EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

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

Introduction

Posaconazole is a triazole antifungal agent active in vitro against *Candida* spp. and *Cryptococcus* spp. as well as *Aspergillus* spp. and certain other moulds. The drug is approved for the following indications:

i) Refractory invasive fungal diseases: invasive aspergillosis, fusariosis, chromoblastomycosis, coccidioidomycosis and mycetoma.
ii) First-line therapy for the treatment of oropharyngeal candidiasis of patients who have severe disease or who are immunocompromised, for whom a response to topical therapy is expected to be poor.
iii) The prophylaxis of invasive fungal disease of patients receiving remission-induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes as well as for hematopoietic stem cell transplant recipients with GvHD.

The species most frequently involved in causing human infections include *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Candida glabrata* and *Candida krusei*. The activity in vitro of posaconazole against species of *Candida* is not uniform. However, the MICs of posaconazole for fluconazole resistant isolates are proportionally higher than are those for fluconazole susceptible isolates. Therefore, every attempt should be made to identify *Candida* isolates to species level.

The European Committee on Antimicrobial susceptibility Testing - Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST) has determined breakpoints for posaconazole against *Candida* spp. These breakpoints are tentative and will be revised after two years.

1. Dosage

	Austria, Denmark, Finland, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, Switzerland, Turkey, UK
Most common dose	In adults, 400 mg (10 mL) x 2. Refractory invasive fungal disease or intolerance, 400 mg (10 mL) x 2. If unable to eat or take a food supplement 200 mg (5 mL) x 4. Oropharyngeal candidiasis, loading dose 200 mg (5 mL) on day 1, then 100 mg (2.5 mL) x 1. Prophylaxis against invasive fungal diseases, 200 mg (5 mL) x 3.
Maximum dose schedule	400 mg (10 mL) x 2 or 200 mg (5 mL) x 4
Available formulations	oral

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	0	0	167	1520	763	347	70	32	18	4	0	2	7	7	0	0	0	0	0	0.064
Candida glabrata	0	0	2	4	11	71	133	152	122	54	23	22	21	1	11	0	0	0	0	1
Candida guilliermondii	0	0	0	2	9	31	21	6	2	0	0	0	0	2	0	0	0	0	0	0.25
Candida krusei	0	0	0	0	14	51	63	31	4	0	0	0	0	0	0	0	0	0	0	0.5
Candida parapsilosis	0	0	20	444	162	15	1	2	1	0	0	1	0	0	0	0	0	0	0	0.064
Candida tropicalis	0	0	7	217	59	14	9	6	1	1	7	8	3	5	0	0	0	0	0	0.064

The table includes MIC distributions available at the time breakpoints were set. They represent combined distributions from multiple 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 breakpoints:		
	NA	NA
Species specific breakpoints:		
	NA	NA

NA = Not available

4. Pharmacokinetics

	Neutropenic patients receiving cytotoxic chemotherapy for AML or MDS(n=215)	Febrile neutropenic patients or patients with refractory invasive fungal diseases (n=23)		
Dosage (mg)	200 mg x 3	400 mg x 2		
Cmax (mg/L)				
Cmin (mg/L)				
Cav (mg/L); Mean (CV %) [Range]	0.58 (65) [0.09 - 2.20]	0.72 (86) [0.01 - 2.26]		
Total body clearance/F (L/h); Mean (CV %) [Range]	51.2 (65) [10.7 – 146]	76.1 (78) [14.9 – 256]		
T ½ (h); Mean (CV %) [Range]	37.2 (39) [19.1 – 148]	31.7 (42) [12.4 – 67.3]		
AUC24h (ng.h/mL) total drug; Mean (CV %) [Range]	15,900 (62) [4100 – 56100]	9093 (80) [1564 – 26794]		
Fraction unbound (%)	2	2		
Volume of distribution/F (L/kG); Mean (CV %) [Range]	2425 (39) [828 – 5702]	3088 (84) [407 – 13140]		
Comments	• Posaconazole absorption is affected by gastric pH, prandial state and the timing of dose administration relative to the time of a meal. Strategies to maximize posaconazole exposure include administration with or after a high-fat meal, with any meal or nutritional supplement with an acid beverage, or in divided doses. The administration of pump inhibitors should be avoided if possible. • Cells are left empty when data are not readily available.			
References	• Posaconazole product information (http://www.spfiles.com/pinoxafil.pdf) • Krishna et al. *AAC* 2009: 53 ; 958-966			

5. Pharmacodynamics				
*f*AUC/MIC for stasis				
*f*AUC/MIC for 2 log reduction				
*f*AUC/MIC from clinical data				
Comments	• Cells are left empty when data are not readily available.			
References				

6. Monte Carlo simulations and Pk/Pd breakpoints

Not available for EUCAST data because there is no clear Pk/Pd target defined.

7. Clinical data

Oropharyngeal and oesophageal candidosis:
Clinical data was collated from four clinical trials involving a total of 506 subjects:
(i) C/I97-330: phase 3 open-label trial for HIV-positive subjects with refractory OPC/EC, dose 400 mg x 4 or x2 for up to 4 weeks;
(ii) C/I97-331: phase 3 comparative study in HIV-positive subjects with OPC, dose of 200 mg x 1 on day one followed by 100 mg x 4 days 2-14;
(iii) P00298: phase 3 open-label trial in HIV-positive subjects with refractory OPC/EC, dose 400 mg x 2 for up to 15 months;
(iv) C/I96-209: phase 2 dose finding comparative study in HIV-positive subjects with OPC, dose of 400 mg x 2 on day 1 and then 100, 200 or 400 mg capsules x 4 days 2-14.
The data set included 488 *C. albicans*, 11 *C. glabrata*, 4 *C. krusei* and 3 *C. tropicalis*. MICs were determined by a reference laboratory. There were 448 (88.5%) successes and 58 (11.5%) failures. For *C. albicans* the rate of response was 89.3%.

Correlation of in vitro MIC data with clinical outcome has not been done as data sets including MICs determined by EUCAST methods are not available. However, EUCAST-AFST take into consideration that clinical information is only relevant for *C. albicans* because the numbers of cases for other common human pathogen yeast species are very small.

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. Clinical information indicates that the wild type population of *C. albicans* is susceptible to posaconazole. Although there is inadequate clinical information on outcome for wild type populations of *C. parapsilosis* and *C. tropicalis*, the MIC distributions are similar to that obtained for *C. albicans.* Therefore, EUCAST AFST considers wild type populations of *C. parapsilosis* and *C. tropicalis* as susceptible to posaconazole. *C. albicans* S ≤0.06, R >0.06 mg/L *C. tropicalis* S ≤0.06, R >0.06 mg/L *C.parapsilosis* S ≤0.06, R >0.06 mg/L Isolates of *C. albicans, C. tropicalis* and *C. parapsilosis* with MICs above these values 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	Epidemiological cut-off values for *C. glabrata, C. guilliermondii* and *C. krusei,* are 1 mg/L, 0.25 mg/L and 0. 5 mg/L respectively, 2-4 twofold dilutions higher than those for *C. albicans, C. parapsilosis* and *C. tropicalis.* In addition, the small number of cases in the clinical trials means that there is insufficient evidence to indicate whether the wild-type populations of these pathogens can be considered as susceptible to posaconazole. Hence, for *C. glabrata, C. guilliermondii* and *C. krusei* there is insufficient evidence (IE) to set breakpoints.
Clinical qualifications	The EUCAST AFST considers posaconazole appropriate therapy for the following *Candida* infections when caused by wild type *C. albicans*, *C. tropicalis* and *C. parapsilosis*: • first-line therapy for the treatment of oropharyngeal candidiasis • the prophylaxis of invasive fungal disease of patients receiving remission-induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes as well as for hematopoietic stem cell transplant recipients with GvHD
Dosage	The EUCAST breakpoints apply to licensed dosing of 100 mg x 1, 200 mg x 3, 200 mg x 4 and 400 mg x 2.

Additional comment	Posaconazole absorption is affected by gastric pH, prandial state and the timing of dose administration relative of the time of a meal, and a correlation between posaconazole plasma concentration and outcome has been found (Krishna et al. *AAC* 2009; 53: 958-966). This suggests a potential role for monitoring posaconazole concentrations in patients treated for fungal infection. The EUCAST AFST will review breakpoints for posaconazole when more data are 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 define more closely therapeutic levels of posaconazole.

9. EUCAST clinical MIC breakpoints

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

10. Exceptions noted for individual national committees

None