EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Rationale for EUCAST clinical breakpoints

Agent	**Anidulafungin**

Current version	**5.0**	**26th June 2025**
Previous versions	4.0	25nd November 2024
	3.0	4th February 2020
	2.0	15th January 2013
	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. Anidulafungin against *Candida*: Rationale for the clinical breakpoints, version 5.0, 2025. http://www.eucast.org.

1. Introduction

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

It is considered appropriate therapy for invasive candidiasis in adults and in paediatric patients aged ≥ 1 month. Anidulafungin susceptibility has been investigated in patients with candidaemia and used, but not systematically investigated, in patients with deep-seated organ infection and abscesses.

The *in vitro* activity of anidulafungin against species of *Candida* is not uniform. The species more frequently associated with human infections include *C. albicans, C. auris* (depending on geography)*, C. dubliniensis, C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis*, of which all but *C. parapsilosis* exhibit low anidulafungin MIC values. The underlying reason for the higher MICs against *C. parapsilosis* (and *C. guilliermondii*) is the presence of a naturally occurring amino-acid substitution at a hot spot region of the target enzyme, known to confer resistance in other species. Therefore, species identification is important and every attempt should be made to identify *Candida* to species level.

As with other echinocandins, some isolates have acquired resistance with elevated MICs and mutations in *fks* target genes that confer echinocandin resistance (1). Laboratory animal model studies have demonstrated a high degree of cross-resistance among the four currently available echinocandins (anidulafungin, caspofungin, micafungin and rezafungin) for isolates with hot spot mutations in the target gene. However, there may be subtle differences depending on the specific genotype (1, 2).

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

In version 4.0 of this rationale document, the MIC distributions have been enriched by new dataset, the ECOFF and breakpoint for *C. albicans* lowered one dilution and established for *C. dubliniensis*, and ECOFFs have been set for *C. auris, C. kefyr, C. lusitaniae* and *S. cerevisiae*.
A notable inter laboratory variation has been noted during the preparation of this version of the rationale document, prompting the question if addition of Tween 20 (as recommended for rezafungin testing) would be preferable. Investigations will be undertaken to address this issue.

In version 5.0 of this rational document, breakpoints have been added for *Candida auris*.

2. Dosage	
Adults	**Licensed dosing***
Invasive candidiasis	
Most common dose	200 mg on day 1, then 100 mg/day
Maximum dose schedule	200 mg/day
Esophageal candidiasis	100 mg on day 1, then 50 mg/day
Paediatric	
Licensed dose	3 mg/kg on day 1 (not to exceed 200 mg), then 1.5 mg/kg/day (not to exceed 100 mg)
Available formulations	iv

*Anidulafungin SPC (EPAR) updated 27/6/2023 found at Search | European Medicines Agency (europa.eu) accessed 25/6/2024

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*
Candida albicans	740	16	249	311	84	46	25	4	2	1	1						1					0.016
Candida auris	150				8	21	54	43	12	6	3	2	1									0.25
Candida dubliniensis	224		1	16	82	87	26	9		3												0.03
Candida glabrata	1076				14	373	563	91	14	5	2	9	2	2	1							0.06
Candida guilliermondii	127							1		14	30	60	19	2			1					2
Candida kefyr	132					24	69	32	5		2											0.125
Candida krusei	293					33	191	60	4	2	2	1										0.06
Candida lusitaniae	182					8	73	70	20	6	1	3	1									0.125
Candida parapsilosis	643								1	8	90	231	287	26								4
Candida tropicalis	456		3	32	133	151	101	29	2	1	1	2	1									0.06
Saccharomyces cerevisiae	78					2	2	30	38	5	1											(0.25)*

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

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple data sources (3-7/species) 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*
Candida albicans	740	2	34	42	11	6	3	1														0.016
Candida auris	150				5	14	36	29	8	4	2	1	1									0.25
Candida dubliniensis	224			7	37	39	12	4		1												0.03
Candida glabrata	1076				1	35	52	8	1			1										0.06
Candida guilliermondii	127							1		11	24	47	15	2			1					2
Candida kefyr	132					18	52	24	4		2											0.125
Candida krusei	293					11	65	20	1	1	1											0.06
Candida lusitaniae	182					4	40	38	11	3	1	2	1									0.125
Candida parapsilosis	643									1	14	36	45	4								4
Candida tropicalis	456		1	7	29	33	22	6														0.06
Saccharomyces cerevisiae	78					3	3	38	49	6	1											(0.25)*

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

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

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple data sources (3-7/species) 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

	Patients (N=262) included in four phase II/III studies (2)	Summary product characteristics (3)	ICU patients (N=125) included in four studies (4)
Dosage (mg)	200/100 mg daily	200/100 mg daily	200/100 mg daily
Cmax, (mg/L) (range, %CV)	7.2 (23.3%)	7	5.86 (3.9–7.7)
Cmin, (mg/L) (range, %CV)	3.3 (41.8%)	3	2.2 (1.8–3.2)
Total body clearance, (L/h) (range, %CV)	1.0 (33.5%)	1.1-1.2	1.3 (0.936–1.9)
T ½ (h), (range, %CV)	26.5 (28.5%)	Approximately 24	16.3 (9.2–42)
AUC24h (mg.h/L) (range, %CV)	110.3 (32.5%)	110	82.7 (55–102.2)
Fraction unbound (%)	≤1%	≤1%	
Volume of distribution (L) (range, %CV)	34.6 (10%)	30-50	38.8 (16.23–120)
Comments	Cells are left empty when data are not readily available.		

5. Pharmacodynamics

Total AUC/MIC±SD for stasis				
Total AUC/MIC±SD for 1 log				
Total AUC/MIC from clinical data				
Comments	• Pharmacodynamics targets for anidulafungin against *Candida* spp. have not been determined using EUCAST method. However, if translating Monte Carlo simulations performed using CLSI methodology for *C. albicans* and *C. parapsilosis* for *C. glabrata* to EUCAST MICs, the analysis supports the established EUCAST breakpoints (5, 6). Nevertheless, PD analysis performed with the EUCAST methodology is warranted.			

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

Not available for EUCAST data.

7. Clinical data

Invasive candidiasis:
Anidulafungin was compared with fluconazole in a randomized, double-blind, non-inferiority trial of treatment for invasive candidiasis (7). All patients could receive oral fluconazole after 10 days of intravenous therapy. Eighty-nine percent of the 245 patients in the primary analysis had candidaemia only. In 62% of the cases, *C. albicans* was the causal organism. *In vitro* fluconazole resistance was infrequent. Most of the patients (97%) did not have neutropenia. At the end of intravenous therapy, treatment was successful in 75.6% of patients treated with anidulafungin, compared with 60.2% of those treated with fluconazole (difference 15.4%; 95% confidence interval [CI] 3.9 to 27.0). The results were similar for other efficacy end points. The statistical analyses failed to show a "centre effect"; when data from the site enrolling the largest number of patients were removed - success rates at the end of intravenous therapy were 73.2% in the anidulafungin group and 61.1% in the fluconazole group (difference 12.1%; 95% CI -1.1 to 25.3). The rate of death from all causes was 31% in the fluconazole group and 23% in the anidulafungin group (P=0.13). A significantly better global response was seen for *C. albicans* (135 patients) and *C. tropicalis* (22 patients) (81% and 93% respectively for anidulafungin versus 62% and 50% for fluconazole, P<0.05). A numerically better global response was observed for *C. glabrata* (38 patients) and other *Candida* spp. (7 patients) (56% and 75% respectively for anidulafungin versus 50% and 67% for fluconazole) except for *C. parapsilosis* (23 patients) (64% for anidulafungin versus 83% for fluconazole, P=0.37).

Retrospective studies have shown good clinical efficacy against *C. auris* infections (8-10). 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 (11) recommends echinocandins as first-line therapy for invasive *C. auris* infections.

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)) (12).

Oesophageal candidiasis:
In a randomized, double-blind, double-dummy study (13) the efficacy and safety of intravenous anidulafungin was compared with that of oral fluconazole in 601 patients with endoscopically and microbiologically documented oesophageal candidiasis. Patients received intravenous anidulafungin (100 mg on day 1, followed by 50 mg per day) or oral fluconazole (200 mg on day 1, followed by 100 mg per day) for 7 days beyond resolution of symptoms (range 14-21 days). At the end of therapy, the rate of endoscopic success for anidulafungin, 242 (97.2%) of 249 treated patients, was found to be statistically non-inferior to that for fluconazole, 252 (98.8%) of 255 treated patients (difference -1.6%; 95% confidence interval -4.1 to 0.8).

In an open-label, non-comparative study (14) the efficacy and safety of anidulafungin were examined in patients with azole-refractory oropharyngeal and oesophageal candidiasis. Patients received intravenous anidulafungin 100 mg on day 1 followed by daily 50 mg doses on day 2 to day 14 or for a maximum of 21 days. Nineteen patients were enrolled and 89% had advanced HIV infection. Clinical success was observed in 95% of patients at the end of therapy, and endoscopic success was observed in 92% of patients with oesophageal candidiasis. At follow-up, clinical success was maintained in 47% of patients.

Correlation of *in vitro* MIC data with clinical outcome has not been performed, as such data sets are not available for EUCAST MIC methods. MICs by the CLSI method are typically 2 dilution steps higher than EUCAST values, particularly for the species with lower EUCAST MICs (6). Therefore, the data sets relating MIC to clinical outcome based on CLSI MICs cannot be translated into relationships for EUCAST MICs.

8. Clinical breakpoints

<table>
<tr><td>Non-species-related breakpoints</td><td colspan="4">There is insufficient evidence to set non-species-related breakpoints.</td></tr>
<tr><td rowspan="10">Species-related breakpoints</td><td rowspan="2">Organism group</td><td colspan="2">MIC breakpoints (mg/L)</td><td rowspan="2">Notes</td></tr>
<tr><td>S ≤</td><td>R ></td></tr>
<tr><td>C. albicans</td><td>0.016</td><td>0.016</td><td></td></tr>
<tr><td>C. auris</td><td>0.25</td><td>0.25</td><td></td></tr>
<tr><td>C. dubliniensis</td><td>0.03</td><td>0.03</td><td></td></tr>
<tr><td>C. glabrata</td><td>0.06</td><td>0.06</td><td></td></tr>
<tr><td>C. tropicalis</td><td>0.06</td><td>0.06</td><td></td></tr>
<tr><td>C. krusei</td><td>0.06</td><td>0.06</td><td></td></tr>
<tr><td>C. parapsilosis</td><td>4</td><td>4</td><td>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. The PK/PD target is lower for C. parapsilosis than for other Candida species and 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 associated to micafungin (and caspofungin) treatment, and echinocandins are generally not recommended as first-line agents for serious infections caused by C. parapsilosis.</td></tr>
<tr><td colspan="4">Breakpoints were based on PK data, microbiological data and clinical experience.</td></tr>
<tr><td>Species without breakpoints</td><td colspan="4">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).</td></tr>
<tr><td>Clinical qualifications</td><td colspan="4">The EMA considers anidulafungin appropriate therapy for invasive candidiasis (except CNS infection) in adults and paediatric patients aged 1 month to <18 years. Of note, ESCMID and IDSA guidelines also regard anidulafungin as appropriate therapy for patients with endocarditis or osteomyelitis, however, the efficacy of anidulafungin for these indications has only been evaluated in a limited number of patients.</td></tr>
<tr><td>Dosage</td><td colspan="4">Breakpoints apply to an i.v. dose of 200 mg on day 1, then 100 mg/day in adults, and in children an i.v. dose of 3 mg/kg on day 1 followed by 1.5 mg/kg daily not to exceed adult dosing recommendation.</td></tr>
</table>

Additional comment	Isolates with mutations in the hot spot regions of the target gene have been associated with clinical failures or breakthrough infections. In animal experiments these mutations confer cross resistance to all four echinocandins in the majority of cases. However, for some specific alterations and species differential susceptibility has been observed (15-17). However, as there is a high degree of cross resistance between the echinocandins, isolates categorised as anidulafungin and micafungin susceptible can be regarded as susceptible to caspofungin until drug specific breakpoints are available for caspofungin. Isolates with discrepant classification to anidulafungin and micafungin (e.g. anidulafungin S and micafungin R), should be further analysed with target gene sequencing as such isolates may harbour “weak mutations” causing a discrete loss of susceptibility.

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