EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Fluconazole	**Rationale for the EUCAST clinical breakpoints, version 2.0**	15 January 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. Fluconazole: Rationale for the clinical breakpoints, version 2.0, 2013. http://www.eucast.org.

Introduction

Fluconazole is a triazole antifungal agent active against *Candida* species. Fluconazole is appropriate 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.

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 2.0 of this rationale document, breakpoints for *C. glabrata* have been modified to species-specific values that categorise the wild type as intermediate in order to accommodate use of fluconazole in some clinical situations.

1. 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

2. MIC distributions and epidemiological cut-off (ECOFF) values (mg/L)

	0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Candida albicans	0	0	0	14	57	275	4010	6737	2518	1081	439	136	154	107	88	247	92	35	1	1
Candida glabrata	0	0	0	2	7	5	14	11	48	110	323	888	1204	1353	534	261	157	75	26	32
Candida guilliermondii	0	0	0	0	0	0	0	1	2	4	21	44	29	7	8	1	1	0	0	16
Candida krusei	0	0	0	0	0	0	0	0	0	0	0	1	9	50	314	229	59	11	0	128
Candida parapsilosis	0	0	0	0	0	4	62	415	980	646	241	70	58	39	11	5	2	2	1	2
Candida tropicalis	0	0	0	0	0	2	119	443	743	513	269	60	24	27	10	9	10	0	0	2

MIC values were determined with EUCAST, CLSI and Etest 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).

3. Breakpoints prior to harmonisation (mg/L) S≤ / R>

	DIN	NWGA	CLSI**
General breakpoint			
	4 / 16	4 / 32	
Species specific breakpoints:			
			C. albicans S ≤2 / R>4 *C. glabrata* S-DD ≤ 32 / R>32 *C. parapsilosis* S≤2 / R>4 *C. tropicalis* 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.

4. Pharmacokinetics				
Dosage (mg)	400	800		
Cmax (mg/L)	18.9-30.6	34		
Cmin (mg/L)	21-23 (iv steady state)	21-23 (iv steady state)		
Total body clearance (L/h)				
T ½ (h), mean (range)	31-37.2	31-37.2		
AUC24h (mg.h/L)	350	813.27		
Fraction unbound (%)	88-89	88-89		
Volume of distribution (L/kg)	0.7-0.8	0.7-0.8		
Comments				
References	• Brammer, K. W. et al. Rev.Infect.Dis. Suppl 3:S318-S326, 1990. • Grant, S. M. & S. P. Clissold. Clin.Pharmacokinet. 24:10-27, 1990. • Goa, K. L. & L. B. Barradell. Drugs 50:658-690, 1995.			

5. Pharmacodynamics				
*f*AUC/MIC for stasis	25 – 50			
*f*AUC/MIC for 2 log reduction	500 – 1000			
*f*AUC/MIC from clinical data	100			
Comments	• A trailing effect in MIC tests and a *f*AUC/MIC of 500-1000 needed to get a 2 log drop in 24h are, respectively, *in vitro* and *in vivo* data showing the fungistatic nature of fluconazole. Therefore, for invasive candidosis it is recommended to attain a *f*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.			
References	• Grant, S. M. & S. P. Clissold. Drugs 39:877-916, 2003. • Goa, K. L. & L. B. Barradell. Drugs 50:658-690, 1995. • Andes, D. & M. van Ogtrop. AAC. 43:2116-2120, 1999. • Andes, D et al. AAC. 47:1179-1186, 2003.			

6. Monte Carlo simulations and PK/PD breakpoints

Probabilities of Target Attainment for 400 mg/day iv are shown in figure 1.

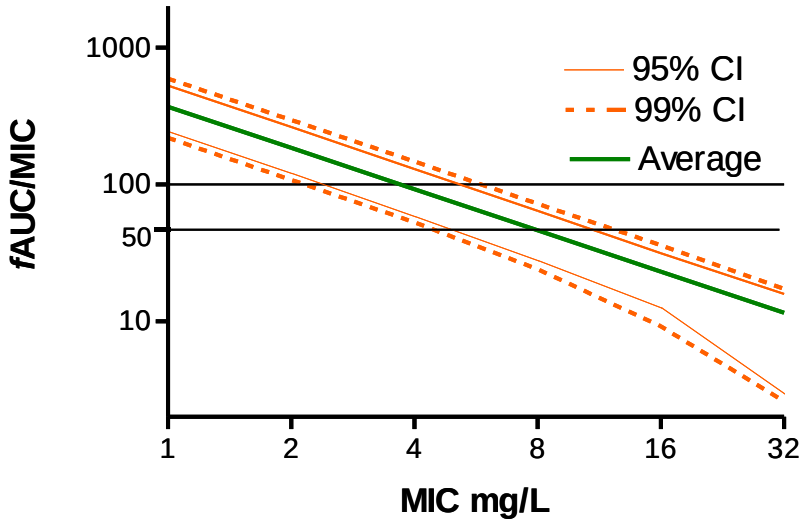

Figure 1. Probabilities of Target Attainment for fluconazole for 400 mg/day iv at steady state.

The horizontal lines indicate PK/PD *f*AUC/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.

7. 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 candidosis 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 candidosis (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 candidosis (OPC)

Dose/MIC*	AUC/MIC**	*f*AUC/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 AUC/MIC were obtained after applying the following equation: AUC = 0.99 x Dose – 9.2.

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

8. Clinical breakpoints

Non-species-related breakpoints	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" (intermediate) to denote strains that are considered neither susceptible nor resistant. 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 - or IE in the EUCAST breakpoint tables). Non-species-related breakpoints are S≤2 mg/L, R>4 mg/L.
Species-related breakpoints	The *in vitro* activity of fluconazole against species of *Candida* is not uniform. The species most frequently associated with human infections are *C. albicans, C. parapsilosis* and *C. tropicalis.* Fluconazole MIC values for these species are ≤2 mg/L in the absence of fluconazole resistance mechanisms. *C. albicans* S ≤2, R >4 mg/L *C. tropicalis* S ≤2, R >4 mg/L *C. parapsilosis* S ≤2, R >4 mg/L *C. glabrata* S ≤0.002, R > 32 mg/L* (see below) * A significant number of infections involve *C. glabrata*, for which fluconazole MICs are 2-32 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 *C. glabrata* infections the use of a higher dosage may be required.
Species without breakpoints	*C. krusei* is inherently resistant to fluconazole and regarded a poor target for the agent. Therefore, EUCAST-AFST has refrained from establishing *C. krusei* breakpoints for fluconazole and advises that an alternative agent should be used. The MICs and ECOFF for *C. guilliermondii* are 4 dilution-steps higher than those for *C. albicans.* 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.

Clinical qualifications	The EUCAST-AFST considers fluconazole appropriate therapy for: • Candidaemia among neutropenic and non-neutropenic patients • Chronic disseminated candidosis • Disseminated cutaneous neonatal candidosis • 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 *Candida* species • non-genital mucocutaneous candidosis • Genital candidosis The EUCAST-AFST considers fluconazole appropriate prophylaxis for: • Neutropenic patients particularly if colonised with *Candida tropicalis* • Allogeneic haematopoietic stem cell transplant (HSCT) recipients • High-risk recipients of liver transplants
Dosage	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 *C. glabrata* the dose may be elevated to 800 mg daily.
Additional comment	The most common dose of 400 mg/day used for treating invasive candidosis results in an AUC about 350 mg.h/L and a *f*AUC of 308 mg.h/L. This *f*AUC would attain a *f*AUC/MIC in excess of 50 for all isolates with MICs $\leq$ 4 mg/L. However, due to the fungistatic nature of fluconazole, for high-risk infections and especially in neutropenic patients, a target *f*AUC/MIC of 100 is recommended. A dose of 400 mg/day would attain a *f*AUC/MIC in excess of 100 for all isolates with $\leq$ 2 mg/L.

9. EUCAST clinical MIC breakpoints

All EUCAST breakpoints can be found at **http://www.eucast.org**

10. Exceptions noted for individual national committees

None