EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Rationale Document for EUCAST clinical breakpoints

Agent	**Posaconazole**

Current version	**2.0**	**24th April 2017**
Previous versions	1.0	19th November 2010 (Posaconazole and *Candida* spp.)
	1.0	17th January 2012 (Posaconazole and *Aspergillus* spp.)

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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This rationale document should be cited as: “European Committee on Antimicrobial Susceptibility Testing. Posaconazole: Rationale for the clinical breakpoints, version 2.0, 2016. http://www.eucast.org.

1. Introduction

Posaconazole is a triazole antifungal agent with *in vitro* activity against *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., Mucorales, and certain other yeasts and moulds. The drug is approved for the following indications in patients >18 years old:

i) Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products
ii) Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B
iii) Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole
iv) Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products
v) Oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor
vi) Patients receiving remission-induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections
i) Hematopoietic stem cell transplant recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections

The *Aspergillus* species most frequently causing human infections include *Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus* and *Aspergillus niger*. The *in vitro* activity of posaconazole against these species of *Aspergillus* is reasonably uniform, but acquired resistance has been reported, even among isolates obtained from triazole naïve patients (hence routine susceptibility testing is of utmost importance). It should be noted that *Aspergillus* spp. are complexes that comprise sibling species that may exhibit differences in their susceptibility to antifungal agents.

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

The European Committee on Antimicrobial Susceptibility Testing Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST) determined breakpoints for posaconazole against *Aspergillus* spp. and *Candida* spp. in 2010 and 2012, respectively.

In version 2.0 of this rationale document, the *Aspergillus* and *Candida* rational documents have been combined into a single document; dosage tables have been updated acknowledging the licensing of a new posaconazole formulation (the gastro resistant tablet and intravenous formulation) and MIC distribution tables updated with more information on *Candida* spp. and with *Cryptococcus neoformans*.

2. Dosage

Most common dose

In adults, oral solution: 400 mg (10 mL) x 2; gastro-resistant tablet or IV: 300 mg x 2 day 1 followed by 300 mg once daily thereafter. The tablet and oral suspension are not to be used interchangeably due to the differences between these two formulations in frequency of dosing, administration with food and plasma drug concentration achieved (posaconazole product information). Therefore, follow the specific dosage recommendations for each formulation

Refractory invasive fungal disease or intolerance:

Oral solution: 400 mg (10 mL) x 2. If unable to eat or take a food supplement 200 mg (5 mL) x 4.
Gastro-resistant tablet: 300 mg x 2 day 1 followed by 300 mg daily thereafter.
IV: 300 mg x 2 day 1 followed by 300 mg daily thereafter.

Oropharyngeal candidiasis (OPC):

Oral solution: loading dose 200 mg (5 mL) on day 1, then 100 mg (2.5 mL) x 1

Refractory OPC and oro-esophageal candidiasis (OEC):

Oral solution: 400 mg x 2 day (1).

Prophylaxis against invasive fungal diseases:

Oral solution: 200 mg (5 mL) x 3.
Gastro-resistant tablet: 300 mg x 2 day 1 followed by 300 mg daily thereafter.
IV: 300 mg x 2 day 1 followed by 300 mg daily thereafter.

Maximum dose schedule

Oral solution: 400 mg (10 mL) x 2 or 200 mg (5 mL) x 4 daily.
Gastro-resistant tablets: 300 mg x 2 day 1 followed by 300 once daily.
IV: 300 mg x 2 day 1 followed by 300 once daily.

Available formulations

Oral solution, gastro-resistant tablet, and IV.

3a. MIC distributions (numbers) 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
Aspergillus flavus	0	0	0	0	5	25	108	90	29	3	2	0	0	1	0	0	0	0	0	0.50
Aspergillus fumigatus	0	0	3	13	213	680	630	282	131	96	26	4	16	15	6	2	0	0	0	0.25
Aspergillus nidulans	0	0	0	4	12	26	24	21	10	1	1	1	1	2	1	0	0	0	0	0.50
Aspergillus niger	0	0	0	1	3	11	78	92	29	7	0	0	0	1	0	0	0	0	0	0.50
Aspergillus terreus	0	0	0	5	25	118	87	21	12	5	3	1	1	0	0	0	0	0	0	0.25
Aspergillus versicolor	0	0	0	0	0	4	7	6	7	1	0	1	0	2	0	0	0	0	0	ND
Aspergillus sydowii	0	0	0	0	4	5	8	18	13	1	0	0	0	0	0	0	0	0	0	ND
*Candida albicans**	0	0	167	1520	763	347	70	32	18	4	0	2	7	7	0	0	0	0	0	0.064
*Candida dubliniensis**	0	0	0	9	27	16	5	0	0	1	0	0	0	1	0	0	0	0	0	0.064
Candida glabrata	0	0	2	11	22	132	310	382	315	131	63	55	51	2	11	0	0	0	0	1
Candida guilliermondii	0	0	0	3	22	42	31	20	6	1	0	0	0	2	0	0	0	0	0	0.25
Candida krusei	0	0	0	3	27	91	153	74	14	0	0	0	0	0	0	0	0	0	0	0.5
*Candida parapsilosis**	0	0	20	489	280	121	7	2	1	0	0	1	0	0	0	0	0	0	0	0.064
*Candida tropicalis**	0	0	7	225	197	46	11	6	1	1	7	8	3	5	0	0	0	0	0	0.064
Cryptococcus neoformans	0	0	0	92	157	246	387	234	69	8	1	0	1	0	0	0	0	0	0	0.5
Cryptococcus gattii	0	0	0	1	1	3	8	24	15	0	0	0	0	0	0	0	0	0	0	1

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 epidemiological cut-off values have not been determined (ND).

* The majority of the MIC datasets for *C. albicans*, *C. dubliniensis*, *C. parapsilosis* and *C. tropicalis* were truncated at 0.016 mg/L. Data from these truncated datasets also supported the ECOFFs. For *C. albicans* 2895/2929 (99%) MICs were ≤0.064 mg/L (5 data sets); for *C. dubliniensis* 74/74 (100%) MICs were ≤0.064 mg/L (3 data sets); for *C. parapsilosis* 284/291 (98%) MICs were ≤0.064 mg/L (2 data sets); and for *C. tropicalis* 208/237 (88%) MICs were ≤0.064 mg/L (3 data sets).

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

	No.	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
Aspergillus flavus	263	0	0	0	0	2	10	41	34	11	1	1	0	0	0	0	0	0	0	0	0.50
Aspergillus fumigatus	2117	0	0	0	1	10	32	30	13	6	5	1	0	1	1	0	0	0	0	0	0.25
Aspergillus nidulans	104	0	0	0	4	12	25	23	20	10	1	1	1	1	2	1	0	0	0	0	0.50
Aspergillus niger	222	0	0	0	1	1	5	35	41	13	3	0	0	0	1	0	0	0	0	0	0.50
Aspergillus terreus	278	0	0	0	2	9	42	31	8	4	2	1	0	0	0	0	0	0	0	0	0.25
Aspergillus versicolor	28	0	0	0	0	0	14	25	21	25	4	0	4	0	7	0	0	0	0	0	ND
Aspergillus sydowii	49	0	0	0	0	8	10	16	37	27	2	0	0	0	0	0	0	0	0	0	ND
*Candida albicans**	2937	0	0	6	52	26	12	2	1	1	0	0	0	0	0	0	0	0	0	0	0.064
*Candida dubliniensis**	59	0	0	0	15	46	27	9	0	0	2	0	0	0	2	0	0	0	0	0	0.064
Candida glabrata	1487	0	0	0	1	2	9	21	26	21	9	4	4	3	0	1	0	0	0	0	1
Candida guilliermondii	127	0	0	0	2	17	33	24	16	5	1	0	0	0	2	0	0	0	0	0	0.25
Candida krusei	362	0	0	0	1	8	25	42	20	4	0	0	0	0	0	0	0	0	0	0	0.5
*Candida parapsilosis**	921	0	0	2	53	30	13	1	0	0	0	0	0	0	0	0	0	0	0	0	0.064
*Candida tropicalis**	517	0	0	1	44	38	9	2	1	0	0	1	2	1	1	0	0	0	0	0	0.064
Cryptococcus neoformans	1195	0	0	0	8	13	21	32	20	6	1	0	0	0	0	0	0	0	0	0	0.5
Cryptococcus gattii	52	0	0	0	2	2	6	15	46	29	0	0	0	0	0	0	0	0	0	0	1

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 epidemiological cut-off values have not determined (ND).

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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

	Oral Suspension			Gastro-resistant tablet (day 8) (2)		Intravenous formulation (day 14) (3)	
	HSCT recipients with Graft-versus-Host Disease (n=246) (4)	Neutropenic patients receiving cytotoxic chemotherapy for AML or MDS (n=215) (5)	Febrile neutropenic patients or patients with refractory invasive fungal diseases (n=24) (6)	Neutropenic patients receiving cytotoxic chemotherapy for AML or MDS (n=19)	Neutropenic patients receiving cytotoxic chemotherapy for AML or MDS (n=32)	Neutropenic patients receiving cytotoxic chemotherapy for AML or MDS (n=15)	Neutropenic patients receiving cytotoxic chemotherapy for AML or MDS (n=19)
Dosage (mg)	200 mg x 3	200 mg x 3	400 mg x 2	200 BID day 1→QD	300 BID day 1→QD	200 BID day 1→QD	300 BID day 1→QD
Cmax (mg/L) Mean (CV %)	1.36		0.85 (82)	1.27 (49)	1.96 (33)	1.95 (50)	2.61 (39)
Cmin (mg/L) Mean (CV %), [Range]			0.64 (98)	[0.19-1.65]	[0.343-2.55]	0.96 (63)	1.07 (50)
Cav (mg/L); Mean (CV %)	0.992	0.58	0.72 (86)	0.95 (50)	1.46 (38)	1.18 (51)	1.43 (42)
Total body clearance/F (L/h)*; Mean (CV %)			283 (354)				
T ½ (h); Range			35 (20-66)		29 (26-31)		
AUC_{24h} (mg.h/mL) total drug; Mean (CV %) [Range]			8.6 (86)	22.7 [7-45]	35.0 [11.8-62.3]	28.2 (51)	34.3 (42)
Fraction unbound (%)	>98%						
Volume of distribution/F (L/kg)*; Mean (CV %) [Range]			2,447 (421)	394 (42%) [294-583]		261	

Comments	* /F: for non-systemic administration only. The absolute bioavailability (F) of the oral delayed-release tablet is approximately 54% under fasted conditions. • Posaconazole serum levels data from the 241 patients who did not experience any breakthrough invasive fungal infection (4) • Half-life was taken from posaconazole product information (posaconazole product information). • Posaconazole oral solution: 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 proton pump inhibitors should be avoided if possible (posaconazole product information). • Posaconazole gastro-resistant tablet: absorption is less influenced by food intake than oral solution however AUC_{0-72} and Cmax are increased by 51% and 16%, respectively, following single dose administration of tablets with a high fat meal (posaconazole product information). • Target posaconazole levels for prophylaxis ($\geq$0.7 mg/mL) and for treatment ($\geq$1.0 mg/L) were reached in 29 of 30 (97%) serum levels and in 25 of 30 (83%), respectively, in patients receiving tablets, in contrast to 12 of 21 (57%) and 5 of 21 (24%) in patients receiving oral solution (7).

6. Pharmacodynamics

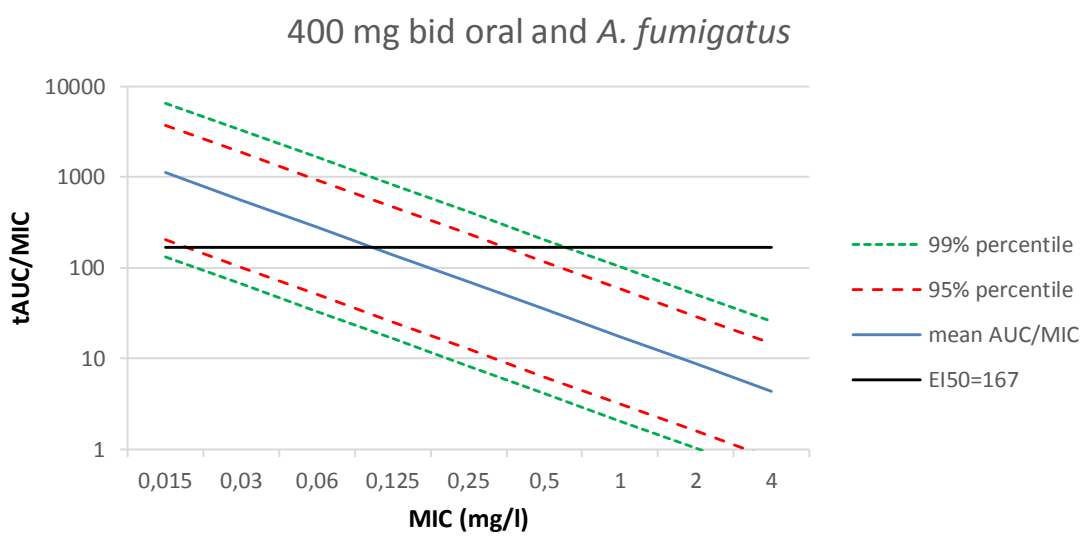
	Aspergillus	*Candida albicans*	*Cryptococcus*	
*f*AUC/MIC for stasis				
*f*AUC/MIC for 2 log reduction		120 ± 106[a]		
*f*AUC/MIC from clinical data				
Total drug AUC:MIC for half-maximum antifungal effect in preclinical studies	167-178			
Total drug AUC associated with a 75% response rate in patients receiving posaconazole as salvage therapy for invasive aspergillosis	~30 mg.h/L			
Comments	[a]This *f*AUC/MIC was recalculated using the CLSI *f*AUC/MIC ratios found previously in a murine model of disseminated candidiasis after determining the EUCAST MICs for the 10 *C. albicans* used in that study (8). • Studies performed so far strongly suggest AUC:MIC is the pharmacodynamics index that best links drug exposure with the observed outcome, as is the case for the other azole compounds (9-11). • An average concentration of 1.25 mg/L is associated with a higher probability of a clinical response for patients with invasive aspergillosis receiving posaconazole as salvage therapy (12). This is equivalent to an AUC of approximately 30 mg.h/L. • The posaconazole MIC for *Aspergillus fumigatus* is an important determinant of exposure-response relationships and outcome in preclinical models of invasive aspergillosis (10, 13). • AUC:MIC of 167-178 was associated with half-maximal effect in three pre-clinical studies (10, 13-15). • Cells are left empty when data are not readily available.			

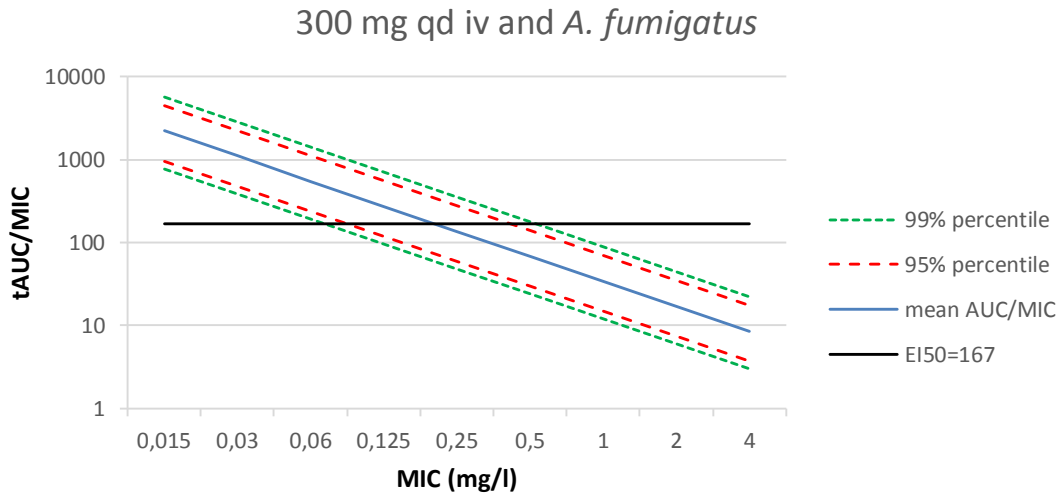
7. Monte Carlo simulations and Pk/Pd breakpoints

Aspergillus

For Monte Carlo simulations, the following mean±SD AUC_{0-24} were used: 17.24±14.83 mg.h/l for the 400 mg b.i.d. of oral solution (6) 34.3±14.4 mg.h/l for 300 mg q.d. of the i.v. formulation (3) and 34.3±12.4 mg.h/l for 300 mg qd of the tablet formulation (2). A Pk-Pd target of 167-178 AUC_{0-24}/MIC was previously determined (Section 6) The proportion of patients infected with an isolate with the following MICs and receiving the above mentioned doses who achieve a pharmacodynamic target AUC:MIC ≥ 178 for *Aspergillus* is as follows:

MIC (mg/L)	% Target attainment		
	Oral sol (400 mg x 2)	tablet	iv
0.015	98%	100%	100%
0.03	88%	100%	100%
0.06	59%	100%	100%
0.125	23%	86%	81%
0.25	5%	19%	20%
0.5	1%	0%	0%





Thus, with standard dosing, drug exposures may not be sufficient to cover the entire wild-type distribution reliably. For *A. fumigatus* isolates that are true wild type with an MIC of 0.12 mg/L, a posaconazole trough concentration of 0.7 mg/L is required to achieve an AUC:MIC of 167 when administered for prophylaxis; for purpose of salvage therapy, an average concentration of 1.25 mg/L should be targeted (14). For isolates with an MIC of 0.06 mg/L, a trough concentration of 0.4 mg/L is required to achieve an AUC:MIC of 167.

Candida and *Cryptococcus*

Not available for EUCAST data because there is no clear Pk/Pd target defined and additionally for *Cryptococcus* no licensed indication.

8. Clinical data

Aspergillus

Posaconazole has not been investigated as a first-line agent for the treatment of invasive aspergillosis. A clinical trial investigated the efficacy and safety of posaconazole oral suspension (800 mg/day in divided doses) as monotherapy in an open-label, multicentre cohort study in patients with invasive aspergillosis and other mycoses who were refractory or intolerant to conventional antifungal therapy (i.e., amphotericin B or itraconazole). A total of 107 posaconazole recipients and 86 external control subjects (modified intent-to-treat population) were included. The overall success was 42% for posaconazole recipients and 26% for control subjects (odds ratio, 4.06; 95% confidence interval, 1.50-11.04; P=0.006). The overall success increased from 53% up to 75% in case of mean plasma posaconazole concentrations at 0.719 and 1.250 mg/L, respectively (12).

Posaconazole is licensed for the prophylaxis of invasive fungal disease, including aspergillosis, of patients receiving remission-induction chemotherapy for acute myelogenous leukaemia or myelodysplastic syndromes as well as for hematopoietic stem cell transplant recipients with graft-versus-host disease (GvHD) (5, 16). In patients undergoing chemotherapy for acute myelogenous leukaemia or the myelodysplastic syndrome, posaconazole prevented the occurrence of invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival (5).

The frequency of posaconazole resistance is largely undefined, as many centres do not routinely test the susceptibility of *Aspergillus* isolates. Itraconazole resistance and cross resistance to other triazoles have currently been reported in most European countries, India, Taiwan, China, Australia, S-America and the USA. Most commonly, resistance is linked to point mutations in the target gene *cyp51A.* However, at some centres a significant proportion of the isolates with elevated posaconazole MICs lack such mutations, suggesting that other mechanisms including upregulated efflux pumps or up-regulation of target production may also play a role. Importantly, in some areas, *A. fumigatus* isolates with acquired resistance mechanisms have been increasingly found in the environment and also found in triazole naive patients failing therapy. This is probably related to agricultural azole pesticide use, but as *Aspergillus* spores are carried with wind, with compost, plants etc., their presence is not restricted to pesticide treated geographic areas. The posaconazole MICs obtained by EUCAST MICs for isolates with different *cyp51A* point mutations vary according to the underlying mechanism but they are ≥0.25 mg/L in most of the isolates (17-30).

Isolates with documented “environmental or clinical” hot spot *cyp51A* mutations associated with itraconazole resistance may, depending on the target alteration, be cross-resistant to posaconazole and/or voriconazole. The posaconazole MICs for such isolates is elevated but separate less well from the wild type population than with itraconazole (posaconazole modal MIC of 0.5 mg/L versus itraconazole modal MIC of >16 mg/L), making separation of such isolates from the wild type population difficult by posaconazole MIC alone. Infections caused by such isolates should not be treated with posaconazole as long as clinical evidence is not available that infections involving such isolates respond to treatment as well as infections caused by wild type organisms (17-30).

Candida

Treatment of oropharyngeal and oesophageal candidosis:

Posaconazole has demonstrated clinical efficacy in the treatment of oropharyngeal candidiasis (OPC) or oesophageal candidosis (EC) and in the prevention of invasive fungal infections (31-33).

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 x 2 for up to 4 weeks (32)
(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 (31)

(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 (33)
(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.

There is no clinical data regarding efficacy against invasive *Candida* infections

Treatment of infections due to other yeast
There is no clinical data regarding efficacy against non-*Candida* yeast infections including *Cryptococcus* infections

9. *Aspergillus* and *Candida* Clinical breakpoints

Non species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.			
Species-related breakpoints	**Organism group**	**MIC breakpoints (mg/L)**		**Notes**
		S ≤	R >	
	A. fumigatus	0.12	0.25	Provided adequate drug exposure has been confirmed using TDM. There remains some uncertainty regarding cut-off values for posaconazole concentrations that separate patients with a high probability of clinical success from those with a low probability of clinical success. In some circumstances (e.g. patients with persistent and profound neutropenia, large lesions, or those with other features associated with a poor clinical outcome) a relatively high total drug trough concentration should be sought. Preclinical and clinical data suggest this value should be >1 mg/L at steady state. For other patient groups a lower trough concentration may be acceptable. (For comparison, a lower threshold has been proposed for prophylaxis a target concentration of >0.7 mg/L has been suggested (34-39)).
	C. albicans	0.06	0.06	Isolates of *C. albicans, C. dubliniensis, C. parapsilosis* and *C. tropicalis* with MICs above the indicated breakpoints are uncommon. 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.
	C. dubliniensis	0.06	0.06	
	C. parapsilosis	0.06	0.06	
	C. tropicalis	0.06	0.06	
	Breakpoints were based on pharmacokinetic data, microbiological data and clinical experience. There are no clinical data regarding the use of posaconazole as primary therapy for invasive aspergillosis. Clinical data suggest that the wild type population of *A. fumigatus* is susceptible to posaconazole providing adequate serum drug exposure is achieved. Optimal clinical efficacy in the setting of salvage therapy of invasive aspergillosis requires mean plasma concentrations of approximately 1.25 mg/L (12). The modal MIC for isolates with mutations in the target gene is 0.5 mg/L, raising concerns that wild type and mutant populations are either poorly separated or overlap. Hence, the breakpoints for *A. fumigatus* are established by classifying the right tail of the wild type distribution as intermediate in order to notify the microbiologist and/or clinician that the isolate may possess acquired resistance mechanisms that may not be an appropriate target for posaconazole. Dose and formulation scheme should be chosen ensuring optimal exposure and such isolates should be retested and if necessary referred for confirmatory investigations such as *cyp51A* sequencing and molecular identification. MICs of itraconazole and voriconazole should also be determined for these isolates. Isolates classified as being posaconazole "intermediate" (MIC = 0.25 mg/L), and which are not susceptible to itraconazole, probably should not be treated with posaconazole until more clinical information is available.			

	No clinical studies have examined the clinical outcome for a significant number of infections caused by species other than *A. fumigatus*. There are no clinical data regarding the use of posaconazole as primary therapy for invasive *Candida* and other yeasts infections but 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. dubliniensis, 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. dubliniensis*, *C. parapsilosis* and *C. tropicalis* as susceptible to posaconazole.
Clinical qualifications	The EUCAST AFST considers posaconazole appropriate therapy for the following *Aspergillus* infections when caused by wild type isolates • Salvage treatment for invasive aspergillosis (oral and intravenous formulations) 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 (oral solution and IV formulation)
Dosage	The EUCAST breakpoints apply to EMA-licensed dosing.
Additional comment	Posaconazole TDM is recommended to ensure optimal drug exposure. Posaconazole oral solution 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 (40). Failure as well as breakthrough infections during prophylaxis have been linked to lower posaconazole serum levels. A trough level of $\geq$0.7 mg/L for prophylaxis and of $\geq$1.0 for salvage treatment of invasive fungal diseases are recommended by several authorities (5,6). The dosage of the gastro-resistant tablet was selected to provide a similar overall exposure compared to the oral solution allowing bridging expected outcome to that for the clinical trials using the oral solution. Therefore, although the tablet provides a less variable exposure it is estimated that up to 10 % of patients receiving this formulation still do not achieve plasma targets > 0.7 mg/L. (2, 3, 40). The percentage of patients not reaching treatment target (> 1 mg/L) will be higher (40-42). Therefore, therapeutic drug monitoring is recommended for patients receiving both oral formulations. Effective quality control is essential to avoid loss of biological potency of posaconazole in susceptibility testing and thereby avoid the risk of susceptible isolates being misclassified as intermediate or resistant. The EUCAST AFST will review breakpoints for posaconazole when more data are available for yeast species, which were not assigned breakpoints during the present review, when there are clinical data for yeast isolates with MIC values outside the wild type distribution.

10. Exceptions noted for individual national committees

None.

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