EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Anidulafungin	Rationale for the EUCAST clinical breakpoints, version 1.0	19th November 2010

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: Rationale for the clinical breakpoints, version 1.0, 2010. http://www.eucast.org.

Introduction

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

It is considered appropriate therapy for invasive candidiasis in adult non-neutropenic patients. Anidulafungin susceptibility is primarily investigated in patients with candidaemia and in only a small number of 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. parapsilosis, C. tropicalis, C. glabrata* and *C. krusei*, of which all but *C. parapsilosis* exhibit low anidulafungin MIC values. The underlying reason for the higher MICs for *C. parapsilosis* (and *C. guilliermondii*) is the presence of a naturally occurring amino-acid substitution at a hot spot region of the target enzyme gene, known to confer resistance in other species. Therefore species identification is important and every attempt should be made to identify *Candida* to species level.

A number of reports on animal model studies have demonstrated cross resistance between the three currently available echinocandins (anidulafungin, caspofungin and micafungin) for isolates with hot spot mutations in the target gene.

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

1. Dosage

	Austria, Denmark, Finland, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, Switzerland, Turkey, UK
Most common dose	200 mg/kg on day 1, then 100 mg/kg/day
Maximum dose schedule	200 mg/kg/day
Available formulations	iv

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

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF*
Candida albicans **	284	360	208	77	16	6	4	1	1	0	0	0	0	0	0	1	0	0	0	0.03
*Candida glabrata***	55	38	60	149	62	8	6	8	2	2	0	0	2	0	0	0	0	0	0	0.06
*Candida krusei***	2	1	12	21	7	12	2	3	0	0	0	0	0	0	0	0	0	0	0	0.06
Candida parapsilosis	0	3	1	0	4	6	2	36	78	171	96	13	7	0	0	2	0	0	0	4
Candida tropicalis **	18	19	12	30	22	4	4	1	0	0	0	0	0	0	0	0	0	0	0	0.06
Candida guilliermondii	0	0	0	0	0	1	0	2	5	17	6	1	0	0	0	0	0	0	0	ND

*Tentative ECOFF values as few data sets are available.
** Data from truncated datasets also supported the ECOFFs. For *C. albicans* 851/863 (98.6%) MICs were ≤ 0.03 mg/L (three data sets). For *C. glabrata* 233/237 (98.3%) MICs were ≤ 0.06 mg/L (two data sets). For *C. tropicalis* 163/163 (100%) MICs were ≤ 0.06 mg/L (three data sets). For *C. krusei* 65/65 (100%) MICs were ≤ 0.06 mg/L (one data set).

MIC values were determined with EUCAST and Etest methodology. MIC values determined by the CLSI method are typically two dilution steps higher than EUCAST values, particularly for the species with lower MIC values (Pfaller MA et al. *J Clin Microbiol* 2010; 48: 52-6). MICs determined with the CLSI method are not included.

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>		
	European breakpoints	**CLSI**
General breakpoint		
	NA	2/- (tentative)
Species specific breakpoints:		
	NA	NA

NA = Not available

4. Pharmacokinetics

Dosage (mg)	100 mg single dose[1]	200/100 mg daily[2]	200/100 mg daily[3]	
Cmax (mg/L)	3.63	5	7	
Cmin (mg/L)		3	3	
Total body clearance (L/h)	0.91	0.95	1.1-1.2	
T ½ (h), mean (range)	27.7	25.9	Approximately 24	
AUC24h (mg.h/L)			110	
Fraction unbound (%)			≤1%	
Volume of distribution (L/kG)	32.6	33.2	30-50	
Comments	• Two values are given where references differ. Cells are left empty when data are not readily available.			
References	• [1]Damle et al. *AAC* 2009; 53: 1149-56 • [2]Dowell et al. *J Clin Pharm* 2004; 44: 590-8 • [3]Ecalta SPC at http://www.ema.europa.eu/humandocs/Humans/EPAR/ecalta/ecalta.htm			

5. Pharmacodynamics				
*f*AUC/MIC for stasis				
*f*AUC/MIC for 2 log reduction				
*f*AUC/MIC from clinical data				
Comments	• Pharmacodynamic parameters for anidulafungin have not been determined using EUCAST or Etest MIC methods. • Cells are left empty when data are not readily available.			
References				

6. Monte Carlo simulations and Pk/Pd breakpoints

Not available for EUCAST data.

7. Clinical data

Invasive candidiasis:

In a randomized, double-blind, non-inferiority trial of treatment for invasive candidiasis (Reboli et al. *N Engl J Med* 2007; 356: 2472-82) anidulafungin was compared with fluconazole. All patients could receive oral fluconazole after 10 days of intravenous anidulafungin 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).

Oesophageal candidiasis:

In a randomized, double-blind, double-dummy study (Krause et al. *Clin Infect Dis* 2004; 39: 770-5) 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 (Vazquez et al. *J Acquir Immune Defic Syndr* 2008; 48: 304-9) 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 done 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 (Pfaller MA et al. *J Clin Microbiol* 2010; 48: 52-6). Therefore, the data sets relating MIC to clinical outcome based on CLSI MICs cannot be translated into relationships for EUCAST MICs.

8. Clinical breakpoints	
Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.
Species-related breakpoints	Breakpoints were based on Pk data, microbiological data and clinical experience. *C. albicans,* S ≤0.03, R >0.03 mg/L *C. glabrata,* S ≤0.06, R >0.06 mg/L *C. tropicalis,* S ≤0.06, R >0.06 mg/L *C. krusei,* S ≤0.06, R >0.06 mg/L
Species without breakpoints	MICs for *C. guilliermondii* are approximately 8 twofold dilutions higher than those for *C. albicans.* In addition, the small number of cases in the clinical trials means that there is insufficient evidence to indicate whether the wild-type population of this pathogen can be considered susceptible to anidulafungin. Hence, for *C. guilliermondii* there is insufficient evidence (IE) to set breakpoints. *C. parapsilosis* was considered a poor target for anidulafungin therapy and for that reason did not receive breakpoints.
Clinical qualifications	The EUCAST-AFST considers anidulafungin appropriate therapy for invasive candidiasis in adult non-neutropenic patients. Anidulafungin susceptibility is primarily investigated in patients with candidaemia and only in a smaller number of patients with deep-seeded organ infection and abscesses.
Dosage	Breakpoints apply to an iv dose of 200 mg/kg on day 1, then 100 mg/kg/day.

Additional comment	Isolates with mutations in the hot spot regions of the target gene have been associated with clinical failures or breakthrough infections. Most clinical cases involve caspofungin treatment. However, in animal experiments these mutations confer cross resistance to all three echinocandins and therefore such isolates are classified as echinocandin resistant until further clinical experience are obtained concerning anidulafungin. The MICs of isolates with mutations in the hot spot regions of the target gene are as follows: *C. albicans*: >0.03 mg/L; *C. glabrata*: >0.06 mg/L; *C. tropicalis*: >0.06 mg/L and *C. krusei*: >0.03 mg/L (Arendrup et al. *AAC* 2010; 54: 426–439). As there is cross resistance between the three echinocandins, isolates categorised as anidulafungin susceptible can be regarded as susceptible to caspofungin and micafungin until drug specific breakpoints are available for caspofungin and micafungin.

9. EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None