EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Rationale for EUCAST clinical breakpoints

Agent	**Itraconazole and *Candida* spp.**

Current version	**1.0**	**26 June 2014**
Previous versions		

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.

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1. Introduction

Itraconazole is a triazole antifungal agent active *in vitro* against *Aspergillus* spp., *Candida* spp., dermatophytes, *Histoplasma* spp., *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Fonsecaea* spp., *Cladosporium* spp., and other dematiaceous fungi, *Blastomyces dermatitidis*, and various other yeasts and fungi. The agent is approved for many indications, but licensed indications vary between European countries.

The activity *in vitro* of itraconazole against species of *Candida* is not uniform. MICs for *C. albicans, C. parapsilosis* and *C. tropicalis* tend to be relatively low, whereas the MICs for *C. krusei* and particularly *C. glabrata* tend to be higher. Therefore, every attempt should be made to identify *Candida* to species level.

For *Candida* spp., itraconazole is mainly used for the treatment of mucosal infections.

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

2. Dosage

	Austria	Belgium	Denmark	Estonia	Germany	Greece	Finland	France	Italy	The Netherlands	Norway	Russia	Spain	Sweden	Turkey	UK
Minimum daily dose (mg/day)	100	100	200	100	200	100	200	200 (for systemic inf)	200	100 superficial 200	100	100	200	Vaginitis 400 Nails 200 Skin 100	200	100
Most common daily dose (mg/day)	200	200	Either 200 or 400 if single day treatment or intermittent treatment	200	200 or 400 (5 mg/kg)	200 or 400	200 or 400	400	200	200	200	400	200	Vaginitis 400 Nails 200 Skin 100	200 or 400	200
Loading dose (mg/day) (when used)	2x200	100-400	None	200	200 x 2 day 1 and 2	200-400 (for invasive disease)	2x200 day 1	600 for 3 days	400 day 1 & 2	400 for 1 or 2 days	400	600/400	400 day 1 & 2	Not used for invasive infection	None	400 day 1 & 2
Maintenance dose (mg/day)	200	100-400	200	200	200/400	100-200	200-400	200	200	100-200	200	400/200	400	Nails 200 Skin 100	200 or 400	200
Most common number of daily doses for which the indicated doses are divided	200-400 for invasive infections	1-2	1-2	1	2	1-2	1-2	1	1 (but 2 for loading)	2	2	2	1 (but 2 for loading)	1-2	1-2	1-2
Maximum daily dose (mg/day)	400	400	400	400	400	400	400	400	400	400	200	600	400	400	400	400
Available formulations	Oral solution; capsules	Capsules, oral solution	Capsules	Capsules	Iv; oral solution; capsules	Iv; oral solution; capsules	Oral solution; capsules	Oral solution; capsules	Iv; oral solution; capsules	iv; oral solution; capsules	Capsules.	Oral solution; capsules	Iv; oral solution; capsules	oral solution; capsules	Iv; oral solution; capsules	Iv; oral solution; capsules

3. MIC distributions 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
Candida albicans[1]				1754	521	221	74	32	14	10	0	0	2	6						0.06
Candida dubliniensis[1]				29	97	13	2	2	0	0	0	0	1	0						0.06
Candida glabrata				5	29	70	185	327	460	336	106	43	71	69						2
Candida guilliermondii				2	2	3	17	54	58	16	2	0	0	1						2
Candida kefyr				10	27	29	10	2	1	0	0	0	0	0						ND
Candida krusei				4	11	27	126	173	83	24	2	1	0	0						1
Candida lusitaniae[1]				19	21	23	12	4	2	0	0	0	1	0						0.125
Candida parapsilosis[1]				190	381	227	89	29	9	2	0	0	0	0						0.125
Candida tropicalis[1]				138	218	129	65	40	12	7	0	1	9	6						0.125
Saccharomyces cerevisiae				1	1	0	3	15	33	9	6	1	0	0						ND

[1]One large dataset was not included as the MIC range was truncated at ≤0.03 mg/L and the MIC for the majority of isolates was ≤0.03 mg/L (1699/1761*C. albicans*, 80/87 *C. dubliniensis*, 23/31 *C. lusitaniae*, 61/133 *C. parapsilosis*, and 96/151 *C. tropicalis* isolates. Hence this dataset was consistent with the distributions from the other data sources.

MIC values were determined using the EUCAST EDEF 7.2 methodology.

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple (8) 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).

4. Breakpoints prior to harmonisation (mg/l) S≤ / R>

	European breakpoints	CLSI
General breakpoint		
		≤ 0.125 / 0.5
Species specific breakpoints:		
		NA

NA = Not available

5. Pharmacokinetics

Dosage (mg)	capsules 200 single dose	oral solution 200 single dose	iv formulation 200 x 2 day 1 & 2 followed by 200 mg daily until day 4	ICU population 200 x 2 day 1 & 2 followed by 200 mg iv daily (itraconazole / hydroxy-itracoazole)
Cmax (mg/L)	0.3-0.5[1]	0.3-0.55[1]	3-6[1]	1.2 ± 0.3 / 0.6 ± 0.2
Cmin (mg/L)			0.5-1	0.37 ± 0.17 / 0.5 ± 0.07
Cav (mg/L)	0.5-2			
Total body clearance/F (L/h)	39.6		16.7	
T ½ (h); Mean (CV %)	22-36	22-36	32.5	
AUC96h (mg*h/L) total drug	4-10	5-15		29.3 ± 6 / NA
Fraction unbound (%)	0.2	0.2	0.2	
Volume of distribution/F (L/kg)	11	11	>700 L	
Comments	• [1]Concentrations determined by bioassay and thus reflect the combined concentration of itraconazole and its metabolite hydroxyl-itraconazole. • Itraconazole bioavailability is around 55% but displays considerable variation on oral administration. Absorption is affected by formulation (optimised by cyclodextrin in the oral solution), gastric pH, prandial state and the timing of dose administration relative to the time of a meal. • Strategies to maximize itraconazole exposure after administration of capsules include administration with or immediately after a meal, with an acid beverage (cola or juice), or in divided doses. The administration of any acid inhibitors should be avoided if possible. • Strategies to maximize itraconazole exposure after administration of oral solution include administration during fasting (30% greater exposure), or in divided doses. The administration of any acid inhibitors should be avoided if possible. • Itraconazole is metabolised to hydroxy-itraconazole which also has antifungal activity. In HPLC determinations these two compounds are measured individually whereas in a bioassay the combined antifungal activity is measured and expressed in itraconazole equivalents. • Itraconazole displays non-linear pharmacokinetics. • Itraconazole undergoes extensive metabolization in the liver and has multiple drug-drug interactions.			

References	• Itraconazole product information : http://www.produktresume.dk/docushare/dsweb/GetRendition/Document-11131/html and http://www.medicines.org.uk/EMC/medicine/7395/SPC/Sporanox+Capsules/ • Poirier JM and Cheymol G. *Clin Pharmacokinet* 1998; 35: 461-73. • Willems L, van der Geest R and de Beule K. *J Clin Pharm Therapeut* 2001; 26: 159-169. • de Beule K and Van Gestel J. *Drugs* 2001; 61 Suppl 1: 27-37. • Barone JA et al. *Antimicrob Agents Chemother* 1998; 42: 1862-65. • Hagihara M. *J Infect Chemother* 2011; 17: 224–230

6. Pharmacodynamics				
*f*AUC/MIC for stasis				
*f*AUC/MIC for 2 log reduction				
*f*AUC/MIC from clinical data				
Comments	• Not available for EUCAST methodology. A single study in a mouse model observed a dose response relationship for strains with MICs (CLSI method) in the 0,016-8 mg/L range and no efficacy against isolates with the highest MICs regardless of the dose used (Uchida et al, 2011). • Cells are left empty when data are not readily available.			
References	• Uchida, K, Shimogawara K, Yamaguchi H. *J Antimicrob Chemother* 2011; 66: 626–634			

7. Monte Carlo simulations and PK/PD breakpoints

Not available.

8. Clinical data

Vaginitis
Itraconazole and fluconazole have been found equally efficacious in several studies and a recent meta-analysis covering six randomised trials and a total of 1092 patients. Most infections involved *C. albicans* and species specific outcome data was not available (Pitsouni E. *Am J Obstet Gynecol* 2008; 198: 153-60).

One clinical study reported species specific outcome data: Urünsak et al (*Mycoses* 2004; 47: 422–427) investigated 52 women with 1 and 4 week clinical and mycological follow up after 200 mg twice on a single day and found the following cure rates at 1 week and 4 weeks: *C. albicans*: 62.5% (25/40) and 95% (38/40), *C. glabrata*: 60% (3/5) and 80% (4/5), *C. kefyr* 100% (5/5) and 100% (5/5), *C.* krusei: 0% (0/2) and 0% (0/2).

Oropharyngeal candidiasis (OPC)
Itraconazole and fluconazole were compared in a prospective randomized, third-party blind, multicentre trial. One hundred and seventy-nine HIV-positive patients with mycologically documented oropharyngeal candidiasis were treated with itraconazole oral solution 200 mg/day for 7 or 14 days, or fluconazole tablets 100 mg/day for 14 days. Severity of disease was scored clinically before treatment and at clinical evaluations on days 3, 7, 14, 21, 35, and 42. Semiquantitative cultures of mouth washings were also obtained on these days. Both 14 day and 7 day regimens of itraconazole oral solution were equivalent to fluconazole for most efficacy parameters. The clinical response rate was 97% after 14 days of itraconazole and 87% after 14 days of fluconazole. Itraconazole oral solution given for 7 days was also equivalent to fluconazole treatment for 14 days. Approximately one half of patients in all three groups relapsed by 1 month after completion of treatment. 96% of the infections involved *C. albicans*. (Graybill JR, et al. *Am J Med* 1998; 104: 33–39).

A similar study comparing itraconazole solution with fluconazole tablets once daily (both at 100-200 mg doses) also found the two compounds equal. For 120 HIV patients, clinical response rates were 94 vs 91%, and mycological response rates were 92 and 78% for itraconazole and fluconazole respectively (Wilcox CM et al. *J Infect Dis* 1997; 176: 227-32).

In a study by Rex et al (*Clin Infect Dis* 1997; 24: 235-47) three hundred and sixteen HIV patients with OPC involving 355 *Candida* isolates (87% *C. albicans*, 9% *C. glabrata*, 2% *C. krusei*, and 2% others) received itraconazole (200 mg/day). MIC determination was by CLSI methodology (with 48 h reading) and a correlation was found between MIC and outcome, with a decreasing response for isolates with an MIC of >0.125 mg/L, or >0.25 mg/L if itraconazole blood levels were >0.5 mg/L. A reanalysis of the Rex dataset performed by EUCAST for the purpose of this Rationale Document used Cart analysis and suggests a CLSI breakpoint for resistance of >0.25 mg/L (MICs for *C. albicans* obtained with the CLSI method are approximately 1-2 twofold dilution steps higher than those with the EUCAST method).

Invasive candidiasis
A non-controlled non-comparative study investigated the efficacy of itraconazole 200 mg x 2 daily iv on day 1 and 2, followed by 200 mg daily. Sixty patients were enrolled and outcome data were presented for 49 patients with proven (63.3%) or presumed (36.7%) invasive candidiasis. Two thirds of the patients were in the ICU. Itraconazole was employed as a first-line agent in 39 patients (79.6%) and as a second-line agent in 10 (20.4%). The improvement ratings of clinical symptoms/findings and the microbiological efficacy rates at the end of the study were 72.4% and 69.6%, respectively, and overall clinical efficacy was higher in the non-ICU setting than in the ICU setting (76.5% vs. 50.0%, respectively) (Takesue Y, et al. *J Infect Chemother* 2012; 18: 515–521).

9. Clinical breakpoints

PK/PD breakpoints	Not available.
Species-related breakpoints	Breakpoints were based on pharmacokinetic data, microbiological data and clinical experience. *C. albicans* S ≤0.06, R > 0.06 mg/L *C. dubliniensis* S ≤0.06, R > 0.06 mg/L *C. lusitaniae* S ≤0.125, R > 0.125 mg/L *C. tropicalis* S ≤0.125, R > 0.125 mg/L *C. parapsilosis* S ≤0.125, R > 0.125 mg/L
Species without breakpoints	*C. glabrata*, *C. guilliermondii*, *C. krusei* and *S. cerevisiae* display higher MICs. There are insufficient clinical data to indicate whether these species are good targets for itraconazole or not. Hence EUCAST has refrained from setting breakpoint for these species.
Clinical qualifications	EUCAST refers to the ESCMID guidelines for treatment of candidiasis.
Dosage	Dosages depend on the clinical indication and vary from a daily dose of 100 mg once daily to 200 mg twice daily and are mainly validated for oro-pharyngeal, oesophageal and vaginal candidiasis.
Additional comment	Itraconazole absorption is affected by the type of formulation, gastric pH, prandial state and the timing of dose administration relative of the time of a meal, and a correlation between itraconazole plasma concentration and outcome has been found in the setting of prophylaxis and of treatment of aspergillosis, but has not explored for *Candida* infections. This suggests a potential role for monitoring itraconazole concentrations in patients with severe infections treated for fungal infection or in patients not responding to therapy.

10. Exceptions noted for individual national committees

None.