

Rationale for EUCAST clinical breakpoints

Agent	Miconazole	
Current version Previous version	4.0	26 th June 2025
	3.0	22 nd November 2024
	2.0	4 th February 2020
	1.0	5 th 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) cut-off values, 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

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Citation of EUCAST documents

This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Micafungin.: Rationale for the clinical breakpoints, version 4.0, 2025. <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/ μ l) 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. Among the species more frequently associated with human infections, *C. albicans*, *C. auris* (depending on geography), *C. dubliniensis*, *C. glabrata* and *C. tropicalis* exhibit low micafungin MIC values. In contrast, micafungin MICs are higher against *C. parapsilosis* and *C. guilliermondii* due to naturally occurring amino-acid substitutions within a hot spot region of the Fks1p target protein. Analogous intrinsic 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.

As for other echinocandins acquired resistance has been described and linked to hot spot mutations in the *fks* target genes (1). Laboratory animal model studies have demonstrated a high degree of cross resistance between the four currently available echinocandins (anidulafungin, caspofungin, micafungin and rezafungin) for such isolates (1). However, there may be subtle differences depending on the specific genotype (1, 2).

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

In version 3.0 of this rationale document, the MIC distributions have been enriched by new dataset, the ECOFF and breakpoint for *C. albicans* increased one dilution, breakpoints have been established for *C. dubliniensis* and *C. tropicalis*, and ECOFFs set for five additional species.

In version 4.0 of this rationale document, clinical breakpoints have been added for *C. auris*.

2. Dosage	
Adults (16 years of age and older)	Micafungin SPC*
Invasive candidiasis	
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
Esophageal candidiasis	150 mg/day
Paediatric patients (4 months – 15 years of age)	
Invasive candidiasis	
Most common dose for invasive candidiasis	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
Esophageal candidiasis	2.5 mg/kg/day (weight ≥30 kg); not to exceed 150 mg/day; 3 mg/kg in patients weighing ≤30 kg
Neonates (<4 months of age)	
Most common dose for invasive candidiasis	4 mg/kg/day
Maximum dose schedule	10 mg/kg/dose If central nervous system (CNS) infection is suspected
Available formulations	iv

*Micafungin EMA EPAR product information document updated 08/01/2024 [Search | European Medicines Agency \(europa.eu\)](#) assessed 25-06-2024.

3a. MIC distributions (numbers) and epidemiological cut-off (ECOFF) values (mg/l)																						
	N	0.001	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	(T)ECOFF*
<i>Candida albicans</i>	3165	11	117	601	1046	1207	131	42	7	1	1						1					0.03
<i>Candida auris</i>	150				1	8	43	70	21	4	3											0.25
<i>Candida dubliniensis</i>	165		5	2	36	69	45	7						1								0.06
<i>Candida glabrata</i>	1244			23	225	491	434	40	11	4	2	7	4	3								0.06
<i>Candida guilliermondii</i>	119								21	58	32	8										1
<i>Candida kefyr</i>	236					16	112	91	15	1	1											0.125
<i>Candida krusei</i>	785			1		8	30	265	379	81	10	5	5		1							0.25
<i>Candida lusitanae</i>	148					1	27	88	26	2	2	2										0.125
<i>Candida parapsilosis</i>	1490					3	1		6	58	190	739	468	25								4
<i>Candida tropicalis</i>	448			9	39	187	149	47	11	4		1	1									0.06
<i>Saccharomyces cerevisiae</i>	72						2	8	36	26												(0.5)*

*Tentative ECOFF, (T)ECOFF, values were determined for MIC distributions with only 3 data sets.

MIC values were determined with the EUCAST E.Def 7.4 methodology.

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple (3-15/species) 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.

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

	N	0.001	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	(T)ECOFF*	
<i>Candida albicans</i>	3165		4	19	33	38	4	1															0.03
<i>Candida auris</i>	150				1	5	29	47	14	3	2												0.25
<i>Candida dubliniensis</i>	165		3	1	22	42	27	4						1									0.06
<i>Candida glabrata</i>	1244			2	18	39	35	3	1			1											0.06
<i>Candida guilliermondii</i>	119								18	49	27	7											1
<i>Candida kefyr</i>	236					7	47	39	6														0.125
<i>Candida krusei</i>	785					1	4	34	48	10	1	1	1										0.25
<i>Candida lusitanae</i>	148					1	18	59	18	1	1	1											0.125
<i>Candida parapsilosis</i>	1490									4	13	50	31	2									4
<i>Candida tropicalis</i>	448			2	9	42	33	10	2	1													0.06
<i>Saccharomyces cerevisiae</i>	72						3	11	50	36													(0.5)*

Percentage values are rounded to nearest whole number. Consequently, the sum can deviate slightly from 100%.

*Tentative ECOFF (T)ECOFF values were determined for MIC distributions with only 3 data sets

MIC values were determined with the EUCAST E.Def 7.4 methodology.

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple (3-15/species) 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.

4. Pharmacokinetics

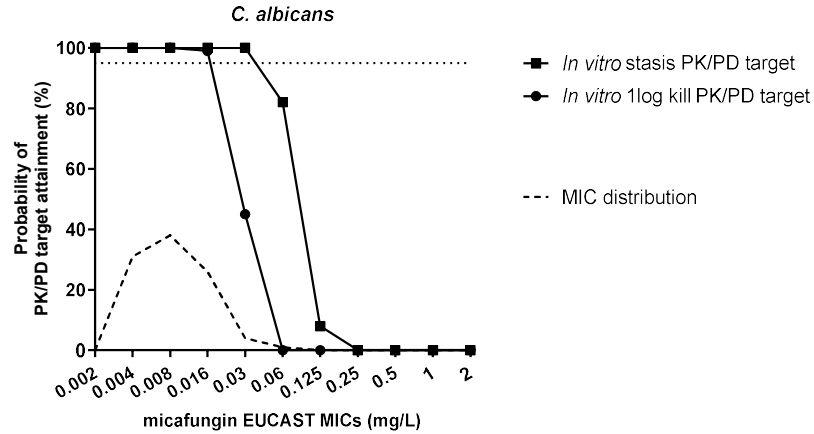
	Adults (micafungin EMA insert)	Adults (3)	Haematology patients (N=10) (4)	ICU patients from 4 studies, (N=151) (5)	Children <5 years (6)	Children >5 years (6)
Dosage	100 mg/day		100 mg/day	100 mg/day	2 mg/kg	2 mg/kg
C_{max} (mg/L), mean/median (range), SD)			10.8 (8.84–13.0)	5.7 (4.7–7.7)	4.66 (2.21)	11.01 (7.53)
C_{min} (mg/L), mean/median (range)			2.02 (1.65–2.51)	1.36 (1.11–1.8)		
Total body clearance, mean/median (range) (SD), (%CV)	(9-18) ml/h/kg*	1.165 (0.83-1.23) L/h*	1.01 (21.3%)	1.43 (1.1–1.5) L/h	42.72 (18.78) ml/h/kg	28.52 (8.10) ml/h/kg
T_{1/2} (h), mean/median (range)	(10-17)			9.8 (8.2–13.3)	10.13	13.81
AUC₀₋₂₄ (mg.h/L), mean/median (range)	115	(81.3 – 121.06)	98.6 (83.7-118.4)	78.7 (65.7–89.6)	72.19	90.43
Fraction unbound (%)	<1%				<1%	<1%
Volume of distribution at steady state (L), mean/median (range), (%CV)	(18-19)	10.43 (central compartment)	18.78 (48%)	20.3 (13–28.7)		
Comments	<p>* Clearance increases with body weight in patients >66 kg (3, 7)</p> <p>Cells are left empty when data are not readily available.</p>					

5. Pharmacodynamics

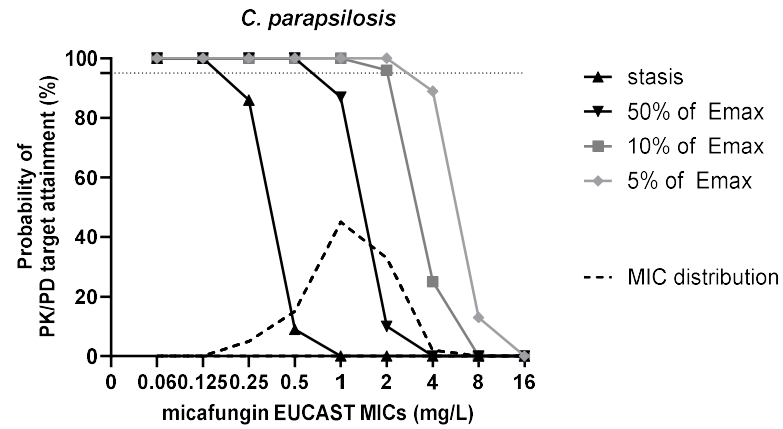
<i>In vitro</i> PK/PD target, MIC test	<i>C. albicans</i> (N=4) (8)	<i>C. parapsilosis</i> (N=3) (9)	
fAUC/MIC for stasis, EUCAST	2.8	0.60	
fAUC/MIC for 1log kill, EUCAST	7.9		
fAUC/MIC for 50% Emax, EUCAST		0.31	
fAUC/MIC for 10% Emax, EUCAST		0.07	
fAUC/MIC for 5% Emax, EUCAST		0.04	
Comments	<p>Pharmacodynamic targets for micafungin against <i>Candida</i> spp. have not been determined in animal models using the EUCAST method. However, pharmacodynamic data and preclinical-to-clinical bridging studies suggest that isolates with <i>Fks1</i> mutations and MIC elevation cannot be adequately treated with micafungin (8, 9). PD analysis performed with the EUCAST methodology is warranted (2, 10).</p> <p>A 10% human serum has been added to the <i>in vitro</i> model in order to account for the protein binding. No difference was found with higher % of serum. The model was validated based on animal data (8, 9).</p> <p>fAUC/MICs were calculated based on 99.75% protein binding.</p> <p>Cells are left empty when data are not readily available</p>		

6. Monte Carlo simulations and PK/PD cut-off values

Probability of target attainment was calculated with Monte Carlo simulation of $tAUC_{0-24}$ of 97 ± 29 mg.h/L of 100 mg i.v. dose using the *in vitro* PK/PD targets of section 5 and 99.75% protein binding as previously described (8, 9).



Maria-loanna Beredaki et al JAC2023 (8)



Maria-loanna Beredaki et al AAC2023 (9)

7. 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 (11).

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 endpoint 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) (12).

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 Fks alterations (13).

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)) (14).

Retrospective studies have shown good clinical efficacy against *C. auris* infections (15-17). *Fks* mutants have been described and were associated with clinical failure. CDC (<https://www.cdc.gov/candida-auris/hcp/clinical-care/index.html>), as well as European guidelines (18) recommends echinocandins as first-line therapy for invasive *C. auris* infections. Preclinical data, showed that micafungin was not effective against clade I *C. auris* isolates with MICs ≥ 1 mg/L that harbored FKS1 mutations in a *Galleria melonella* infection model (19).

A retrospective study of 12 patients who had >1 positive culture for *C. auris* and most of them (92%) treated with micafungin showed that 10 (83%) met criteria for clinical success defined as absence of all-cause mortality, *C. auris* recurrence, and infection-related readmission at 30 days from the first positive culture (<https://pubmed.ncbi.nlm.nih.gov/32310077/>)

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* (20).

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%) (21).

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 (22).

8. Clinical breakpoints

	Organism group	MIC breakpoints (mg/L)			Notes
		S ≤	R >	ATU	
Species-related breakpoints	<i>C. albicans</i>	0.03	0.03		
	<i>C. auris</i>	0.25	0.25		
	<i>C. dubliniensis</i>	0.06	0.06		
	<i>C. glabrata</i>	0.06	0.06		
	<i>C. parapsilosis</i>	4	4		* <i>C. parapsilosis</i> 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 <i>Candida</i> species. Clinical trials suggest that the echinocandins can be used to treat invasive infections caused by <i>C. parapsilosis</i> . However, <i>C. parapsilosis</i> 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 <i>C. parapsilosis</i> .
	<i>C. tropicalis</i>	0.06	0.06		
	Breakpoints are based on PK data, laboratory animal PK/PD data, microbiological data and clinical experience.				
Species without breakpoints	<p>MICs for <i>C. krusei</i> are approximately two two-fold dilution steps higher than those for <i>C. albicans</i>. In addition, only a small number of cases involved this species in the clinical trials. This means there is insufficient evidence to indicate whether the wild-type population of <i>C. krusei</i> can be considered susceptible to micafungin. Hence, for <i>C. krusei</i> there is insufficient evidence (IE) to set breakpoints.</p> <p>Clinical breakpoint setting requires information on species-specific clinical outcome data, which are generally non-existent for species other than the common pathogens. For interpretation of MICs for species for which clinical breakpoints have not been set, please consult the document "EUCAST guidance on Interpretation of MICs for rare yeast without breakpoints in breakpoint tables" found on the EUCAST website (What to do when there are no breakpoints - guidance for rare yeasts).</p>				
Clinical qualifications	<p>The EMA considers micafungin appropriate therapy in adults and children for invasive candidiasis, for prophylaxis of invasive fungal infection in special patient populations and in adults specifically also for oesophageal candidiasis when iv treatment is indicated.</p> <p>Of note, micafungin is almost universally protein bound and similar to the other echinocandins does not penetrate well into the CNS except in neonates.</p> <p>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.</p>				

Dosage	<p>Breakpoints apply to patients 4 months of age or older with invasive candidiasis receiving a standard iv dose of 100 mg/day for patients ≥ 40 kg and 2 mg/kg/day for patients < 40 kg. The licenced dose is 150 mg/day (3 mg/kg/day) for oesophageal candidiasis in adults. The dose can be raised to 200 mg/day for patients ≥ 40 kg or 4 mg/kg/day for patients < 40 kg when necessary.</p> <p>For children including neonates < 4 months of age, the licensed dose is 4 mg/kg, unless CNS infection is suspected in which case the maximum dose should be used (10 mg/kg).</p>
Additional comment	<p>Isolates with elevated MICs and mutations in the hot spot regions of the target genes have been associated with clinical failures or breakthrough infections. 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: <i>C. albicans</i> > 0.03 mg/L; <i>C. glabrata</i> > 0.016 mg/L; <i>C. tropicalis</i> > 0.06 mg/L and <i>C. krusei</i> > 0.5 mg/L (23).</p> <p>One exception to this general rule may be low-MIC <i>fks</i> mutants of <i>C. glabrata</i> (MICs below the ECOFF), as a preliminary observation indicated micafungin efficacy may be less affected compared with that of anidulafungin and caspofungin (2). 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.</p>

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