EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Rationale for EUCAST clinical breakpoints

Agent	**Isavuconazole**

Current version	**1.0**	**19 October 2015**
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 documents
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. Isavuconazole and *Aspergillus* spp.: Rationale for the clinical breakpoints, version 1.0, 2015. http://www.eucast.org.

1. Introduction

Isavuconazole is a triazole antifungal agent with broad-spectrum in vitro activity against *Aspergillus* spp., and other medically important fungal pathogens. It is available for i.v. and oral administration as a water soluble prodrug (isavuconazonium sulphate). It is approved for the following indications in adults

- invasive aspergillosis
- mucormycosis in patients for whom amphotericin B is inappropriate

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

The mould species most frequently causing human infections include *Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus* and *Aspergillus niger*. The *in vitro* activity of isavuconazole against these species of *Aspergillus* is reasonably uniform, although *A. niger* seems somewhat less susceptible (as with other triazole agents). Noticeably, acquired resistance has been reported, even among *A. fumigatus* isolates obtained from triazole naive patients (hence routine susceptibility testing is of utmost importance). *A. fumigatus* is a species complex including rarer sibling species that may exhibit notable differences in their intrinsic susceptibility to antifungal agents. This is also true for several other species although susceptibility differences within these species complexes are less well characterised.

2. Dosage

	European Union
Standard dose schedule	200 mg three times daily the first 2 days (a total of 6 times), then 200 mg daily (iv or oral)
Maximum dose schedule	200 mg/day
Available formulations	IV, oral

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

Organism	0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	>512	ECOFF
Aspergillus flavus	0	0	0	0	0	0	1	5	44	285	96	3	0	0	0	0	0	0	0	2
Aspergillus fumigatus	0	0	0	0	0	1	2	21	199	174	12	9	5	3	0	0	0	0	0	2
Aspergillus nidulans	0	0	0	0	1	19	95	36	5	0	0	0	0	0	0	0	0	0	0	0.25
Aspergillus niger	0	0	0	0	0	0	0	3	8	53	118	35	7	0	0	0	0	0	0	4
Aspergillus terreus	0	0	0	0	0	1	8	83	165	75	9	1	7*	0	0	0	0	0	0	1

* All 7 *A. terreus* isolates with an isavuconazole MIC of 8 harboured a CYP51A target gene hot spot mutation M217I known to confer MIC elevation to other azoles.

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. Some combined distributions may include distributions truncated at concentrations below 512 mg/L.

4. Breakpoints prior to harmonisation (mg/L) S≤ / R>		
	European breakpoints	**CLSI**
General breakpoints:		
	NA	NA
Species specific breakpoints:		
	NA	NA

NA = Not available

5. Pharmacokinetics

Dosage (mg)	200 mg x 1 oral (37 healthy subjects)[a]	400/200/200 d1, 200x2 d2, 200 mg x 1 iv (8 patients on Day 7)[b]	200x3 for 2 d, 200 mg daily oral or iv (232 patients)[c]
Cmax (mg/L) (mean (range))	7.5±1.89	3.6±1.0	
Cmin (mg/L)			3.91±1.91
Total body clearance (L/h)	2.5-3.5 L/h		2.4±1.03
T ½ (h), mean (range)	100 h (range 50-150 h)		
AUC_{24h} (mg.h/L) + SD	121±36	60.1±22.3	97.9 ± 57.2
Fraction unbound (%)	1%		
Volume of distribution (L)	> 400 L		347±152 L
Comments	• Oral absorption is 98% • Pharmacokinetic data correspond to steady state which is reached on day 14 unless otherwise stated. • Cells are left empty when data are not available.		
References	[a] Isavuconazole product information. EMA document (http://www.ema.europa.eu/ema/) [b] O. Cornely et al. Antimicrob Agents Chemother.2015;59(4):2078-2085 [c] A. Desai et al. (A-697) 54th Interscience Conference for Antimicrobial Agents and Chemotherapy 2014, Washington, DC, USA		

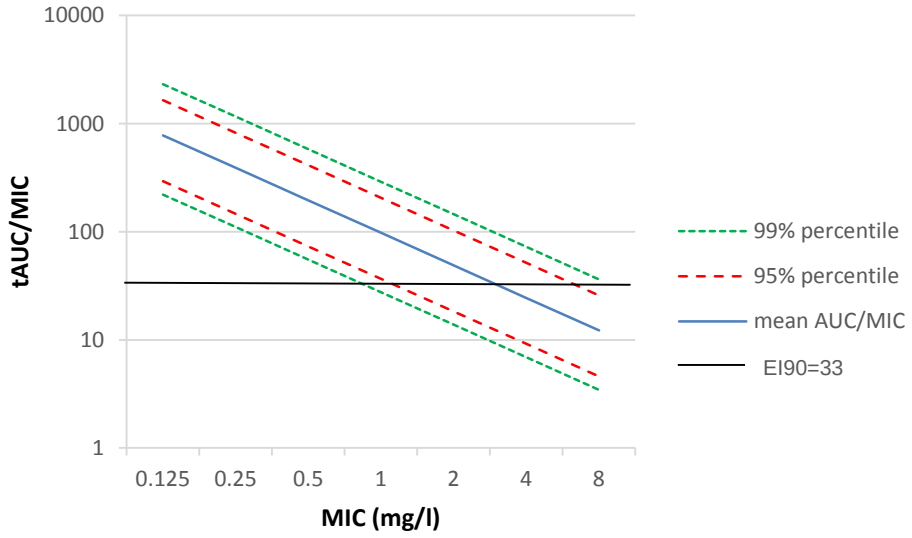
6. Pharmacodynamics				
Animal data for *A.fumigatus*				
Total AUC/MIC for achieving EI50/90	25/33[1]			
Clinical Data				
Comments	• [1] In a non-neutropenic murine model of disseminated aspergillosis, the total AUC/MIC associated with 50% and 90% survival was 24.7 and 33.4 which correspond to AUC/MICs of 25 and 33, respectively (Seyedmousavi et al AAC 2015). • A neutropenic animal model of pulmonary aspergillosis using PCR conidia equivalents in lung homogenates has suggested a stasis endpoint was achieved for all isolates with a CLSI MIC of<1 mg/L and 1-log10 killing in all isolates with a CLSI MIC of <0.5 mg/L, regardless of the presence or absence of the cyp51 mutation. The static-dose range was 65 to 617 mg/kg/12 h. The corresponding median free-drug AUC/CLSI-MIC ratio was near 5. The 1-log10 killing dose range was 147 to 455 mg/kg/12 h, and the corresponding median free-drug AUC/CLSI-MIC ratio was 11.1. MICs obtained by the CLSI method is in general 1-step lower than those obtained by the EUCAST method. (Lepak et al 2013).			
References	• Seyedmousavi et al AAC 2015; 59: 2855-66. • Lepak et al. AAC 2013: 57; 6284-9.			

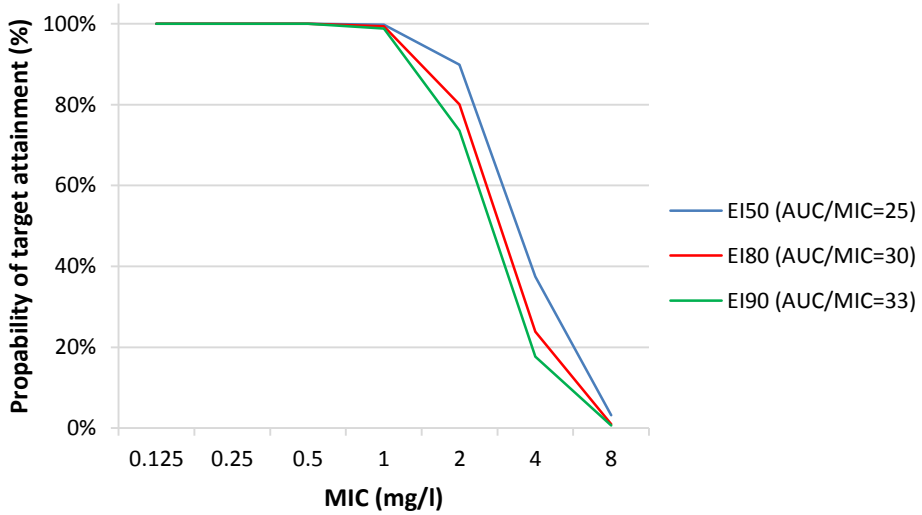
7. Monte Carlo simulations and PK/PD breakpoints

Total AUC/MIC by MIC following isavuconazole 200 mg t.i.d. x 48h followed by 200 mg qd. Mean $AUC_{0\text{-}24}$ ±SD = 97.9 ± 57.2

tAUC/MIC plot for *A. fumigatus* (Left diagram): Monte Carlo simulations (MCS) with 5000 subjects were performed. The average tAUC of this population was derived. The mean tAUC/ MIC together with the 95% and 99% percentiles of 5000 subjects were plotted against a range of MICs.

Probability of Target Attainment (PTA) for *A. fumigatus* by MIC following isavuconazole 200 mg t.i.d. x 48h followed by 200 mg qd
TAR plot (right diagram): MCS with 5000 subjects were performed. For each subject the AUC/MIC was derived and the % of subjects above the exposure indices (EI) 50%, 80% or 90% were plotted against MIC values.





With fixed dosing of 200 mg t.i.d. x 48h followed by 200 mg qd, drug exposures reliably cover *A. fumigatus* isolates with an MIC of 1 mg/L, which is 1 fold higher than the modal MIC (representing the true MIC of the wild type population) for this species. The PK/PD breakpoint was determined using the EI90 and a PTA >90%.
For patients with infections due to isolates that are true wild type with an MIC of 2 mg/L, approx. 25% will not have an AUC/MIC ratio of 33 needed for 90% efficacy.

8. Clinical data

A multicentre, randomized, double-blind, non-inferiority study compared the efficacy of isavuconazole versus voriconazole for the treatment of invasive fungal disease caused by *Aspergillus* species or other filamentous fungi. 527 patients were randomized.
Design: Non-inferiority study design. Isavuconazole (200 mg x 2 for 3 days, then 200 mg daily iv or po) compared to voriconazole (VRC 6mg/kg i.v. x 2 daily day one followed by 4 mg/kgx 2 i.v. or 200 mg x 2 daily thereafter, (no TDM driven dose adjustment).
Primary endpoint of all-cause mortality through Day 42 in the intention to treat population.
Main secondary efficacy endpoints:

- Data Review Committee (DRC) -assessed Overall Success Rate at End of Treatment (EOT)
- DRC-assessed Overall Success Rate at Day 42 and Day 84
- DRC-assessed Clinical Response, Mycological Response,
- Radiological Response, at EOT, Day 42 and Day 84
- All-cause mortality through Day 84

Results: Isavuconazole was non inferior to voriconazole with respect to all cause mortality and success in the intention to treat and modifies intention to treat groups at all time points. Specifically, a total of 45 patients with culture proven invasive *Aspergillus* infections were enrolled with the following species distribution (Isavuconazole arm/voriconazole arm): *A. flavus* 9/7, *A. fumigatus* 25/16, *A. niger* 5/0, *A. terreus* (5/1), *A. westerdijkiae* 1/0. Overall mortality among culture proven *Aspergillus* cases: 6/45 (13%) voriconazole 8/24 (33%) across these species.

References:
SECURE~WSA-CS-004/9766-CL-0104 – NOTE published as abstracts/posters only at this time:
A. J. Ullmann, S. Shoham, W. Huang, S. Mujais. A Phase 3 Randomized, Double-Blind, Non-Inferiority Trial Evaluating Isavuconazole (ISA) vs Voriconazole (VRC) for the Primary Treatment of Invasive Fungal Disease (IFD) Caused by Aspergillus spp. or other Filamentous Fungi (SECURE): Outcomes by Malignancy Status. ICAAC 2014 M-1756.
K.A. Marr, E. Bow, W. Heinz, M. Lee, R. Maher, B. Zeiher, J. Maertens. A Phase 3 Randomized, Double-Blind, Non-Inferiority Trial Evaluating Isavuconazole (ISA) vs Voriconazole (VRC) for the Primary Treatment of Invasive Mold Infection (SECURE): Outcomes in Subset of Patients with Hematologic Malignancies (HM). ICAAC 2014 M-1757.
D. Andes, M. Ghannoum, L. Kovanda, W. Huang, Q. Lu, B. Zeiher, M. Jones, W. Hope. Outcomes by Minimum Inhibitory Concentrations from Isavuconazole Phase 3 Trial of Invasive Aspergillosis (SECURE). ICAAC 2014 M-1761.

9. Clinical breakpoints

PK/PD breakpoints

PK/PD breakpoints have been determined using PK/PD data and are independent of MIC distributions of specific species. They are for use only as a guide for organisms that do not have specific breakpoints. PK/PD breakpoints have been termed “non-species-related breakpoints” but this has led to confusion and it has become clear that PK/PD breakpoints for some agents may differ for different organisms.

Species-related breakpoints

Organism group	MIC breakpoints (mg/L) S ≤	MIC breakpoints (mg/L) R >	Notes
Aspergillus flavus	IE	IE	There is insufficient evidence that the species in question is a good target for therapy with the agent.
Aspergillus fumigatus	1	1	
Aspergillus nidulans	0.25	0.25	
Aspergillus niger	I.E	I.E	There is insufficient evidence that the species in question is a good target for therapy with the agent.
Aspergillus terreus	1	1	

Breakpoints for *A. fumigatus* were based on PK data, microbiological data and patient outcomes from clinical trials. Clinical information suggests that the wild type population of *A. fumigatus* is susceptible to isavuconazole. The breakpoint was set at the PK/PD breakpoint (1 mg/L) for *A. fumigatus*, which is 1 step lower than the ECOFF (of 2 mg/L). Monte Carlo analysis indicate that isavuconazole may be a appropriate for infections due to isolates with an MIC 2 mg/L provided high drug exposure is achieved, however, there are not clinical data to support this and currently no option for dose escalation. An MIC of 2 mg/L was found for 2.9% of the isolates, and may represent wild type isolates as well as isolates with target gene mutations (Howard et al AAC 2013, 57:5426-31). For example, an MIC of 2 mg/L was found for 17.5% of *A. fumigatus* isolates harbouring the most common resistance mechanism (TR_{34}/L98H, MIC_{50} of 4 mg/L range 1->8 mg/L), which is reported increasingly commonly in Europe, Africa, Asia-Pacific and Australia and which is clinically resistant to itraconazole, posaconazole and voriconazole (Howard et al AAC 2013, 57:5426-31). Repeated MIC testing is strongly recommended for isolates with an MIC of 2 mg/L (preferably also including itraconazole and voriconazole MIC testing, as additional markers for azole resistance). Additionally, *CYP51A* sequencing might be adopted to identify if such isolates harbour target gene mutations.

No clinical studies have so far presented outcome data for a significant number of cases involving the other species. While there is inadequate clinical information on outcome for wild type populations of *A. nidulans* and *A. terreus*, the MIC distributions are similar with an ECOFF of 1 mg/L or lower. Since there is no clinical data on the efficacy of isavuconazole against *A. nidulans* and *A. terreus* isolates with MICs above the ECOFF the clinical breakpoint was set at the ECOFF for these species. Finally, breakpoints were not established for *A. flavus* and *A. niger* as the MICs for these species are in general 1 and 2 two-fold dilutions higher and above the PK/PD breakpoint for *A. fumigatus*. Hence, there is insufficient evidence that the species in question is a good target for therapy with the agent.
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Clinical qualifications

Dosage	The EUCAST breakpoints apply to licensed dosing of isavuconazole. Loading dose 200 mg three times daily for 2 days (total of 6 doses), then 200 mg once daily.
Additional comment	Due to the increasing resistance in *A. fumigatus* isolates in the environment and in azole naïve patients in certain regions of the world (including Western Europe) susceptibility testing should be performed for every clinically significant *A. fumigatus* isolate.

10. Exceptions noted for individual national committees
None.