EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Voriconazole	Rationale for the EUCAST clinical breakpoints, version 2.0	20 March 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. Voriconazole: Rationale for the clinical breakpoints, version 2.0, 2010. http://www.eucast.org.

Introduction

Voriconazole is an azole antifungal agent active against *Candida* species, *Cryptococcus* species, *Aspergillus species, Scedosporium apiospermum* and other less common pathogens.

The approved indications in Europe are the following: (i) Treatment of invasive aspergillosis; (ii) candidaemia in non-neutropenic patients; (iii) serious invasive candidosis due to fluconazole-resistant *Candida* species (including *C. krusei*); (iv) serious invasive fungal disease caused by *Scedosporium* spp. and *Fusarium* spp.

The activity *in vitro* of voriconazole against species of *Candida* is not uniform. The species most frequently involved in causing human infections include *C. albicans, C. parapsilosis, C. tropicalis, C. glabrata* and *C. krusei,* all of which usually exhibit MICs of less than 1 mg/L for voriconazole. However the MICs of voriconazole for fluconazole-resistant isolates are proportionally higher than are those of fluconazole-susceptible isolates. 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 voriconazole for *Candida* species. The tentative breakpoints set two years ago are confirmed except that *C. krusei* is listed as “insufficient evidence (IE)” rather than “inappropriate target (-)”.

1. Dosage

		Austria Finland Germany	France Greece Norway	Denmark Italy The Netherlands Spain Sweden Switzerland	Turkey	UK
Most common dose						
IV (mg/kg/day)	1st day	12	12	12	12	12
	2nd day	8	8	8	8	8
Oral (mg/day in >40 kg)	1st day	800	800	800	800	800
	2nd day	400	400	400	400	400
Oral (mg/day in <40 kg)	1st day	400	400	400	400	400
	2nd day	200	200	200	200	200
Maximum dose						
IV (mg/kg/day)			NR	NR	NR	
Oral (mg/day)			>40 kg = 600 <40 kg = 300	NR	>40 kg: 600 <40 kg: 300	NR but normally 600
Available formulations		Tablets, oral suspension, iv	Tablets, oral suspension, iv	Tablets, oral suspension, iv	Tablets, IV	Tablets, oral suspension, iv

NR = No recommendation

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	ECOFF≤ (mg/L)
Candida albicans	50	996	5139	5235	1107	530	207	106	63	42	18	13	18	22	78	6	0.125
Candida glabrata	0	5	26	63	192	534	1218	1244	781	341	196	139	69	20	2	6	1
Candida krusei	0	0	2	10	23	29	152	489	424	119	30	10	1	0	0	0	1
Candida parapsilosis	0	6	287	1326	510	197	123	77	23	16	3	2	1	0	0	0	0.125
Candida tropicalis	0	28	133	602	934	732	274	113	51	32	8	2	10	20	16	3	0.125

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods and are based on MIC values determined with EUCAST, CLSI and Etest methodology. 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.

3. Breakpoints prior to harmonisation (mg/L) S≤/R>		
	European breakpoints	**CLSI[1]**
General breakpoints		
	NA	1/2
Species related breakpoints		
	NA	NA

NA = Not available

[1]CLSI breakpoints converted to European terminology. CLSI states that isolates exhibiting a MIC of voriconazole of 2 mg/L are considered susceptible dependent upon dose (S-DD). CLSI takes into account the nonlinear pharmacokinetics and the dosing flexibility of voriconazole. The S-DD category implies that an infection caused by an isolate with such a MIC may be appropriately treated in body sites where the drug is physiologically concentrated or when a high dose of the drug can be used. In addition, this category may also serve as a “buffer zone” to prevent small, uncontrolled technical factors.

4. Pharmacokinetics		
Dosage	6 mg/kg iv x 2 on day 1; maintenance dose 4 mg/kg x 2 Steady state in patients with venous haemofiltration	400 mg oral x 2 on day 1; maintenance dose 200 mg x 2
Cmax (mg/L)	5.9 ± 2.9	2-2.3
Cmin (mg/L)	1.1 ± 0.3	NA
Total body clearance (L/h)	12.9 ± 6.7	19.9
T ½ (h), mean (range)	6	6
AUC_{24h} (mg.h/L)	44.8	18-22
Fraction unbound (%)	42	42
Volume of distribution (L/kg)	4.6	NA
Comments	NA – not available. Pks of voriconazole are non-linear and are likely due to saturation of its metabolism with respect to dose. The variability in plasma concentrations and systemic exposure varies >100-fold between subjects (based on trough concentrations), depending partly on the respective genotype of the hepatic cytochrome P450. CYP2C19 exhibits genetic polymorphism resulting in an approximately 4-fold higher exposure for poor metabolisers than for extensive metabolisers. The coefficient of variation of the AUC has been estimated to be 74-100%.	
References	Theuretzbacher et al. Clin Pharmacokinet. 2006; 45: 649-663 Purkins et al. AAC. 2002; 46: 2546-2553 Fuhrmann et al. JAC. 2007; 60: 1085-1090 Denning et al. Clin Infect Dis 2002; 34: 563-571	

5. Pharmacodynamics				
	Candida spp			
*f*AUC/MIC for achieving ED50[1]	24 ± 17			
*f*AUC/MIC for 2 log reduction in 24 h	75-100			
*f*AUC/MIC from clinical data (CART)				
Comments	• [1] *f*AUC/MIC for achieving ED50 is the mean *f*AUC/MIC equivalent to ED50 in mg/kg/24h. • ED50 is the dose required to achieve 50% of Emax after 24 h of treatment. • Emax is the change in the Log_{10} number of CFU per kidney compared with the value of untreated controls after 24 h of treatment. • *f*AUC/MIC for achieving ED50 gave a reduction of around 1.5 log_{10} CFU per kidney after 24 h of treatment.			
References	• Andes et al. Antimicrob Agents Chemother 2003; 47: 3165-3169			

6. Monte Carlo simulations and Pk/Pd breakpoints

Probabilities of Target Attainment (PTA) for 4 mg/kg x 2 iv in steady state are shown in figure 1.

Probabilities of Target Attainment for 200 mg x 2 oral in steady state are shown in figure 2.

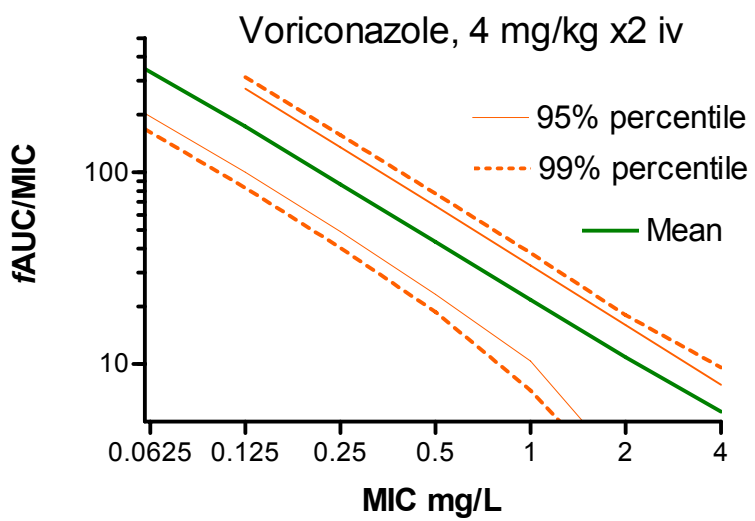

Figure 1. Probabilities of Target Attainment for voriconazole at 4 mg/kg x 2 iv in steady state.

The following pharmacokinetic parameters were used to obtain the PTA:
Area under curve (AUC) 50 mg·h/L, CV 25%
Fraction unbound (Fu): 42%

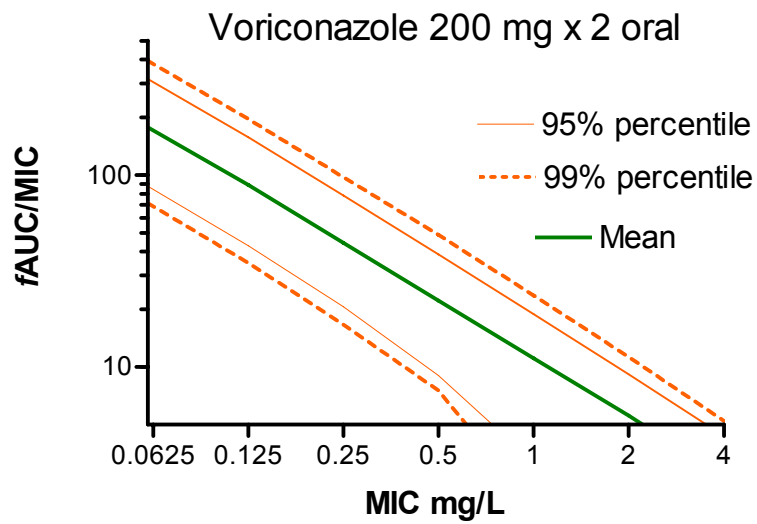

Figure 2. Probabilities of Target Attainment for voriconazole at 200 mg x 2 oral in steady state.

The following pharmacokinetic parameters were used to obtain the PTA:
Area under curve (AUC): 25 mg·h/L, CV 30%
Fraction unbound: 42%

7. Clinical data

Clinical data have been obtained from studies 608 (Global Candidemia Study), 603 (Empirical Therapy Study), 309/604 (Global Rare and Refractory Studies), 301 (Compassionate Use Protocol), and 606 (Emergency Use Protocol-U.S. and Canada).

Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 h for the first 24 h, followed by either 3 mg/kg (studies 603 and 608) or 4 mg/kg every 12 h for 3 days, after which patients were given 200 mg oral every 12h. If oral therapy was administered initially, a loading dose of 400 mg every 12 h on day 1 was followed by a maintenance dose of 200 mg twice daily thereafter. The response to voriconazole therapy was determined by the investigator at the end of therapy as either cure, improvement, which were deemed a success or failure. Clinical outcomes at the end of therapy were compared with the MIC of voriconazole for each *Candida* isolated at baseline, i.e. before treatment. MICs were determined using CLSI M27 A2 methodology.

Geometric mean MICs and global response for different *Candida* species were as follows:

Species	No. isolates	Geometric mean MIC (mg/L)	% response
C. albicans	96	0.0164	72
C. tropicalis	51	0.1283	73
C. glabrata	47	0.7937	55
C. parapsilosis	34	0.0266	85
Candida spp	12	0.0712	92
C. krusei	9	0.3650	78

The response was above 72% for infections caused by every species except *C. glabrata* where the percentage response was only 55%. Geometric MICs were below 0.25 mg/L except for *C. glabrata* and *C. krusei.* CART analysis of response versus MIC or Log_2MIC yielded an MIC value that allowed discrimination between successes and failures. However, the statistical support for this classification tree was limited as the relative error for the best tree was 0.78, the relative risk was 1.09 and the area under ROC curve was 0.6 with a true positive rate of 78% but a false positive rate exceeding 50%.
CART analysis was made separately for infections due to *C. glabrata* because of the lower response rate. CART analysis of outcome versus MIC was unable to produce an interpretable classification tree of MIC values versus successes and failures.

Reference: Pfaller et al. JCM. 2006; 44: 819-826

In summary, the data at hand support breakpoints that will categorise wild type *Candida albicans*, *C. tropicalis* and *C. parapsilosis* susceptible to voriconazole. However, beyond that there is poor statistical support for any clinical correlation between outcome and MIC.

8. Clinical breakpoints	
Non-species-related breakpoints	Non-species related breakpoints are determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes. In the case of voriconazole, the pharmacokinetics are variable and clinical data for species other than C. *albicans, C. parapsilosis* and *C. tropicalis* and for isolates with higher MICs are scarce. EUCAST has therefore refrained from determining non-species related breakpoints for voriconazole.
Species-related breakpoints	A clinical response of 76% was achieved in infections caused by the species listed below when MICs were lower than or equal to the epidemiological cut-offs. Therefore, we considered wild type populations of *C. albicans, C. tropicalis and C. parapsilosis* as susceptible. There is not enough information available for the response to voriconazole of infections caused by *Candida* isolates with higher MICs. Monte Carlo simulations showed that a target attainment of 24 would encompass more than 99% of the population for an MIC of 0.125 mg/L. *C. albicans* S≤ 0.125 mg/L, R>0.125 *C. tropicalis* S≤ 0.125 mg/L, R>0.125 *C. parapsilosis* S≤ 0.125 mg/L, R>0.125 Strains with MIC values above the S/I breakpoint are rare. The identification and antimicrobial susceptibility testing of any such isolate must be repeated and, if the result is confirmed, the isolate should be sent to a reference laboratory. Isolates with an MIC above the current resistant breakpoint should be reported resistant until evidence has accumulated regarding the clinical response of infections due to such isolates.
Species without breakpoints	A 21% lower response to voriconazole in invasive candidosis caused by *C glabrata* has been shown in clinical studies when compared to the response in infections caused by *C. albicans, C. parapsilosis* and *C. tropicalis.* CART analysis of outcome versus MIC did not find higher MICs to be the variable causing this reduced response so higher MICs were not the explanation for the lower response. Consequently, there is currently insufficient evidence to set clinical breakpoints for *C. glabrata.* The apparent clinical response in infections caused by *C. krusei* is similar to that in infections caused by *C. albicans, C. parapsilosis* and *C. tropicalis.* However, as there were only 9 cases available for analysis, there is currently insufficient evidence to set clinical breakpoints for *C. krusei*.
Clinical qualifications	The EUCAST-AFST considers voriconazole appropriate therapy for the following *Candida* infections when caused by wild type *C. albicans*, *C. tropicalis* and *C. parapsilosis*: • Candidaemia in non-neutropenic patients • Invasive candidosis • Oesophageal candidosis

Dosage	Breakpoints apply to: (i) an intravenous dose of 12 mg/kg on day 1 and then 8 mg/kg/day (ii) an oral dose of 800 mg on day 1 and then 400 mg/day for people weighing > 40 kg, and; (iii) an oral dose of 400 on day 1 and then 200 mg/day for people weighing <40 kg.
Additional comment	The pharmacokinetics of voriconazole are highly variable. Although, limited information is available, it has been shown that there is a decrease in the response of patients when voriconazole trough blood levels are below 1 mg/L. Conversely, voriconazole trough blood levels above 5.5 mg/L have been associated with an increase in toxicity (Pascual et al. Clin Infect Dis 2008; 46:201-211). Others report a favourable response when random voriconazole blood concentrations exceed 2.05 mg/L (Smith et al. Antimicrob Agents Chemother 2006; 50: 1570-1572).This suggests a potential role for monitoring voriconazole blood concentrations, though there are not enough data to show whether there is a better response when voriconazole trough levels are above 1 mg/L. The EUCAST AFST will review breakpoints for voriconazole when there are more data available for *Candida* species which were not assigned breakpoints during the present review, when there are clinical data for *Candida* isolates with MIC values outside the wild type distribution or when there are data to more closely define therapeutic and toxic levels of voriconazole.

9. Voriconazole - EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None