

Rationale for EUCAST clinical breakpoints

Agent	Fluconazole	
Current version	3.0	4th February, 2020 (Fluconazole)
Previous versions	2.0	15 th of January, 2013 (Fluconazole)
	1.0	6 th of July, 2007

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. Fluconazole: Rationale for the clinical breakpoints, version 3.0, 2020. <http://www.eucast.org>.

1. Introduction

Fluconazole is a triazole antifungal agent active against *Candida* species. Fluconazole is appropriate primary or consolidation (depending on the host, severity of infection and susceptibility of the infecting *Candida* isolate) therapy for: candidaemia in neutropenic and non-neutropenic patients, chronic disseminated candidiasis, disseminated cutaneous neonatal candidiasis, urinary tract infections, lower respiratory tract infections, osteomyelitis, arthritis, infections of gallbladder, pancreas and peritoneum, endocarditis, pericarditis, suppurative phlebitis, myocarditis, meningitis and endophthalmitis due to *Candida* species, non-genital mucocutaneous candidiasis and genital candidiasis. In addition, can be used in the prevention of *Candida* infections following stem cell and solid organ transplantation and in neutropenic patients. Moreover, fluconazole is indicated for the treatment of cryptococcal meningitis and some dermatomycosis. Clinical indications may vary among countries.

The activity *in vitro* of fluconazole against species of *Candida* is not uniform. *C. albicans*, *C. parapsilosis* and *C. tropicalis* tend to have relatively low MICs, whereas the MICs for *C. glabrata* tend to be higher. In addition, *C. krusei* is inherently resistant to fluconazole. Therefore, every attempt should be made to identify *Candida* to species level if fluconazole is used. Moreover, resistance rates vary between local centres and depending on prior exposure in the individual patient.

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

In version 3.0 of this rationale document, ECOFFs for *C. albicans*, *C. tropicalis* and *C. glabrata* have been revised based on new cumulative MIC datasets exclusively obtained using EUCAST methodology that support a lower ECOFF than those originally established based upon EUCAST, CLSI and Etest MICs. Additionally, the clinical breakpoint for *C. glabrata* has been revised to accommodate the revised definition of “I” as “Susceptible, increased exposure”. Finally, new breakpoints for *C. dubliniensis* have been adopted.

2. Dosage

	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, Switzerland, UK	Turkey
Most common dose	400	200
Maximum dose schedule	800	800
Available formulations	iv, capsule, oral suspension	iv, capsule, oral suspension

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/ [T-ECOFF]*
<i>Candida albicans</i>	0	0	0	0	9	86	813	986	178	15	15	17	23	14	3	7	9	0	0	0.5
<i>Candida dubliniensis</i>	0	0	0	0	0	8	49	52	19	4	2	1	0	1	4	2	0	0	0	[0.5]
<i>Candida glabrata</i>	0	0	0	0	0	0	2	4	6	45	243	488	271	59	51	74	46	0	0	16
<i>Candida krusei</i>	0	0	0	0	0	0	0	0	0	1	0	5	6	79	138	116	16	2	0	128
<i>Candida parapsilosis</i>	0	0	0	0	0	1	27	201	328	159	38	25	17	14	11	8	6	0	0	2
<i>Candida tropicalis</i>	0	0	0	0	0	1	23	203	217	51	21	9	9	4	4	4	5	0	0	1
<i>Candida guilliermondii</i>	0	0	0	0	0	0	0	0	1	1	20	17	8	6	1	3	9	0	0	[16]
<i>Candida kefyr</i>	0	0	0	0	0	1	2	34	23	4	1	1	2	1	0	0	0	0	0	[1]

MIC values were determined with EUCAST methodology.

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple 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).

* tentative T-ECOFF was determined because <5 qualified MIC distributions were aggregated, and is indicated in square brackets.

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

	No.	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/ [T-ECOFF]*	
<i>Candida albicans</i>	2175	0	0	0	0	0	4	37	45	8	1	1	1	1	1	0	0	0	0	0	0	0.5
<i>Candida dubliniensis</i>	224	2	4	4	4	5	5	29	31	9	2	1	1	0	0	2	1	0	0	0	0	[0.5]
<i>Candida glabrata</i>	1289	0	0	0	0	0	0	0	0	0	3	19	38	21	5	4	6	4	0	0	0	16
<i>Candida krusei</i>	363	0	0	0	0	0	0	0	0	0	0	0	1	2	22	38	32	4	1	0	0	128
<i>Candida parapsilosis</i>	835	0	0	0	0	0	0	3	24	39	19	5	3	2	2	1	1	1	0	0	0	2
<i>Candida tropicalis</i>	551	0	0	0	0	0	0	4	37	39	9	4	2	2	1	1	1	1	0	0	0	1
<i>Candida guilliermondii</i>	66	0	0	0	0	0	0	0	0	2	2	30	26	12	9	2	5	14	0	0	0	[16]
<i>Candida kefyr</i>	69	0	0	0	0	0	1	3	49	33	6	1	1	3	1	0	0	0	0	0	0	[1]

MIC values were determined with EUCAST methodology.

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple 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).

* tentative T-ECOFF was determined because <5 qualified MIC distributions were aggregated, and is indicated in square brackets.

4. Breakpoints prior to harmonisation (mg/L) S _≤ / R _{>}			
	DIN	NWGA	CLSI**
General breakpoint			
	4 / 16	4 / 32	
Species specific breakpoints:			
			<i>C. albicans</i> S _{≤2} / R _{>4} <i>C. glabrata</i> S-DD _{≤ 32} / R _{>32} <i>C. parapsilosis</i> S _{≤2} / R _{>4} <i>C. tropicalis</i> S _{≤2} / R _{>4}

DIN, Deutsches Institute for Normung eV. (Germany); NWGA, Norwegian Working Group for Antibiotics (Norway) and CLSI, Clinical and laboratory Standards Institute (USA)
 ** CLSI states that isolates for which the MIC of fluconazole is between the S and R categories are considered susceptible dependent upon dose (S-DD), to indicate that dosage escalation may be required adequately to treat infections caused by isolates with a higher MICs. The novel category "susceptibility dose/delivery dependent" (S-DD) indicates that optimisation of drug exposure is critical for successful therapy. The CLSI breakpoints do not apply to *C. krusei*, which is considered inherently resistant to fluconazole.

5. Pharmacokinetics

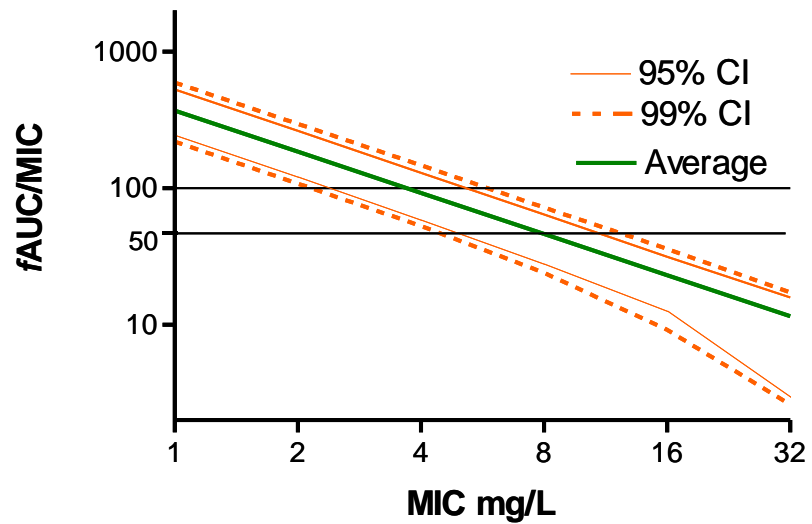
Dosage	25 mg capsule in healthy volunteers	100 mg iv/oral in HIV patients	200 mg capsule in healthy volunteers	400 mg	800 mg	400 mg in ICU patients	400 mg in surgical patients	800 mg in healthy volunteers	50 mg in elderly patients	2-8 mg/kg in children	6 mg/kg q72h in neonates
Oral bioavailability	>90%										
C _{max} ± SD (range) [%CV] (mg/L)	0.45 ± 0.06	2.34 ± 0.46	3.4 ± 0.5	18.9-30.6	34	20 [14%]	25 (22–28)	34 [6]	1.54		
T _{max} (h)	4.0 ± 1.9	2.8 ± 2.34	4.9 ± 1.7	0.5-1.5 h for oral					1.3h		
C _{min} (mg/L)				21-23 (iv steady state)		14 [11%]	15 (10–20)	20 (NR)			
Total body clearance (L/h)											
T _{1/2} (h), mean (range)		39.7 ± 16.75		31-37.2					46.2	15-18h	D1=74 (44-185), D13=47(27-68)
AUC _{24h} (mg.h/L)	19.9 ± 3.3	106 ± 41.44	151.3 ± 31.1	350	813.27	359 [259%]	409 (336–482)	608 (118)	76.4 ± 20.3	38 per 1 mg/kg dose unit	D1=271(173-385), D13=360(167-566)
Fraction unbound (%)				88-89 ^a							
Volume of distribution (L/kg)				0.7-0.8						0.88	D1= 1.18 (1.07-1.47), D13= 1.33 (1.04-1.68)
References	PMID: 8489572	PMID: 8257143	PMID: 8489572	Pfizer labelling		PMID: 25888060	PMID:11280621	PMID:15206988	SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET		
Comments	Steady state is reached after 4-5d without LD and after 2d with LD. ^a Higher protein binding (22.96 ± 3.60%) was reported in cancer patients (PMID: 8556224)										

6. Pharmacodynamics

	<i>Candida</i> spp.	<i>Cryptococcus</i>		
<i>t</i> AUC/MIC associated with 50%/100% of maximal efficacy corresponding to 1 and 2 log ₁₀ reduction from untreated animals in neutropenic murine model of disseminated candidiasis by <i>C. albicans</i> (PMID:10471550)	12-25/~100-500			
Mean ± SD <i>t</i> AUC/MIC associated with stasis in neutropenic murine model of disseminated candidiasis by <i>C. auris</i> (PMID: 28584152)	26.3 ± 18.5			
<i>t</i> AUC/MIC associated with 50%/100% of maximal efficacy in non-neutropenic murine model of disseminated candidiasis by <i>C. albicans</i> (PMID: 9593135)	45.4/60			
Dose/MIC (~ <i>f</i> AUC/MIC) associated with clinical success (PMID:17646421, PMID:21050800)	>25-100			
<i>t</i> AUC/MIC ratio associated with stasis non-immunosuppressed murine model of cryptococcal meningitis (PMID: 23571544)		389 (308-454)		
Comments	<ul style="list-style-type: none"> • Protein binding in mice is 10-11% (PMID:10471550) • A trailing effect in MIC tests and a <i>f</i>AUC/MIC of >100 needed to get a 2 log drop in 24h are, respectively, <i>in vitro</i> and <i>in vivo</i> data showing the fungistatic nature of fluconazole. Therefore, for invasive candidosis it is recommended to attain a <i>f</i>AUC/MIC for stasis of at least 100. This target is supported by clinical data shown in table 2 of section 7 in this document. • MICs in most pharmacodynamic studies were determined with CLSI methodology. Because the CLSI and EUCAST epidemiological cut-offs values are now the same (0.5 mg/l), the same <i>C. albicans</i> PK/PD endpoints apply for EUCAST methodology. 			

7. Monte Carlo simulations and PK/PD breakpoints

Probabilities of Target Attainment for 400 mg/day iv against *C. albicans* infection at steady state are shown in figure 1.



The horizontal lines indicate PK/PD $fAUC/MIC$ targets of 100 and 50.

The following pharmacokinetic parameters were used to obtain the PTA:
Vd 45 l. CV 12%
Half-life 32 h, CV 15%
Fraction unbound 88%

Results of simulations for the 400 mg oral dose do not markedly influence conclusions (PMID: 17646421).

8. Clinical data

There is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidiasis and, to a lesser, extent candidaemia to treatment. Similarly, cure is less likely for infections caused by strains with a higher MIC. In tables 1 and 2, data correlating clinical outcome with MICs obtained by means of EUCAST methodology, and with dose/MIC, is shown. More than 90% of patients responded to treatment when the MIC for the yeast was ≤ 2 mg/L when all cases are included (table 1). These data show that when the dose is >100 mg/day, all patients with isolates with MICs of ≤ 4 mg/L responded to treatment. More than 90% of patients with a dose/MIC ≥ 100 also responded to treatment (Table 2). (Rodriguez-Tudela JL. 2007. Antimicrob Agents Chemother. 51: 3599-3604).

Table 1. Correlation of fluconazole MIC with outcome of treatment with different dosages in patients with candidaemia or oropharyngeal candidiasis (OPC)

MIC* (mg/L)	Doses of fluconazole % Clinical success (N cured / N total)						All cases % Clinical success (n cured / n total)
	100 mg/day		>100 mg/day		All doses		
	Candidaemia	OPC	Candidaemia	OPC	Candidaemia	OPC	
≤ 0.5	75 (3/4)	100 (21/21)	92 (95/103)	100 (5/5)	91 (98/107)	100 (26/26)	93 (124/133)
1	-	100 (4/4)	100 (6/6)	-	100 (6/6)	100 (4/4)	100 (10/10)
2	-	100 (1/1)	100 (1/1)	-	100 (1/1)	100 (1/1)	100 (2/2)
4	-	20 (1/5)	100 (3/3)	100 (4/4)	100 (3/3)	69 (5/9)	67 (8/12)
8	-	0 (0/15)	40 (2/5)	41 (7/17)	40 (2/5)	26 (7/32)	24 (9/37)
≥ 16	-	0 (0/19)	75 (3/4)	0 (0/41)	75 (3/4)	2 (0/60)	5 (3/64)

Table 2. Correlation of fluconazole dose/MIC, AUC/MIC and fAUC/MIC with outcome of treatment in patients with candidaemia or oropharyngeal candidiasis (OPC)

Dose/MIC*	tAUC/MIC**	fAUC/MIC***	Range of doses administered	Range of MICs (mg/l) of isolates	% Clinical success (N cured / N total)		
					Candidaemia	OPC	All
400-4800	359-4678	316- 4117	100-800	0.12 - 1	92 (102/111)	100 (5/5)	92 (107/116)
150-200	146-189	129-166	100-600	0.5 - 4	100 (3/3)	100 (21/21)	100 (24/24)
100	90	79	100-800	1 - 8	100 (4/4)	100 (5/5)	100 (9/9)
50	45	40	100-400	2 – 8	33 (1/3)	57 (4/7)	50 (5/10)
25	22	20	100-200	4 – 16	50 (1/2)	42 (8/19)	43 (9/21)
12.5	11	10	100-400	8 – 32	100 (1/1)	0 (0/34)	3 (1/35)
6.25	6	5	200	32	100 (1/1)	0 (0/22)	4 (1/23)
3.13	3	2	100-200	32 - 64	0 (0/1)	0 (0/19)	0 (0/20)

*MICs determined by EUCAST method (Subcommittee on Antifungal Susceptibility Testing (ASFT) of the ESCMID European Committee for Antimicrobial Susceptibility Testing (EUCAST), EUCAST Definitive Document E.DEF 7.1: method for the determination of broth dilution of antifungal agents for fermentative yeasts. *CMI* 2008; 14:398-405).

**The values of tAUC/MIC were obtained after applying the following equation: $tAUC = 0.99 \times Dose - 9.2$.

***fAUC/MIC was calculated taking in consideration that the fraction of fluconazole unbound is 88%.

9. *Candida* clinical breakpoints

Non-species-related breakpoints	<p>These have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. EUCAST does not advocate terms such as SDD (susceptible dose-dependent) preferring to use “I” (Susceptible, increased exposure) to denote strains that are considered susceptible but require higher fluconazole exposure to be treated. The column of non-species related breakpoints is for use only for species not included in the table. They should not be used for species where susceptibility testing is not recommended (marked with - in the EUCAST breakpoint tables).</p> <p>Non-species-related breakpoints are S ≤2 mg/L, R >4 mg/L.</p>			
Species-related breakpoints	Organism group	MIC breakpoints (mg/L)		Notes
		S ≤	R >	
	<i>C. albicans</i>	2	4	
	<i>C. dubliniensis</i>	2	4	
	<i>C. tropicalis</i>	2	4	
	<i>C. parapsilosis</i>	2	4	
<i>C. glabrata</i>	0.001	16	<p>The entire wild-type population is classified as “I” (Susceptible, Increased exposure). Semi-automated machines and laboratory information systems prefer numerical values. 0.001 mg/L is an arbitrary value designed only to prevent the occasional organism to erroneously be reported as “S”.</p> <p>A significant number of infections involve <i>C. glabrata</i>, for which fluconazole MICs are ≤16 mg/L in the absence of resistance mechanisms. As there are few agents suitable for the treatment of urinary tract infections and mucosal infections managed in the primary health care setting, fluconazole may be a suitable choice. In cases where fluconazole is the only available antifungal agent for treating <i>C. glabrata</i> infections the use of a higher dosage may be required.</p>	
Breakpoints for these <i>Candida</i> species were based on PK data, microbiological data, and patient outcomes.				
Species without breakpoints	<p><i>C. krusei</i> is inherently resistant to fluconazole and regarded a poor target for the agent. Therefore, EUCAST-AFST has refrained from establishing <i>C. krusei</i> breakpoints for fluconazole and advises that an alternative agent should be used.</p> <p>The MICs and ECOFF for <i>C. guilliermondii</i> are 5 two-fold dilution-steps higher than those for <i>C. albicans</i>. There are insufficient clinical data to indicate whether this species is a good target for fluconazole or not. Hence, EUCAST has refrained from setting breakpoint for this species.</p>			

Clinical qualifications	<p>The EUCAST-AFST considers fluconazole appropriate therapy for:</p> <ul style="list-style-type: none"> • Consolidation therapy for candidaemia among neutropenic and non-neutropenic patients once susceptibility is confirmed • Chronic disseminated candidiasis • Disseminated cutaneous neonatal candidiasis • Urinary tract infections, lower respiratory tract infections, osteomyelitis, arthritis, infections of the gall bladder, pancreas and peritoneum, endocarditis, pericarditis, suppurative phlebitis, myocarditis, meningitis and endophthalmitis due to <i>Candida</i> species • non-genital mucocutaneous candidiasis • Genital candidiasis • Cryptococcal meningitis • <i>Candida</i> related dermatomycosis <p>The EUCAST-AFST considers fluconazole appropriate prophylaxis for:</p> <ul style="list-style-type: none"> • Neutropenic patients particularly if colonised with <i>Candida tropicalis</i> • Allogeneic haematopoietic stem cell transplant (HSCT) recipients • High-risk recipients of liver transplants
Dosage	<p>The EUCAST breakpoints apply to oral and intravenous administration of fluconazole of 400 – 800 mg per day. Typically, a loading dose of 800 mg day one followed by 400 mg should be used, however for severe infections, high body mass index (BMI) or infections involving <i>C. glabrata</i> the dose may be elevated to 800 mg daily (or 12 mg/kg).</p>
Additional comment	<p>The ECOFFs have been reviewed and revised for <i>C. albicans</i>, <i>C. glabrata</i> and <i>C. tropicalis</i>. The previous MICs were based upon EUCAST, CLSI and Etest values, but the current version only include EUCAST determinations. This slight shift in MICs motivated the decrease of the ECOFFs for these species and of the revised breakpoint for <i>C. glabrata</i>.</p>

10. Exceptions noted for individual national committees
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None
