight <50 kg) for the prophylaxis of invasive fungal infections in haematological stem cell transplant recipients. The study design was a randomized, double-blind, multi-institutional, comparative phase III trial. Success was defined as the absence of suspected, proven, or probable invasive fungal infection through to the end of therapy and as the absence of proven or probable invasive fungal infection through to the end of four weeks after therapy. Of 882 adult and paediatric patients, 830 were evaluable for efficacy (397 for micafungin and 433 for fluconazole). Overall efficacy was superior for micafungin (80% vs. 73.5%, p 0.03) and mainly driven by breakthrough *Aspergillus* infections in the fluconazole arm (van Burik, Clin Inf Dis 2004; 39: 1407–16).

Target attainment analysis for invasive candidiasis:
The Micafungin PK/PD MIC cut off values were determined based on the clinical data from two clinical studies (Kuse et al, Lancet 2007; 369: 1519–27 and Pappas et al, Clin. Inf. Dis. 2007; 45: 883–93). The approved micafungin regimen for treatment of invasive candidiasis or candidemia (100 mg/day) was used. MIC determination according to CLSI was used. Micafungin exposures were estimated using a population pharmacokinetic model, and univariable and multivariable logistic regressions were used to identify factors associated with outcome, including the micafungin area under the concentration-time curve (AUC)/MIC ratio. Monte Carlo simulation was used to evaluate the probability of achieving AUC/MIC ratios associated with efficacy. If one considered the total AUC/MIC ratio target for efficacy identified for the *C. parapsilosis* cohort (AUC/MIC ratio > 285), the target would be expected to be attained for organisms with MIC values ≤ 0.25 mg/l. If one considered the total AUC/MIC ratio target for efficacy identified for the non-*C. parapsilosis* cohort (mainly *C. albicans,* total AUC/MIC ratio > 5000), the target would be expected to be attained for organisms with MIC values ≤ 0.016 mg/l. (Andes et al, Antimicrobial Agents Chemother, 2011; 55: 2113-2121).

9. Clinical breakpoints

Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.				
Species-related breakpoints	**Organism group**	**MIC breakpoints (mg/L)**			**Notes**
		S ≤	**R >**	**ATU**	
	C. albicans	0.016	0.016	0.03	Isolates with MIC=0.03 mg/L (ATU): If S to anidulafungin, report as S and add the following comment: Isolates susceptible to anidulafungin with micafungin MIC of 0.03 mg/L do not harbour an *fks* mutation conferring resistance to the echinocandins. If not S to anidulafungin, report as R and refer to reference laboratory for *fks* sequencing and confirmation of MICs.
	C. glabrata	0.03	0.03		
	C. parapsilosis	2	2		**C. parapsilosis* is a low virulent organism that harbours an intrinsic alteration in the target gene and the MICs of the echinocandins are higher than with other *Candida* species. Clinical trials suggest that the echinocandins can be used to treat invasive infections caused by *C. parapsilosis*. However, *C. parapsilosis* breakthrough cases have been significantly linked to micafungin (and caspofungin) treatment and echinocandins are generally not recommended as first line agents for serious infections caused by *C. parapsilosis.*
	Breakpoints are based on PK data, laboratory animal PK/PD data, microbiological data and clinical experience.				
Species without breakpoints	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. Hence there is insufficient evidence (IE) to set breakpoints for *C. tropicalis.* MICs for *C. krusei* are approximately three two-fold dilution steps higher than those for *C. albicans* and, similarly, those for *C. guilliermondii* are approximately eight 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. Hence, for *C. krusei* and *C. guilliermondii* there is insufficient evidence (IE) to set breakpoints.				

Clinical qualifications	The EUCAST-AFST considers micafungin appropriate therapy for invasive candidiasis, for prophylaxis of invasive fungal infection in special patient populations and in adults for oesophageal candidiasis when iv treatment is indicated, as licensed by EMA. In the EMA license for micafungin there is a comment advising caution in use of the agent due to an observation of liver tumour development in rats. The clinical implications of this observation are unknown. Please refer to the EMA product specification for further information.	
Dosage		Breakpoints apply to a standard iv dose of 100 mg/day for patients ≥40 kg and 2 mg/kg/day for children <16 years of age. The dose is 150 mg/day (3 mg/kg/day) for oesophageal candidiasis. The dose can be raised to 200 mg/day for patients ≥40 kg or 4 mg/kg/day for patients <40 kg when necessary.
Additional comment		Isolates with raised MICs and mutations in the hot spot regions of the target gene have been associated with clinical failures or breakthrough infections. Most clinical cases involve caspofungin or micafungin treatment. Most of these mutations confer cross resistance to all three echinocandins in animal experiments and therefore such isolates are classified as echinocandin resistant until further clinical experience is obtained with micafungin. The micafungin MICs of isolates with mutations in the hot spot regions of the target gene are as follows: *C. albicans* >0.03 mg/L; *C. glabrata* >0.016 mg/L; *C. tropicalis* >0.06 mg/L and *C. krusei* >0.5 mg/L (Arendrup et al, Antimicrob Agents Chemother. 2010; 54: 426–39). One exception to this general rule may be low-MIC *fks* mutants of *C. glabrata* (MICs below the ECOFF), as a preliminary observation indicated micafungin efficacy may be less affected compared with that of anidulafungin and caspofungin (Arendrup et al. Antimicrob Agents Chemother 2012; 56: 2435-42). Thus, the proposed clinical breakpoints have been established to categorise isolates with raised MICs and mutations in the hot spot regions of the target gene as resistant.

10. Exceptions noted for individual national committees
None