

Fluconazole	Rationale for the EUCAST clinical breakpoints, version 1.0	5 April 2007
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Introduction

Fluconazole is an azole antifungal agent active against *Candida* species and *Cryptococcus* species.

It is considered 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 gallbladder, pancreas and peritoneum, endocarditis, pericarditis, suppurative phlebitis, myocarditis, meningitis and endophthalmitis due to *Candida* species, non-genital mucocutaneous candidosis and genital candidosis

In addition, fluconazole is considered appropriate **prophylaxis** for neutropenic patients particularly if colonised with *Candida tropicalis*, allogeneic haematological stem cell transplant (HSCT) recipients and recipients of liver transplants.

The activity *in vitro* of fluconazole against species of *Candida* is not uniform. The species more frequent associated with human infections include *C. albicans*, *C. parapsilosis* and *C. tropicalis*, which usually exhibit low fluconazole MIC values, but a significant number involve *C. glabrata*, which usually exhibits high MICs. In addition, fluconazole is not indicated for treating any infection caused by *C. krusei*, which is considered inherently resistant to fluconazole. Therefore, every attempt should be made to identify *Candida* to species level.

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

1. Dosage													
	Austria	Denmark	Finland	France	Germany	Greece	Italy	The Netherlands	Norway	Spain	Sweden	Switzerland	UK
Most common dose (mg/day)	400	400	400	400	400	400	400	400	400	400	400	400	400
Maximum dose (mg/day)	800	800	800	800	800	800	800	800	800	800	800	800	800
Available formulations	Capsules, iv	Capsules, iv	Capsules, iv	Capsules, iv	Capsules, iv, oral suspension	Capsules, iv	Capsules, iv	Capsules, iv, oral suspension	Capsules, iv	Capsules, iv	Capsules, iv	Capsules, iv	Capsules, iv

2. MIC distributions and epidemiological cut-off (ECOFF) values																	
Species	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF\leq (mg/L)*
<i>Candida albicans</i>	14	57	275	4039	7062	2857	1112	443	141	157	109	92	249	92	35	1	1
<i>Candida glabrata</i>	2	7	5	14	11	48	110	323	917	1271	1414	556	269	166	75	26	32
<i>Candida krusei</i>	0	0	0	0	0	0	0	0	1	9	50	320	238	61	11	0	128
<i>Candida parapsilosis</i>	7	50	10	78	447	1134	791	328	89	62	44	14	5	2	2	1	2
<i>Candida tropicalis</i>	0	13	22	151	522	928	706	418	112	40	37	14	16	39	4	3	2

*ECOFF, epidemiological cut-off value (mg/L) as defined by EUCAST

3. Breakpoints before harmonisation (mg/L) S< R>			
	DIN	NWGA	CLSI¹
General Breakpoints			
	4 / 16	4 / 32	8 / 16-32 / 64

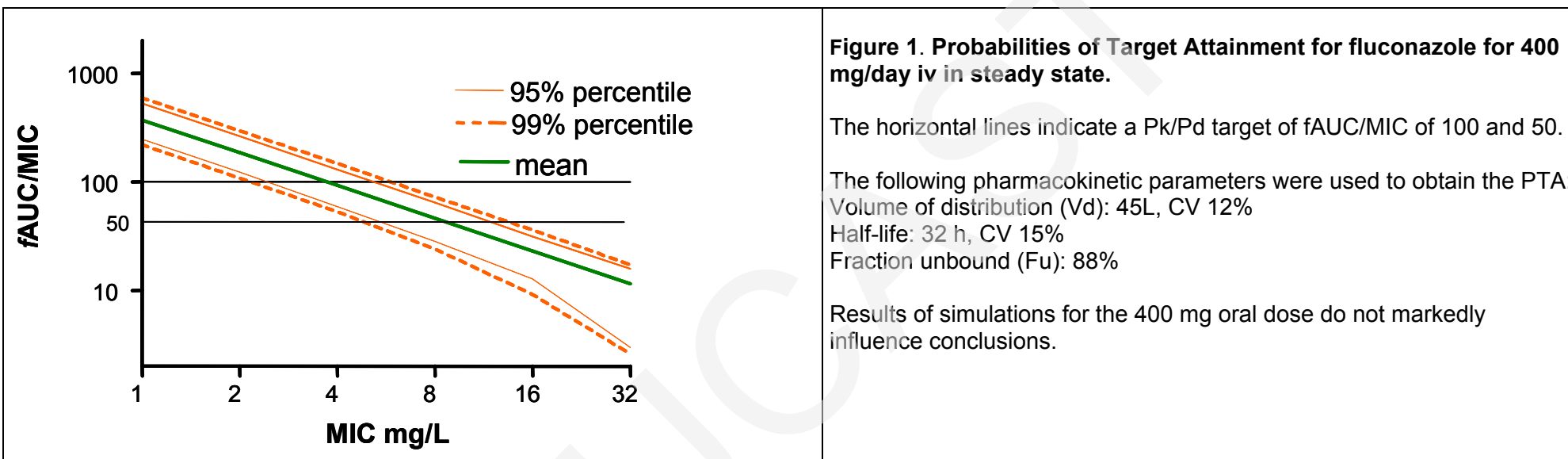
¹CLSI states that isolates for which the MIC of fluconazole is 16-32 mg/L are considered susceptible dependent upon dose (S-DD), on the basis of data indicating a satisfactory clinical response when at least 100 mg/day of fluconazole is given. The novel category "susceptibility dose/delivery dependent" (S-DD) indicates that maximization of dosage and bioavailability are critical to successful therapy. The CLSI breakpoints do not apply to *C. krusei*, which is considered inherently resistant to fluconazole.

4. Pharmacokinetics		
Dosage (mg)	400/day iv	800/day iv
Cmax (mg/L)	18.9-30.6	34
Cmin (mg/L)	21-23 (IV steady state)	
Total body clearance (L/h)		
T $\frac{1}{2}$ (h)	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	<ul style="list-style-type: none"> • Brammer et al., Rev.Infect.Dis. 1990; Suppl 3: S318-S326 • Grant & Clissold, Drugs 1990; 39:877-916 • Goa & Barradell, Drugs1995; 50: 658-690 	

5. Pharmacodynamics				
	<i>Candida</i> spp			
<i>f</i> AUC/MIC for fungistasis	25 – 50			
<i>f</i> AUC/MIC for 2 log drop in 24h	500 – 1000			
<i>f</i> /AUC/MIC from clinical data	100			
Comments	<ul style="list-style-type: none"> The trailing effect and a <i>f</i>AUC/MIC of 500-1000 needed to obtain a 2 log reduction in growth in 24h are derived from <i>in vitro</i> and <i>in vivo</i> data showing the fungistatic nature of fluconazole. Therefore, for invasive candidosis it is recommended that an <i>f</i>AUC/MIC for fungistasis of at least 100 is attained. This target is supported by clinical data showed in table 2 of point 7, in this document. 			
References	<ul style="list-style-type: none"> Grant & Clissold. <i>Drugs</i> 1990; 39: 877-916 Goa & Barradell, <i>Drugs</i> 1995; 50: 658-690 Andes & van Ogtrop, <i>AAC</i> 1999; 43: 2116-2120 Andes, <i>AAC</i> 2003; 47:1179-1186 			

6. Monte Carlo simulations and Pk/Pd breakpoints

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



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 the tables below the dose/MIC is shown. The data were obtained after correlating the clinical outcome with MICs obtained by means of EUCAST methodology. More than 90% of patients respond to treatment irrespective of the dose when the MIC of the yeast was ≤ 2 mg/L (Table 1). When considering only doses >100 mg/day, all patients with isolates with MICs of ≤ 4 mg/L responded to treatment. When the dose/MIC is ≥ 100 , as shown in Table 2, more than 90% of patients respond to treatment. (Rodriguez-Tudela JL et al, Antimicrob Agents Chmother, in press)

Table 1. Correlation of fluconazole MIC with treatment outcome for different fluconazole doses

MIC (mg/L)	% Clinical success (number cured/total) for indicated fluconazole dose						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)	66 (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)	4 (3/64)

Table 2. Correlation of dose/MIC (and their conversions to AUC/MIC¹ and fAUC/MIC² ratios) and clinical outcome for patients with candidemia or oropharyngeal candidiasis (OPC)

Dose/MIC	AUC/MIC	fAUC/MIC	Range of doses administered	Range of MICs (mg/L) of isolates	% Clinical success (n cured/n total)		
					Candidaemia	OPC	All
400-4,800	359-4,678	316- 4,117	100-800	0.12-1.0	92 (102/111)	100 (5/5)	92 (107/116)
150-200	146-189	129-166	100-600	0.5-4.0	100 (3/3)	100 (21/21)	100 (24/24)
100	90	79	100-800	1.0-8.0	100 (4/4)	100 (5/5)	100 (9/9)
50	45	40	100-400	2.0-8.0	33 (1/3)	57 (4/7)	50 (5/10)
25	22	20	100-200	4.0-16.0	50 (1/2)	42 (8/19)	42 (9/21)
12.5	11	10	100-400	8.0-32.0	100 (1/1)	0 (0/34)	3 (1/35)
6.25	6	5	200	32.0	100 (1/1)	0 (0/22)	4 (1/23)
3.13	3	2	100-200	32.0-64.0	0 (0/1)	0 (0/19)	0 (0/20)

¹The values of AUC/MIC were obtained by applying the following equation: $AUC = 0.99 \times Dose - 9.2$

²fAUC/MIC was calculated taking in consideration that the fraction of unbound fluconazole is 88%

8. 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" (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).</p> <p>Non-species-related breakpoints are S≤2 mg/L, R>4 mg/L.</p>						
Species-related breakpoints	<p>The in vitro activity of fluconazole against species of <i>Candida</i> is not uniform. The species most frequently associated with human infections are <i>C. albicans</i>, <i>C. parapsilosis</i> and <i>C. tropicalis</i>. These exhibit MIC values of ≤2 mg/L when without resistance mechanisms to fluconazole.</p> <table border="0"> <tr> <td><i>C. albicans</i></td> <td>S≤2, R>4 mg/L</td> </tr> <tr> <td><i>C. tropicalis</i></td> <td>S≤2, R>4 mg/L</td> </tr> <tr> <td><i>C. parapsilosis</i></td> <td>S≤2, R>4 mg/L</td> </tr> </table>	<i>C. albicans</i>	S≤2, R>4 mg/L	<i>C. tropicalis</i>	S≤2, R>4 mg/L	<i>C. parapsilosis</i>	S≤2, R>4 mg/L
<i>C. albicans</i>	S≤2, R>4 mg/L						
<i>C. tropicalis</i>	S≤2, R>4 mg/L						
<i>C. parapsilosis</i>	S≤2, R>4 mg/L						
Species without breakpoints	<p>A significant number of infections involve <i>C. glabrata</i>, which exhibits fluconazole MICs of 2-32 mg/L when without resistance mechanisms, and <i>C. krusei</i>, which is considered inherently resistant with even higher MIC values, also when without resistance mechanisms. Any reasonable breakpoint would divide wild type <i>C. glabrata</i>, obviating reproducible susceptibility testing. For these reasons, EUCAST-AFST has refrained from giving <i>C. krusei</i> and <i>C. glabrata</i> breakpoints for fluconazole and advise that other drugs be chosen for treating infections caused by these species. As there are few drugs suitable for the treatment of urinary tract infections caused by <i>Candida</i> spp. fluconazole may be a suitable choice for <i>C. glabrata</i> infections regardless of the MIC, as fluconazole is concentrated in the urine. However, this emphasises the need for correct species identification.</p>						
Clinical qualifications	<p>The EUCAST-AFST considers fluconazole appropriate therapy for:</p> <ul style="list-style-type: none"> • 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 gallbladder, pancreas and peritoneum, endocarditis, pericarditis, suppurative phlebitis, myocarditis, meningitis and endophthalmitis due to <i>Candida</i> species • non-genital mucocutaneous candidosis • Genital candidosis 						

	<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 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.
Additional comment	

9. Fluconazole - EUCAST clinical MIC breakpoints

These can be found at <http://www.eucast.org>.

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10. Exceptions noted for individual national committees
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None.

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