

Rationale for EUCAST clinical breakpoints

Agent	Itraconazole
--------------	---------------------

Current version	3.0	6th October, 2021
Previous versions	2.0	4 th February, 2020 (Itraconazole and <i>Aspergillus</i>)
	1.0	26 th June, 2014 (Itraconazole and <i>Candida</i>)
	1.1	6 th June, 2012 (Itraconazole and <i>Aspergillus</i>)
	1.0	11 th January, 2012 (Itraconazole and <i>Aspergillus</i>)

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

The copyright of all documents and data published on the EUCAST website remains with EUCAST. All are freely available for re-use if reference to the EUCAST website is given and documents and data are not resold. Any secondary publication of the data must be referenced with the declaration that "These data have (or this document has) been produced in part under ECDC service contracts, is made available at no cost by EUCAST and can be accessed freely on the EUCAST website www.eucast.org. EUCAST recommendations are frequently updated and the latest versions are available at www.eucast.org."

This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Itraconazole: Rationale for the clinical breakpoints, version 3.0, 2021. <http://www.eucast.org>."

1. Introduction

Itraconazole is a triazole antifungal agent active *in vitro* against *Aspergillus* spp., *Candida* spp., dermatophytes, *Histoplasma* spp., *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Fonsecaea* spp., *Cladosporium* spp., *Blastomyces dermatitidis*, and various other yeasts and fungi. The agent is approved for many indications, but licensed indications vary between European countries.

The mould species complexes most frequently causing human acute and chronic aspergillosis include *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus terreus* and *Aspergillus niger*. The *in vitro* activity of itraconazole against these species is reasonably uniform except against *A. niger*, which is less susceptible. However, acquired resistance has been increasingly reported, even among isolates obtained from triazole naive patients and sibling species within the species complexes may display differential susceptibility. Hence routine susceptibility testing is of utmost importance.

The *Candida* species most frequently involved in causing human infections include *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. krusei*. The *in vitro* activity of itraconazole against species of *Candida* is not uniform. MICs against *C. albicans*, *C. parapsilosis*, and *C. tropicalis* tend to be relatively low, whereas the MICs against *C. glabrata* and *C. krusei* are higher. Therefore, every attempt should be made to identify *Candida* to species level.

In version 3.0 of this rationale document, the *Aspergillus* and *Candida* rationale documents have been combined into a single document and MIC distribution tables updated with more information on *Candida* spp. and *Aspergillus* spp. and new information on *Trichophyton* spp. The clinical breakpoints apply to the new definition of the “I” category (Susceptible, Increased exposure) which was implemented in 2020.

2. Dosage

Itraconazole is licensed separately in each European country. Hence dosing recommendations may vary and should be consulted. The most common dosing practises upon which the EUCAST recommendations apply are summarised below.

Aspergillosis	Loading dose	200 mg x 2 for first days (2-4d) iv/po	
	Maintenance dose	200 mg x 1 (increased to 200 mg x 2, in severe cases) (daily)	The dose should be adjusted according to TDM (see below)
Candidiasis	Loading dose	200 mg x 2 for first day	
	Maintenance dose	100* - 400** mg iv/po (daily)	Notes: *Superficial infections only **Daily doses up to 200 mg x 2 may be given depending on the infection. Capsules have 30% lower bioavailability than the oral solution
	Children	100 - 200 mg (daily) for <i>Candida</i> esophagitis	
Trichophytosis	Cutaneous infections	100-200 mg x 1 or x 2 (daily)	
	Onychomycosis	200 mg x 1 (daily) or 200 mg x 2 (daily) (repeated one-week pulses per month)	
Maximum dose schedule	Increase the dose up to 200 mg x 2 (or 3) in case of invasive or disseminated disease.		
Available formulations	Capsules (100 mg), iv; and oral solution. Note: not all formulations are available in all countries.		
TDM	For itraconazole, a serum trough concentration of >0.5 mg/L for prophylaxis and >1 mg/L for therapy (measured by HPLC or LC-MS/MS) is recommended for treatment of invasive aspergillosis.		

3a. MIC distributions (numbers) and epidemiological cut-off (ECOFF) values (mg/L)¹

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF/ [T-ECOFF]*
<i>Aspergillus flavus</i>	0	0	2	2	0	8	44	146	104	46	11	0	0	2	0	0	0	0	0	1
<i>Aspergillus fumigatus</i>	0	0	0	2	6	15	150	860	1254	527	77	44	31	62	121	0	0	0	0	1
<i>Aspergillus nidulans</i>	0	0	0	1	2	9	30	32	16	5	5	0	3	4	2	0	0	0	0	[1] ^a
<i>Aspergillus niger</i>	0	0	0	0	0	1	6	18	108	121	27	8	6	20	3	0	0	0	0	2
<i>Aspergillus sydowii</i> #	0	0	0	0	0	1	8	8	17	10	1	2	1	7	0	0	0	0	0	ND
<i>Aspergillus terreus</i>	0	0	0	0	5	21	192	325	61	10	2	0	2	2	0	0	0	0	0	[0.5]
<i>Aspergillus versicolor</i> #	0	0	0	0	0	1	2	3	8	7	1	0	1	0	0	0	0	0	0	ND
<i>Candida albicans</i>	0	11	93	138	30	5	3	1	2	0	1	0	0	1	0	0	0	0	0	0.03
<i>Candida dubliniensis</i>	0	1	24	27	33	9	4	0	0	0	0	0	0	0	0	0	0	0	0	0.06
<i>Candida glabrata</i>	0	0	0	5	32	77	202	368	511	353	109	46	76	77	20	0	0	0	0	2
<i>Candida guilliermondii</i>	0	0	0	2	2	3	15	46	57	16	2	0	0	1	0	0	0	0	0	[1]
<i>Candida kefyr</i>	0	0	0	10	28	31	11	2	1	0	0	0	0	0	0	0	0	0	0	ND ^b
<i>Candida krusei</i>	0	0	0	3	11	26	117	165	79	23	2	1	0	0	0	0	0	0	0	1
<i>Candida lusitanae</i>	0	0	0	10	41	24	11	2	1	1	0	0	0	0	0	0	0	0	0	[0.125]
<i>Candida parapsilosis</i>	0	0	0	192	386	230	85	25	9	2	0	0	0	0	0	0	0	0	0	0.125
<i>Candida tropicalis</i>	0	0	14	169	229	131	72	43	14	7	0	3	2	6	0	0	0	0	0	0.125
<i>Saccharomyces cerevisiae</i>	0	0	0	1	1	5	4	22	36	11	6	1	0	0	0	0	0	0	0	[2] ^c
<i>Trichophyton indotineae</i> ^d	0	0	5	7	21	17	14	5	0	0	0	0	0	0	0	0	0	0	0	[0.25] ^d
<i>Trichophyton rubrum</i>	0	0	11	17	17	13	8	9	1	0	0	0	0	0	0	0	0	0	0	[0.25] ^{d,e}

The table includes MIC distributions available at the time breakpoints were set ([link to EUCAST website of MIC distributions and ECOFFs](#)). They represent combined distributions from multiple sources and time periods with the exceptions of *A. sydowii*, and *A. versicolor*. 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).

¹In general, the MIC distributions reflect results for species complexes, as not all laboratories submitting data perform identification to the sensu stricto level. However, the number of sibling species with differential susceptibility compared to the sensu stricto species must be low as the main distribution is Gaussian.

* tentative T-ECOFFs was determined when <5 qualified MIC distributions were aggregated, and are indicated in square brackets.

MIC distributions from a single centre.

^a The aggregated MIC distribution for *A. nidulans* is based on 109 isolates from 6 data sets, 4 with ≥5 isolates but only 1 MIC distribution with >15 isolates.

^b The aggregated MIC distribution for *C. kefyr* is based on 83 isolates from 7 data sets, 4 with ≥5 isolates but only 1 MIC distribution with >15 isolates.

^c The aggregated MIC distribution for *S. cerevisiae* is based on 69 isolates from 6 data sets, 6 with ≥5 isolates but only 2 MIC distribution with >15 isolates.

^d T-ECOFFs against *T. indotineae* (formerly the Indian variant of *T. interdigitale*) and *T. rubrum* were determined based on a shared isolate collection tested in 10 laboratories as part of the “Multicentre validation of a EUCAST method for the antifungal susceptibility testing of microconidia-forming dermatophytes” study (1).

^e MIC distributions were wider than normally, the T-ECOFF is therefore associated with uncertainty. They apply to MICs determined using E.Def 11.0 and with 50% endpoint criteria.

3b. MIC distributions (%) and epidemiological cut-off (ECOFF) values (mg/L)¹

	No.	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF/ [T-ECOFF]*
<i>Aspergillus flavus</i>	365	0	0	0.5	0.5	0	2	12	40	28	13	3	0	0	1	0	0	0	0	0.5	1
<i>Aspergillus fumigatus</i>	3149	0	0	0	0	0	0	5	27	40	17	2	1	1	2	4	0	0	0	0	1
<i>Aspergillus nidulans</i>	109	0	0	0	1	2	8	28	30	15	5	5	0	3	4	2	0	0	0	0	[1] ^a
<i>Aspergillus niger</i>	318	0	0	0	0	0	0	2	6	34	38	8	3	2	6	1	0	0	0	0	2
<i>Aspergillus sydowii</i> #	55	0	0	0	0	0	2	15	15	31	18	2	4	2	13	0	0	0	0	0	ND
<i>Aspergillus terreus</i>	620	0	0	0	0	1	3	31	52	10	2	0	0	0	0	0	0	0	0	0	[0.5]
<i>Aspergillus versicolor</i> #	23	0	0	0	0	0	4	9	13	35	30	4	0	4	0	0	0	0	0	0	ND
<i>Candida albicans</i>	285	0	4	33	48	11	2	1	0	1	0	0	0	0	0	0	0	0	0	0	0.03
<i>Candida dubliniensis</i>	98	0	1	24	28	34	9	4	0	0	0	0	0	0	0	0	0	0	0	0	0.06
<i>Candida glabrata</i>	1876	0	0	0	0	2	4	11	20	27	19	6	2	4	4	1	0	0	0	0	2
<i>Candida guilliermondii</i>	144	0	0	0	1	1	2	10	32	40	11	1	0	0	1	0	0	0	0	0	[1]
<i>Candida kefyr</i>	83	0	0	0	12	34	37	13	2	1	0	0	0	0	0	0	0	0	0	0	ND ^b
<i>Candida krusei</i>	427	0	0	0	1	3	6	27	39	19	5	0	0	0	0	0	0	0	0	0	1
<i>Candida lusitanae</i>	90	0	0	0	11	46	27	12	2	1	1	0	0	0	0	0	0	0	0	0	[0.125]
<i>Candida parapsilosis</i>	929	0	0	0	21	42	25	9	3	1	0	0	0	0	0	0	0	0	0	0	0.125
<i>Candida tropicalis</i>	690	0	0	2	24	33	19	10	6	2	1	0	0	0	1	0	0	0	0	0	0.125
<i>Saccharomyces cerevisiae</i>	87	0	0	0	1	1	6	5	25	41	13	7	1	0	0	0	0	0	0	0	[2] ^c
<i>Trichophyton indotineae</i> ^d	69	0	0	7	10	30	25	20	7	0	0	0	0	0	0	0	0	0	0	0	[0.25] ^d
<i>Trichophyton rubrum</i>	76	0	0	14	22	22	17	11	12	1	0	0	0	0	0	0	0	0	0	0	[0.25] ^{d,e}

The table includes MIC distributions available at the time breakpoints were set ([link to EUCAST website of MIC distributions and ECOFFs](#)). They represent combined distributions from multiple sources and time periods with the exceptions of *A. sydowii*, and *A. versicolor*. 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).

¹In general, the MIC distributions reflect results for species complexes, as not all laboratories submitting data perform identification to the sensu stricto level. However, the number of sibling species with differential susceptibility compared to the sensu stricto species must be low as the main distribution is Gaussian.

* tentative T-ECOFFs was determined when <5 qualified MIC distributions were aggregated, and are indicated in square brackets.

MIC distributions from a single centre.

^a The aggregated MIC distribution for *A. nidulans* is based on 109 isolates from 6 data sets, 4 with ≥5 isolates but only 1 MIC distribution with >15 isolates.

^b The aggregated MIC distribution for *C. kefyr* is based on 83 isolates from 5 data sets, 4 with ≥5 isolates but only 1 MIC distribution with >15 isolates.

^c The aggregated MIC distribution for *S. cerevisiae* is based on 69 isolates from 6 data sets, 6 with ≥5 isolates but only 2 MIC distribution with >15 isolates

^d T-ECOFFs against *T. indotineae* (formerly the Indian variant of *T. interdigitale*) and *T. rubrum* were determined based on a shared isolate collection tested in 10 laboratories as part of the “Multicentre validation of a EUCAST method for the antifungal susceptibility testing of microconidia-forming dermatophytes” study (1).

^e MIC distributions were wider than normally, the T-ECOFF is therefore associated with uncertainty. They apply to MICs determined using E.Def 11.0 and with 50% endpoint criteria.

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

NA = Not available

5. Pharmacokinetics

Dosage (mg)	capsules 100 mg once daily (with standard breakfast) for 15 days (5 healthy volunteers) (2)	capsules 200 mg once daily (with standard breakfast) for 15 days (5 healthy volunteers) (2)	capsules 200 mg b.i.d (with a full meal) for 15 days (27 healthy male volunteers) (3)	oral solution 200 mg (under fasting conditions) for 15 days (6 healthy male volunteers) (3)	SUperBioAvailable (SUBA) capsules ^a 65 mg BID (16 healthy subjects) ^a (4)	iv formulation 200 x 2 day 1 & 2 followed by 200 mg daily until day 4 (29 patients with advanced HIV infection) (3)	iv formulation 200 x 2 day 1 & 2 followed by 200 mg daily (10 ICU patients) (5)	oral solution 5 mg/kg for 15 days (haematologi cal adult patients) (6)
C _{max} (mg/L); mean±SD	0.41 ± 0.08	1.07 ± 0.05	2.23 ± 0.51	1.96 ± 0.6	1.6 ± 0.4	2.86 ± 0.87	1.2 ± 0.3	1.29 ± 0.36
C _{min} (mg/L); mean±SD	0.12 ± 0.05	0.42 ± 0.18	1.86 ± 0.54		1.2 ± 0.4		0.37 ± 0.17	0.85 ± 0.22
C _{av} (mg/L); mean±SD	0.39 ± 0.95	1.03 ± 0.45						
Total body clearance (L/h); mean±SD			23.46 ± 5.85			16.7 ± 4.74		
T _½ (h); mean±SD (CV %)	34.0 ± 8.5	36.5 ± 4.3	64 ± 32	39.7 ± 13		35.4 ± 29.4		
T _{max} (h); mean±SD (range)	3.0 ± 1.2	4.4 ± 2.1	4.6 ± 1.8	2.5 ± 0.8	7 (1-10)	1.08 ± 0.14		
AUC ₀₋₂₄ (mg.h/L); mean±SD	5.3 ± 1.4	15.4 ± 6.9	45.2 ± 10.8	29.3 ± 10.3	31.2 ± 7.4	30.6 ± 8.96	29.3 ± 6	25.15 ± 6.46
Fraction unbound (%)	0.2							
Volume of distribution (L); mean±SD	796 ± 185							

Comments	<ul style="list-style-type: none"> • Itraconazole bioavailability is around 55% but displays considerable variation on oral administration. Absorption is affected by formulation (optimised by cyclodextrin in the oral solution), gastric pH, prandial state and the timing of dose administration relative to the time of a meal (6-9). • Strategies to maximize itraconazole exposure include: <ul style="list-style-type: none"> ○ <u>Capsules</u>: administration with or immediately after a meal, with an acid beverage (cola or juice). ○ <u>Oral solution</u>: administration during fasting (30% greater exposure). ○ <u>Both oral formulations</u>: administer in divided doses. Avoid any acid inhibitors if possible. ○ <u>Oral solution supplemented with iv loading doses (day 1 and 2) result in the majority of patients reaching a trough concentration of >1 mg/L within the first week (6).</u> • Itraconazole is metabolised to hydroxyl-itraconazole which also has antifungal activity. In HPLC determinations these two compounds are measured individually whereas in a bioassay the combined antifungal activity is measured and expressed in itraconazole equivalents. • Itraconazole displays non-linear pharmacokinetics. • Itraconazole has multiple drug-drug interactions. • <u>^aSUBA-itraconazole formulation is approved in some European countries with the brand name LOZANOC® / TOLSURA®. SUBA technology utilizes a solid dispersion of drug in a polymer matrix to improve the dissolution of poorly soluble drugs resulting in improved absorption of these drugs in the gastrointestinal tract. It was bioequivalent to conventional capsules in healthy subjects and has demonstrated superior relative bioavailability of 173% compared with conventional capsules and 21% less interpatient variability (4, 10, 11).</u>
----------	--

6. Pharmacodynamics

fAUC/MIC for stasis				
fAUC/MIC for 2 log reduction				
tAUC/MIC from clinical data				
Comments	<ul style="list-style-type: none"> • No pharmacodynamic data are available for EUCAST MICs and <i>Aspergillus</i> or <i>Candida</i> spp. • The AUC/MIC is generally regarded as the significant parameter for <i>Candida</i> infections and the same is likely to be so for <i>Aspergillus</i>, but no data are available for <i>Aspergillus</i>. • For invasive pulmonary aspergillosis, outcome in animal models and patients is associated with exposure (with better outcome for patients with higher trough levels), but no international agreement has been reached regarding the exact target range. Examples are listed below: <ul style="list-style-type: none"> ○ In a rabbit model of invasive aspergillosis near-peak concentrations of itraconazole + hydroxy-itraconazole (by bioassay) below 6 mg/L were associated with failure (12). ○ Target trough concentrations of itraconazole ≥ 0.5 mg/L (by HPLC or LC-MS/MS and thus not including OH-itraconazole) in the setting of prophylaxis has been associated with fewer breakthrough infections and survival in a haematological population (13, 14). ○ Levels above 17 mg/L (by bioassay) have been associated with toxicity (15). ○ A target trough level of ≥ 0.5-1 mg/l (itraconazole only and by HPLC or LC-MS/MS) is recommended for TDM for prophylaxis and treatment of aspergillosis (16). • In established <i>Aspergillus</i> infections higher levels may be required but remain undefined. • For invasive candidiasis, <ul style="list-style-type: none"> ○ Outcome in animal models of experimental disseminated candidiasis by 12 <i>C. albicans</i> isolates with CLSI MICs ≤ 0.016->8 mg/L, >60% survival was found for isolates with CLSI 24h MICs ≤ 0.25 mg/L with 10 and 40 mg/kg q24h of intravenous itraconazole (17). ○ Pharmacokinetic-pharmacodynamic analysis in 10 ICU patients with invasive candidiasis treated with intravenous itraconazole (200 mg q12h for first 2 days and then 200mg q24h) had a better outcome with an $AUC_{0-24}/MIC > 25$ compared to those that had $AUC_{0-24}/MIC < 25$ (4/8 vs 2/2, respectively) (5). • Cells are left empty when data are not readily available. 			
References				

7. Monte Carlo simulations and Pk/Pd breakpoints

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

8. Clinical data

Aspergillosis

Orally administered itraconazole has been used to treat patients with invasive aspergillosis (18, 19). In the largest open multicentre trial of 76 evaluable patients (39 with no prior antifungal treatment, 16% failing amphotericin B therapy and 45% with prior iv amphotericin B), 30 patients (39%) had a complete or partial response, with success rates varying widely according to site of disease and underlying disease group. Four percent had stable disease. The overall failure rate at the end of the study was 56% including 26% classified as itraconazole therapy failures and 30% failing for other reasons. Of note, a substantial number of patients who failed therapy had undetectable levels of itraconazole in blood whereas none of the responders had undetectable levels (18, 19). More recent studies of the parenteral formulation of β -hydroxy-propyl-cyclodextrin itraconazole in the treatment of invasive pulmonary aspergillosis that was refractory to various forms of amphotericin B have been reported, with overall response rates of 32-52% (20). Salvage therapy with itraconazole for treatment of invasive pulmonary aspergillosis that is refractory to primary therapy despite appropriate levels of voriconazole is not recommended because most isolates resistant to voriconazole are also resistant to itraconazole. Therapy with itraconazole for treatment of invasive pulmonary aspergillosis that has failed posaconazole prophylaxis despite appropriate levels of posaconazole in the haematology setting is also not recommended because isolates resistant to posaconazole mostly are also resistant to itraconazole. For chronic aspergillosis, itraconazole (400 mg daily) with supportive care has been found efficacious compared to supportive care alone (21). A total of 31 patients (mean age, 37 years) were randomised to itraconazole (n = 17) or the control (n = 14) group. The number of patients showing overall response was 76.5% in the itraconazole group vs. 35.7% the control group (P = 0.02). Moreover, more patients demonstrated clinical or radiological response in the itraconazole group (P = 0.016 and 0.01 respectively). Hence, itraconazole is recommended for the treatment of chronic aspergillosis (22).

Acquired Resistance

The first cases of itraconazole resistant *A. fumigatus* were from the late 1980s (23, 24), yet the vast majority has been detected since the turn of the millennium. The frequency is largely undefined, as many centres do not routinely test the susceptibility of their *Aspergillus* isolates. Resistance has currently been reported on all five continents (25-30). Most commonly, resistance is linked to point mutations in the target gene *cyp51A*. However, at some centres (particularly those managing patients with chronic aspergillosis and long term azole therapy) a significant proportion of the isolates with elevated itraconazole MICs lack such mutations, suggesting other mechanisms like efflux pumps or up-regulation of target production may also play a role (31). Importantly, *A. fumigatus* isolates with acquired resistance mechanisms have been increasingly found in the environment, probably due to agricultural azole fungicide use, and have also been found in azole-naïve patients failing therapy (32-35). The EUCAST itraconazole MICs for such isolates vary with the underlying mechanism but are >4 mg/L for the most commonly-identified mutants (alterations at G54, G138, M220, and the environmental phenotype TR₃₄/L98H) (36). Correlation of *in vitro* itraconazole MIC data with clinical outcome has not been done as such data sets are not available for EUCAST MIC method (37).

Vaginitis

Itraconazole and fluconazole have been found equally efficacious in several studies and a metaanalysis covering six randomised trials and a total of 1092 patients. Most infections involved *C. albicans* and species-specific outcome data was not available (38).

One clinical study reported species-specific outcome data: Urünsak M et al investigated 52 women with 1 and 4 week clinical and mycological follow-up after 200 mg twice on a single day and found the following cure rates at 1 week and 4 weeks: *C. albicans*: 62.5% (25/40) and 95% (38/40), *C. glabrata*: 60% (3/5) and 80% (4/5), *C. kefyr* 100% (5/5) and 100% (5/5), *C. krusei*: 0% (0/2) and 0% (0/2) (39).

Oropharyngeal candidiasis (OPC)

Itraconazole and fluconazole were compared in a prospective randomized, third-party blind, multicentre trial. One hundred and seventy-nine HIV-positive patients with mycologically documented oropharyngeal candidiasis were treated with itraconazole oral solution 200 mg/day for 7 or 14 days, or fluconazole tablets 100 mg/day for 14 days. Severity of disease was scored clinically before treatment and at clinical evaluations on days 3, 7, 14, 21, 35, and 42. Semiquantitative cultures of mouth washings

were also obtained on these days. Both 14 day and 7 day regimens of itraconazole oral solution were equivalent to fluconazole for most efficacy parameters. The clinical response rate was 97% after 14 days of itraconazole and 87% after 14 days of fluconazole. Itraconazole oral solution given for 7 days was also equivalent to fluconazole treatment for 14 days. Approximately one half of patients in all three groups relapsed by 1 month after completion of treatment. 96% of the infections involved *C. albicans*. (40).

A similar study comparing itraconazole solution with fluconazole tablets once daily (both at 100-200 mg doses) also found the two compounds equal. For 120 HIV patients, clinical response rates were 94 vs 91%, and mycological response rates were 92 and 78% for itraconazole and fluconazole respectively (41).

In a study by Rex (1997) three hundred and sixteen HIV patients with OPC involving 355 *Candida* isolates (87% *C. albicans*, 9% *C. glabrata*, 2% *C. krusei*, and 2% others) received itraconazole (200 mg/day). MIC determination was by CLSI methodology (with 48 h reading) and a correlation was found between MIC and outcome, with a decreasing response for isolates with an MIC of >0.125 mg/L, or >0.25 mg/L if itraconazole blood levels were >0.5 mg/L (42). A reanalysis of the Rex dataset performed by EUCAST for the purpose of this Rationale Document used Cart analysis and suggests a breakpoint for resistance of >0.25 mg/L with the CLSI method. As MICs for *C. albicans* obtained with the CLSI method are approximately 1-2 twofold dilution steps higher than those obtained with the EUCAST method, this data and analysis support the EUCAST breakpoint of 0.06 mg/l for *C. albicans*.

Invasive candidiasis

A non-controlled non-comparative study investigated the efficacy of itraconazole 200 mg x 2 daily iv on day 1 and 2, followed by 200 mg daily. Sixty patients were enrolled and outcome data were presented for 49 patients with proven (63.3%) or presumed (36.7%) invasive candidiasis. Two thirds of the patients were in the ICU. Itraconazole was employed as a first-line agent in 39 patients (79.6%) and as a second-line agent in 10 (20.4%). The improvement ratings of clinical symptoms/findings and the microbiological efficacy rate at the end of the study were 72.4% and 69.6%, respectively, and overall clinical efficacy was highest in the non-ICU setting (76.5% vs. 50.0%, respectively) (43).

A retrospective multicentre study of different empirical antifungal agents on the clinical outcome of 136 critically ill patients with invasive candidiasis, showed that empirical therapy with an echinocandin (n=43) was associated with decreased hospital- (p=0.006) and ICU- (p=0.011) mortality and greater clinical success than empirical therapy with fluconazole (n=61, OR=0.22), voriconazole (n=20 OR=0.11) or itraconazole (n=12, OR=0.12) (44).

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 >	ATU*	
	<i>Aspergillus flavus</i>	1	1	2	An isolate with an MIC = 2 mg/L should be reported as R with the following comment: "In some clinical situations (non-invasive infections forms) itraconazole can be used provided sufficient exposure is ensured".
	<i>Aspergillus fumigatus</i>	1	1	2	
	<i>Aspergillus nidulans</i>	1	1	2	
	<i>Aspergillus terreus</i>	1	1	2	
	<i>Candida albicans</i>	0.06	0.06		
	<i>Candida dubliniensis</i>	0.06	0.06		
	<i>Candida tropicalis</i>	0.125	0.125		
	<i>Candida parapsilosis</i>	0.125	0.125		
<p>* Area of Technical Uncertainty. Breakpoints were based on microbiological data and clinical experience.</p> <p>In general, the MIC distributions reflect results for species complexes, as not all laboratories submitting data perform identification to the sensu stricto level. However, sibling species with differential susceptibility compared to the sensu stricto species must be low as the main distribution is Gaussian. Clinical information shows that the wild type population of <i>A. fumigatus</i> is susceptible to itraconazole. No clinical studies have so far presented outcome data for a significant number of cases involving the other species.</p> <p>Although there is inadequate clinical information on outcome for wild type populations of <i>A. flavus</i>, <i>A. nidulans</i>, and <i>A. terreus</i>, the MIC distributions are similar to (or a single dilution lower than) that obtained for <i>A. fumigatus</i>. Therefore, EUCAST AFST considers wild type populations of these species as susceptible to itraconazole.</p> <p>There is insufficient evidence that an isolate with an MIC of 2 mg/L is susceptible at standard dosing, but also which high dose target might be efficacious therapy for such isolates. However, with very few oral options for outpatient with non-acute infections itraconazole may be considered provided sufficient exposure is ensured.</p>					
Species without breakpoints	<p>The MIC values for isolates of <i>A. niger</i> and <i>A. versicolor</i> are in general higher than those for <i>A. fumigatus</i>. Whether this translates into a poorer clinical response is unknown. There is insufficient evidence (IE) to set breakpoints for these species.</p> <p><i>C. glabrata</i>, <i>C. guilliermondii</i>, <i>C. krusei</i> and <i>S. cerevisiae</i> display higher MICs. There are insufficient clinical data to indicate whether these species are good targets for itraconazole or not. Hence EUCAST has refrained from setting breakpoint for these species.</p>				

Clinical qualifications	(45-47)
Dosage	<p>The EUCAST breakpoints apply to licensed dosing. Dosage adjustment is recommended when serum concentrations are outside the therapeutic range.</p> <p>Dosages depend on the clinical indication and vary from a daily dose of 100 mg once daily (e.g. uncomplicated oral candidiasis to 200 mg twice daily e.g. <i>Aspergillus</i> infection) and are mainly validated for oro-pharyngeal, oesophageal and vaginal candidiasis and chronic forms of aspergillosis.</p>
Additional comment	<p>Isolates susceptible to itraconazole but resistant to voriconazole or posaconazole are so far extremely rare (but reported for a minority of the environmental TR₄₆/Y121F/T289A isolates), whereas itraconazole resistant isolates may or may not be resistant to voriconazole, isavuconazole and posaconazole, depending on the underlying mechanism. Isolates with elevated itraconazole MIC should be checked for cross resistance to other azole agents active against <i>Aspergillus</i> spp.</p> <p>Itraconazole 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 itraconazole plasma concentration and outcome has been found (see 7. Clinical data). Monitoring of itraconazole trough concentrations in patients treated for invasive, chronic or refractory fungal infection is recommended.</p> <p>Breakpoints for itraconazole are mainly based upon ECOFFs and clinical experience with wild type and resistant mutants of <i>A. fumigatus</i>. Breakpoints will be reviewed when more data are available for other <i>Aspergillus</i> species, when more PK/PD data are available or when there are further data related to optimal drug exposures for itraconazole.</p>

10. Exceptions noted for individual national committees
--

None

References

1. Arendrup MC, Jorgensen KM, Guinea J, Lagrou K, Chryssanthou E, Hayette MP, et al. Multicentre validation of a EUCAST method for the antifungal susceptibility testing of microconidia-forming dermatophytes. *J Antimicrob Chemother.* 2020;75(7):1807-19.
2. Hardin TC, Graybill JR, Fetchick R, Woestenborghs R, Rinaldi MG, Kuhn JG. Pharmacokinetics of itraconazole following oral administration to normal volunteers. *Antimicrob Agents Chemother.* 1988;32(9):1310-3.
3. Administration Si-UFaD. <https://www.accessdata.fda.gov>.
4. Thompson GR, 3rd, Lewis P, Mudge S, Patterson TF, Burnett BP. Open-Label Crossover Oral Bioequivalence Pharmacokinetics Comparison for a 3-Day Loading Dose Regimen and 15-Day Steady-State Administration of SUBA-Itraconazole and Conventional Itraconazole Capsules in Healthy Adults. *Antimicrob Agents Chemother.* 2020;64(8).
5. Hagihara M, Kasai H, Umemura T, Kato T, Hasegawa T, Mikamo H. Pharmacokinetic-pharmacodynamic study of itraconazole in patients with fungal infections in intensive care units. *J Infect Chemother.* 2011;17(2):224-30.
6. Prentice AG, Glasmacher A. Making sense of itraconazole pharmacokinetics. *J Antimicrob Chemother.* 2005;56 Suppl 1:i17-i22.
7. Poirier JM, Cheymol G. Optimisation of itraconazole therapy using target drug concentrations. *Clinical pharmacokinetics.* 1998;35(6):461-73.
8. Willems L, van der Geest R, de Beule K. Itraconazole oral solution and intravenous formulations: a review of pharmacokinetics and pharmacodynamics. *J Clin Pharmacy and Therapeutics.* 2001;26(3):159-69.
9. De Beule K, Van Gestel J. Pharmacology of itraconazole. *Drugs.* 2001;61 Suppl 1:27-37.
10. Abbotsford J, Foley DA, Goff Z, Bowen AC, Blyth CC, Yeoh DK. Clinical experience with SUBA-itraconazole at a tertiary paediatric hospital. *J Antimicrob Chemother.* 2021;76(1):249-52.
11. Lindsay J, Mudge S, Thompson GR, 3rd. Effects of Food and Omeprazole on a Novel Formulation of Super Bioavailability Itraconazole in Healthy Subjects. *Antimicrob Agents Chemother.* 2018;62(12).
12. Berenguer J, Ali NM, Allende MC, Lee J, Garrett K, Battaglia S, et al. Itraconazole for experimental pulmonary aspergillosis: comparison with amphotericin B, interaction with cyclosporin A, and correlation between therapeutic response and itraconazole concentrations in plasma. *Antimicrob Agents Chemother.* 1994;38(6):1303-8.
13. Glasmacher A, Hahn C, Leutner C, Molitor E, Wardelmann E, Losem C, et al. Breakthrough invasive fungal infections in neutropenic patients after prophylaxis with itraconazole. *Mycoses.* 1999;42(7-8):443-51.
14. Boogaerts MA, Verhoef GE, Zachee P, Demuynck H, Verbist L, De Beule K. Antifungal prophylaxis with itraconazole in prolonged neutropenia: correlation with plasma levels. *Mycoses.* 1989;32 Suppl 1:103-8.
15. Lestner JM, Roberts SA, Moore CB, Howard SJ, Denning DW, Hope WW. Toxicodynamics of itraconazole: implications for therapeutic drug monitoring. *Clin Infect Dis.* 2009;49(6):928-30.
16. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother.* 2014;69(5):1162-76.
17. Uchida K, Shimogawara K, Yamaguchi H. Correlation of in vitro activity and in vivo efficacy of itraconazole intravenous and oral solubilized formulations by testing *Candida* strains with various itraconazole susceptibilities in a murine invasive infection. *J Antimicrob Chemother.* 2011;66(3):626-34.
18. Stevens DA, Lee JY. Analysis of compassionate use itraconazole therapy for invasive aspergillosis by the NIAID Mycoses Study Group criteria. *Arch Intern Med.* 1997;157(16):1857-62.

19. Denning DW, Lee JY, Hostetler JS, Pappas P, Kauffman CA, Dewsnup DH, et al. NIAID Mycoses Study Group Multicenter Trial of Oral Itraconazole Therapy for Invasive Aspergillosis. *Am J Med.* 1994;97(2):135-44.
20. Caillot D. Intravenous itraconazole followed by oral itraconazole for the treatment of amphotericin-B-refractory invasive pulmonary aspergillosis. *Acta Haematol.* 2003;109(3):111-8.
21. Agarwal R, Vishwanath G, Aggarwal AN, Garg M, Gupta D, Chakrabarti A. Itraconazole in chronic cavitary pulmonary aspergillosis: a randomised controlled trial and systematic review of literature. *Mycoses.* 2013;56(5):559-70.
22. Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S, et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. *Eur Respir J.* 2016;47(1):45-68.
23. Denning DW, Venkateswarlu K, Oakley KL, Anderson MJ, Manning NJ, Stevens DA, et al. Itraconazole resistance in *Aspergillus fumigatus*. *Antimicrob Agents Chemother.* 1997;41(6):1364-8.
24. Chryssanthou E. In vitro susceptibility of respiratory isolates of *Aspergillus* species to itraconazole and amphotericin B. acquired resistance to itraconazole. *Scand J Infect Dis.* 1997;29(5):509-12.
25. Resendiz Sharpe A, Lagrou K, Meis JF, Chowdhary A, Lockhart SR, Verweij PE. Triazole resistance surveillance in *Aspergillus fumigatus*. *Medical mycology.* 2018;56(suppl_1):83-92.
26. Mortensen KL, Mellado E, Lass-Flörl C, Rodríguez-Tudela JL, Johansen HK, Arendrup MC. Environmental study of azole-resistant *Aspergillus fumigatus* and other aspergilli in Austria, Denmark, and Spain. *Antimicrob Agents Chemother.* 2010;54(11):4545-9.
27. Lestrade PPA, Buil JB, van der Beek MT, Kuijper EJ, van Dijk K, Kampinga GA, et al. Paradoxal Trends in Azole-Resistant *Aspergillus fumigatus* in a National Multicenter Surveillance Program, the Netherlands, 2013-2018. *Emerging Infect Dis.* 2020;26(7):1447-55.
28. Risum M, Hare RK, Gertsen JB, Kristensen L, Johansen HK, Helweg-Larsen J, et al. Azole-Resistant *Aspergillus fumigatus* Among Danish Cystic Fibrosis Patients: Increasing Prevalence and Dominance of TR34/L98H. *Front Microbiol.* 2020;11:1850.
29. van der Linden JW, Arendrup MC, Warris A, Lagrou K, Pelloux H, Hauser PM, et al. Prospective multicenter international surveillance of azole resistance in *Aspergillus fumigatus*. *Emerging Infect Dis.* 2015;21(6):1041-4.
30. Escribano P, Rodríguez-Sánchez B, Díaz-García J, Martín-Gómez MT, Ibanez-Martínez E, Rodríguez-Mayo M, et al. Azole resistance survey on clinical *Aspergillus fumigatus* isolates in Spain. *Clin Microbiol Infect.* 2022;27(8):1170.e1-1170.e7.
31. Howard SJ, Cerar D, Anderson MJ, Albarrag A, Fisher MC, Pasqualotto AC, et al. Frequency and evolution of Azole resistance in *Aspergillus fumigatus* associated with treatment failure. *Emerg Infect Dis.* 2009;15(7):1068-76.
32. Snelders E, Huis In 't Veld RA, Rijs AJ, Kema GH, Melchers WJ, Verweij PE. Possible environmental origin of resistance of *Aspergillus fumigatus* to medical triazoles. *Appl Environ Microbiol.* 2009;75(12):4053-7.
33. Snelders E, van der Lee HA, Kuijpers J, Rijs AJ, Varga J, Samson RA, et al. Emergence of azole resistance in *Aspergillus fumigatus* and spread of a single resistance mechanism. *PLoS Med.* 2008;5(11):e219.
34. van der Linden JW, Jansen RR, Bresters D, Visser CE, Geerlings SE, Kuijper EJ, et al. Azole-resistant central nervous system aspergillosis. *Clin Infect Dis.* 2009;48(8):1111-3.
35. Mortensen KL, Jensen RH, Johansen HK, Skov M, Pressler T, Howard SJ, et al. *Aspergillus* species and other molds in respiratory samples from patients with cystic fibrosis: a laboratory-based study with focus on *Aspergillus fumigatus* azole resistance. *J Clin Microbiol.* 2011;49(6):2243-51.
36. Howard SJ, Arendrup MC. Acquired antifungal drug resistance in *Aspergillus fumigatus*: epidemiology and detection. *Med Mycol.* 2011;49 Suppl 1:S90-5.

37. Dannaoui E, Garcia-Hermoso D, Naccache JM, Meneau I, Sanglard D, Bouges-Michel C, et al. Use of voriconazole in a patient with aspergilloma caused by an itraconazole-resistant strain of *Aspergillus fumigatus*. J Med Microbiol. 2006;55(Pt 10):1457-9.
38. Pitsouni E, Iavazzo C, Falagas ME. Itraconazole vs fluconazole for the treatment of uncomplicated acute vaginal and vulvovaginal candidiasis in nonpregnant women: a metaanalysis of randomized controlled trials. Am J Obstet Gynecol. 2008;198(2):153-60.
39. Urunsak M, Ilkit M, Evruke C, Urunsak I. Clinical and mycological efficacy of single-day oral treatment with itraconazole (400 mg) in acute vulvovaginal candidosis. Mycoses. 2004;47(9-10):422-7.
40. Graybill JR, Vazquez J, Darouiche RO, Morhart R, Greenspan D, Tuazon C, et al. Randomized trial of itraconazole oral solution for oropharyngeal candidiasis in HIV/AIDS patients. Am J Med. 1998;104(1):33-9.
41. Wilcox CM, Darouiche RO, Laine L, Moskovitz BL, Mallegol I, Wu J. A randomized, double-blind comparison of itraconazole oral solution and fluconazole tablets in the treatment of esophageal candidiasis. J Infect Dis. 1997;176(1):227-32.
42. Rex JH, Pfaller MA, Galgiani JN, Bartlett MS, Espinel-Ingroff A, Ghannoum MA, et al. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro-in vivo correlation data for fluconazole, itraconazole, and candida infections. Subcommittee on Antifungal Susceptibility Testing of the National Committee for Clinical Laboratory Standards. Clin Infect Dis. 1997;24(2):235-47.
43. Takesue Y, Oda S, Fujishima S, Mikamo H, Aikawa N. Clinical efficacy and safety of intravenous itraconazole in the management of invasive candidiasis in patients of surgery and critical care. J Infect Chemother. 2012;18(4):515-21.
44. Cui N, Wang H, Qiu H, Li R, Liu D. Impact of initial empirical antifungal agents on the outcome of critically ill patients with invasive candidiasis: analysis of the China-SCAN study. Int J Antimicrob Agents. 2017;50(1):74-80.
45. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24 Suppl 1:e1-e38.
46. Ullmann AJ, Cornely OA, Donnelly JP, Akova M, Arendrup MC, Arikan-Akdagli S, et al. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: developing European guidelines in clinical microbiology and infectious diseases. Clin Microbiol Infect. 2012;18 Suppl 7:1-8.
47. Lortholary O, Petrikos G, Akova M, Arendrup MC, Arikan-Akdagli S, Bassetti M, et al. ESCMID* guideline for the diagnosis and management of *Candida* diseases 2012: patients with HIV infection or AIDS. Clin Microbiol Infect. 2012;18 Suppl 7:68-77.