EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

# Rationale Document for EUCAST clinical breakpoints

| **Agent** | **Voriconazole** |
|---|---|

| | | |
|---|---|---|
| **Current version** | **3.0** | **19 December 2017 (Voriconazole)** |
| Previous versions | 1.0 | 20 May 2012 (Voriconazole and *Aspergillus* spp.) |
| | 2.0 | 20 March 2010 (Voriconazole) (vs. *Candida*) |
| | 1.0 | 22 May 2008 (Voriconazole) (vs. *Candida*) |

## 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. Voriconazole: Rationale for the clinical breakpoints, version 3.0, 2017. http://www.eucast.org.

## 1. Introduction

Voriconazole is a triazole antifungal agent with *in vitro* activity against *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp.*, Scedosporium apiospermum* and other less common pathogens.

The drug is approved in Europe for the following indications:

(i) Treatment of invasive aspergillosis.
(ii) Treatment of candidaemia in non-neutropenic patients.
(iii) Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*).
(iv) Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.
(v) Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

The mould species most frequently causing human invasive aspergillosis include *Aspergillus fumigatus, Aspergillus flavus*, *Aspergillus terreus* and *Aspergillus niger*. The *in vitro* activity of voriconazole against these species of *Aspergillus* is reasonably uniform, but acquired resistance has been reported, even among 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 differences in their susceptibility to antifungal agents.

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 voriconazole against species of *Candida* is not uniform. MICs are approx. 10 times higher for *C. glabrata* and *C. krusei* than for *C. albicans*. Therefore, every attempt should be made to identify *Candida* to species level. In general, the MICs of voriconazole for fluconazole-resistant isolates are proportionally higher than are those of fluconazole-susceptible isolates.

The European Committee on Antimicrobial Susceptibility Testing Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST) determined breakpoints for voriconazole against *Aspergillus* spp. and *Candida* spp. in 2012 and 2008, respectively.

In version 3.0 of this rationale document, the *Aspergillus* and *Candida* rational documents have been combined into a single document, ECOFFs for *Cryptococcus neoformans* have been included, and MIC distribution tables updated with more information on *Candida* spp, *Aspergillus* spp., and *Cryptococcus neoformans*.

## 2. Dosage

| | | IV (mg/kg/day) | Oral (mg/day unless otherwise stated) |
|---|---|---|---|
| **Adults** | **Loading dose** | 6 x 2 | **In >40 kg** 400 x 2; **In <40 kg** 200 x 2 |
| | **Maintenance dose** | 4 x 2 | **In >40 kg** 200 x 2; **In <40 kg** 100 x 2 |
| **Children (2 to <12 years) and young adolescents (12 to 14 years) with low body weight (<50 kg)** | **Loading dose** | 9 x 2 | NR |
| | **Maintenance dose** | 8 x 2 | 9 x 2<br>(a maximum dose of 350 mg twice daily) |
| **Maximum dose schedule** | **Adults**. If patient response to treatment is inadequate, the oral maintenance dose may be increased to 300 mg twice daily. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily.<br><br>**Children:** If patient response to treatment is inadequate, the dose may be increased by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially). | | |
| **Available formulations** | Voriconazole is available in the following pharmaceutical forms: film-coated tablets (50 or 200 mg), powder for oral suspension (40 mg/ml), and powder for solution for infusion (200 mg). | | |
| **Comments on dosing** | The recommended dosing regimen for prophylaxis and treatment are similar.<br><br>Treatment duration should be as short as possible depending on the patient's clinical and mycological response. Long-term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance. If an adult patient is unable to tolerate treatment at a higher dose, reduce the oral dose by 50 mg steps to the 200 mg twice daily (or 100 mg twice daily for patients less than 40 kg) maintenance dose.<br><br>On the basis of the high oral bioavailability (96%), switching between intravenous and oral administration is appropriate when clinically indicated. Use in paediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied. | | |
| **TDM** | The bioavailability of voriconazole is variable due to variable metabolism and potential drug interactions. Dose adjustment based upon therapeutic drug monitoring (TDM) is recommended (trough concentration determination, see below). Voriconazole displays a non-linear kinetics in adults but a linear kinetics in children. | | |

NR = Not recommended

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

| | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Aspergillus flavus* | 0 | 0 | 0 | 0 | 2 | 4 | 8 | 25 | 46 | 149 | 42 | 4 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 2 |
| *Aspergillus fumigatus* | 0 | 0 | 0 | 0 | 3 | 9 | 85 | 405 | 906 | 288 | 67 | 54 | 44 | 30 | 54 | 0 | 0 | 0 | 0 | 1 |
| *Aspergillus nidulans* | 0 | 0 | 0 | 3 | 2 | 5 | 18 | 42 | 24 | 6 | 1 | 0 | 1 | 5 | 0 | 0 | 0 | 0 | 0 | 1 |
| *Aspergillus niger* | 0 | 0 | 0 | 1 | 1 | 2 | 4 | 13 | 68 | 84 | 35 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 |
| *Aspergillus terreus* | 0 | 0 | 0 | 0 | 1 | 2 | 2 | 18 | 52 | 154 | 67 | 9 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| *Aspergillus versicolor* | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 6 | 7 | 7 | 3 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | ND |
| *Aspergillus sydowii* | 0 | 0 | 0 | 0 | 1 | 1 | 4 | 11 | 17 | 21 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |
| *Candida albicans** | 50 | 996 | 5139 | 5235 | 1107 | 530 | 207 | 106 | 63 | 42 | 18 | 13 | 18 | 22 | 78 | 6 | 0 | 0 | 0 | 0.032 |
| *Candida auris*** | 0 | 0 | 2 | 0 | 2 | 1 | 17 | 12 | 35 | 37 | 13 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | ND |
| *Candida dubliniensis** | 0 | 0 | 0 | 59 | 38 | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.032 |
| *Candida glabrata* | 0 | 5 | 26 | 115 | 258 | 745 | 1519 | 1454 | 855 | 384 | 227 | 196 | 95 | 20 | 2 | 6 | 0 | 0 | 0 | 1 |
| *Candida guilliermondii* | 0 | 0 | 0 | 5 | 11 | 53 | 26 | 16 | 6 | 5 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |
| *Candida krusei* | 0 | 0 | 0 | 3 | 3 | 7 | 43 | 179 | 149 | 33 | 6 | 3 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| *Candida parapsilosis** | 0 | 6 | 287 | 1326 | 510 | 197 | 123 | 77 | 23 | 16 | 3 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0.06 |
| *Candida tropicalis** | 0 | 28 | 133 | 602 | 934 | 732 | 274 | 113 | 51 | 32 | 8 | 2 | 10 | 20 | 16 | 3 | 0 | 0 | 0 | 0.125 |
| *Candida kefyr* | 0 | 0 | 5 | 23 | 3 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |
| *Candida lusitaniae* | 0 | 0 | 10 | 56 | 14 | 3 | 3 | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |
| *Saccharomyces cerevisiae* | 0 | 0 | 0 | 3 | 2 | 12 | 15 | 17 | 8 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |
| *Cryptococcus neoformans* | 0 | 0 | 0 | 34 | 44 | 126 | 127 | 101 | 33 | 9 | 3 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0.5 |
| *Cryptococcus gattii* | 0 | 0 | 0 | 1 | 1 | 7 | 11 | 11 | 19 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |

The table includes EUCAST 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 ECOFFs have 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* 4149/4237 (98%) MICs were ≤0.125 mg/L (15 data sets); for *C. parapsilosis* 1325/1362 (97%) MICs were ≤0.125 mg/L (16 data sets); and for *C. tropicalis* 676/747 (91%) MICs were ≤0.125 mg/L (14 data sets). The MIC dataset for *Cryptococcus* were truncated at 0.016 mg/L. ** *C. auris* MIC data-set is from a single centre. It includes isolates from several centres in India, but may include genetically related isolates due to the outbreak characteristics of *C. auris* infections. Although not fulfilling the criteria for ECOFF setting, this data is included for general information and comparison given the emergence of this organism worldwide.

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

| | 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Aspergillus flavus* | 283 | 0 | 0 | 0 | 0 | 1 | 1 | 3 | 9 | 16 | 53 | 15 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 |
| *Aspergillus fumigatus* | 1945 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 21 | 47 | 15 | 3 | 3 | 2 | 2 | 3 | 0 | 0 | 0 | 0 | 1 |
| *Aspergillus nidulans* | 107 | 0 | 0 | 0 | 3 | 2 | 5 | 17 | 39 | 22 | 6 | 1 | 0 | 1 | 5 | 0 | 0 | 0 | 0 | 0 | 1 |
| *Aspergillus niger* | 210 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 6 | 32 | 40 | 17 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| *Aspergillus terreus* | 306 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 6 | 17 | 50 | 22 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| *Aspergillus versicolor* | 27 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 22 | 26 | 26 | 11 | 0 | 4 | 4 | 0 | 0 | 0 | 0 | 0 | ND |
| *Aspergillus sydowii* | 55 | 0 | 0 | 0 | 0 | 2 | 2 | 7 | 20 | 31 | 38 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |
| *Candida albicans** | 13630 | 0 | 7 | 38 | 38 | 8 | 4 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0.032 |
| *Candida auris*** | 126 | 0 | 0 | 2 | 0 | 2 | 1 | 13 | 10 | 28 | 29 | 10 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | ND |
| *Candida dubliniensis** | 101 | 0 | 0 | 0 | 58 | 38 | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.032 |
| *Candida glabrata* | 5907 | 0 | 0 | 0 | 2 | 4 | 13 | 26 | 25 | 14 | 7 | 4 | 3 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *Candida guilliermondii* | 125 | 0 | 0 | 0 | 4 | 9 | 42 | 21 | 13 | 5 | 4 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |
| *Candida krusei* | 427 | 0 | 0 | 0 | 1 | 1 | 2 | 10 | 42 | 35 | 8 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| *Candida parapsilosis** | 2571 | 0 | 0 | 11 | 52 | 20 | 8 | 5 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.06 |
| *Candida tropicalis** | 2958 | 0 | 1 | 4 | 20 | 32 | 25 | 9 | 4 | 2 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0.125 |
| *Candida kefyr* | 34 | 0 | 0 | 15 | 68 | 9 | 6 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |
| *Candida lusitaniae* | 91 | 0 | 0 | 11 | 62 | 15 | 3 | 3 | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |
| *Saccharomyces cerevisiae* | 60 | 0 | 0 | 0 | 5 | 3 | 20 | 25 | 28 | 13 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |
| *Cryptococcus neoformans* | 478 | 0 | 0 | 0 | 7 | 9 | 26 | 27 | 21 | 7 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.5 |
| *Cryptococcus gattii* | 58 | 0 | 0 | 0 | 2 | 2 | 12 | 19 | 19 | 33 | 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | ND |

This table contains a percentage presentation of the MIC data from table 3a. Footnotes for Table 3a apply for this table as well.

## 4. Breakpoints prior to harmonisation (mg/L) S≤/R>

| | European breakpoints | CLSI[1] | |
|---|---|---|---|
| **General breakpoints:** | | | |
| | NA | | |
| **Species related breakpoints:** | | | |
| | NA | *C. albicans*<br>*C. krusei*<br>*C. parapsilosis*<br>*C. tropicalis* | S≤0.12 / R>0.5<br>S≤0.5 / R>1<br>S≤0.12 / R>0.5<br>S≤0.12 / R>0.5 |

NA = Not available

[1]CLSI breakpoints converted to European terminology

| **5. Pharmacokinetics** | | | | | | |
|---|---|---|---|---|---|---|
| | Intravenous formulation | | | Oral formulation | | |
| Dosage | 6 mg/kg x 2 on day 1; maintenance dose 4 mg/kg x 2<br>Steady state in patients with venous haemofiltration (1) | 6 mg/kg x 2 on day 1; maintenance dose 4 mg/kg x 2<br>454 patients with IA (2) | 6 mg/kg x 2 on day 1; maintenance dose 3 mg/kg x 2<br>Healthy volunteers (3, 4) | 400 mg x 2 on day 1; maintenance dose 200 mg x 2<br>Healthy volunteers (3, 4) | 400 mg x 2 on day 1; maintenance dose 200 mg x 2<br>31 AML patients (5) | 6 mg/kg x 2 on day 1; 4 mg/kg x 2 days 2-7; maintenance dose 300 mg x 2<br>454 patients with IA (2) |
| Cmax ± SD (mg/L)<br>Mean (CV ), [Range] | 5.9 ± 2.9 | | [3-4.7] | [2-2.3] | 3.57 ± 1.73 | |
| Cmin ± SD (mg/L)<br>Mean (CV ), [Range] | 1.1 ± 0.3 | 3.10 (52) | [0.39-0.46] | NA | 1.40 ± 1.29 | 1.51 (74) |
| Cav (mg/L)<br>Mean (CV) | | | | | | |
| Total body clearance/F± SD (L/h);<br>Mean (CV ) | 12.9 ± 6.7 | | 14-35 (F>0.9)* | | 11.52 ± 8.49 | |
| T ½ ± SD (h),<br>Mean (range) | 14. 7± 6.5 | | ~6 | | 11.31 ± 9.87 | |
| $AUC_{24h}$ ± SD (mg.h/L) total drug;<br>Mean (CV ), [Range] | 44.8 ± 7.4 | 100.2 ± 43.08 | 26 | 18-22 | 52.40 ± 37.16 | 65.8 ± 29.62 |
| Fraction unbound (IQR) | 42 | | | | | |
| Volume of distribution/F (L/kg)*;<br>Mean (CV ), [Range] | 2.96 ± 0.55 | | 4.6 | | | |
| Comments | *Excellent bioavailability in healthy patients (85-92%), but reduced oral bioavailability (60-65%) in some populations, including pediatrics (6, 7). Co-administration with high fat meals decreases absorption (AUC ↓ 35).<br>• The pharmacokinetics of voriconazole are non-linear in adults likely due to saturation of its metabolism with respect to dose. The variability in plasma concentrations and systemic exposure varies >100-fold between subjects (based on trough concentrations), depending partly on the respective genotype of the hepatic cytochrome P450. CYP2C19 exhibits genetic polymorphism resulting in an approximately 4-fold higher exposure for poor metabolisers than for extensive metabolisers. | | | | | |

| | |
|---|---|
| | • The coefficient of variation of the AUC has been estimated to be 74-100. Comparable exposures are obtained in children with 8 mg/kg x 2 iv or 350 mg x 2 oral (voriconazole product information). Similar dose adjustments may be required for other patient populations. Protein binding has been estimated to 58% (voriconazole product information). In a recent study it was however lower in ICU patients 49.6 (42.5-52.5) (8) |

## 6. Pharmacodynamics

| | *Aspergillus* spp | *Candida* spp | *Cryptococcus* spp | |
|---|---|---|---|---|
| Total drug $tAUC_{24}$:MIC ratio associated with near maximum effect in a dynamic *in vitro* model of invasive pulmonary aspergillosis | *A. fumigatus*=32.1 (9) | | | |
| *f*$AUC_{24}$/MIC (95% CI) associated with 50% of maximal effect in an *in vitro* pharmacokinetic/pharmacodynamic model | *A. fumigatus*=25.28 (18-35.6) (10) | *C. krusei*=31 (18-52)<br>*C. glabrata*=23 (11-47) (11) | | |
| *f*$AUC_{24}$/MIC±SD (95% CI) associated with 50% survival in non-neutropenic animal model of disseminated aspergillosis | *A. fumigatus*= 5.86[b] (12)<br>*A. flavus*= 14 ± 9[c] (13) | | | |
| *f*$AUC_{24}$/MIC±SD [range] for achieving ED50 | | *C. albicans*= 58.9 ± 66.4 [2-190] (14) | | |
| *f*AUC/MIC for 2 log reduction in 24 h | | | | |
| *f*AUC/MIC from clinical data (CART) | | | | |
| Trough (Cmin) concentration associated with an approximately 70% response rate in adult patients | >1-2 mg/L | | | |
| Comments | [a] *f*$AUC_{24}$/CLSI MIC for achieving ED50 is the mean *f*$AUC_{24}$/CLSI MIC equivalent to ED50 in mg/kg/24h. ED50 is the dose required to achieve 50% of Emax after 24 h of treatment. The f$AUC_{24}$/EUCAST MIC was calculated based on the EUCAST MICs of the *Candida* isolates used by Andes et al (14). The EUCAST MICs were 0.4 (1.6-0) twofold dilutions lower than CLSI MICs.<br>[b] the tAUC/EUCAST MIC associated with 50% survival was 17.6 (15). Since the unbound fraction of voriconazole in animals is 29.87% (12), the fAUC/EUCAST MIC is estimated to be 5.86.<br>[c] This is the average fAUC/MIC among four *A. flavus* isolates with voriconazole MICs of 0.25-4 mg/L. A relatively higher exposure was required for the susceptible *A. flavus* strains in order to produce the same effect compared to *A. fumigatus*.<br><br>• A trough concentration of >1 mg/L has been associated with a higher probability of a successful outcome in a cohort of patients most of whom had invasive aspergillosis (16) and in the paediatric setting (17).<br>• A trough concentration:MIC ratio of 2-5 (CLSI MIC method) is associated with a higher probability of a successful clinical outcome, but clinical outcomes from both *Candida* and *Aspergillus* were considered to derive this endpoint (18). A trough/EUCAST MIC ratio of 1 was associated with 50% of maximal effect in an in vitro pharmacokinetic/pharmacodynamic model of invasive aspergillosis (10).<br>• Pharmacodynamic studies have not been performed for *Cryptococcus* spp. yet.<br>• Cells are left empty when data are not readily available. | | | |

## 7. Monte Carlo simulations and Pk/Pd breakpoints

### *Aspergillus* and *Candida*

The steady state mean ± SD $tAUC_{24}$s after a loading dose of 6 mg/kg x 2 on day 1 followed by 1) the i.v. maintenance dose of 4 mg/kg x 2 (100.2 ± 43.08 mg.h/l), 2) the oral maintenance dose of 300 mg x 2 (65.8 ± 29.62 m.h/l) or 3) the oral maintenance dose of 200 mg x 2 (52.4 ± 37.16 mg.h/l) were used in Monte Carlo analysis in order to determine the probability of 5,000 simulated patients attaining the pharmacodynamic targets 60 $fAUC_{24}$/MIC for *Candida* and 15 $fAUC_{24}$/MIC for *Aspergillus* considering that the unbound fraction is 58% (2, 5)

| MIC (mg/L) | Target attainment for *A. fumigatus* | | | Target attainment for *C. albicans* | | |
|---|---|---|---|---|---|---|
| | Oral 200x2 mg | Oral 300x2 mg | Iv 4x2 mg/kg | Oral 200x2 mg | Oral 300x2 mg | Iv 4 x2 mg/kg |
| 0.015 | 100 | 100 | 100 | 100 | 100 | 100 |
| 0.03 | 100 | 100 | 100 | 100 | 100 | 100 |
| 0.06 | 100 | 100 | 100 | 99 | 100 | 100 |
| 0.125 | 100 | 100 | 100 | 92 | 100 | 100 |
| 0.25 | 99 | 100 | 100 | 61 | 89 | 99 |
| 0.5 | 92 | 100 | 99 | 21 | 34 | 74 |
| 1 | 62 | 88 | 74 | 3 | 2 | 15 |
| 2 | 21 | 34 | 14 | 0 | 0 | 0 |
| 4 | 3 | 2 | 0 | 0 | 0 | 0 |

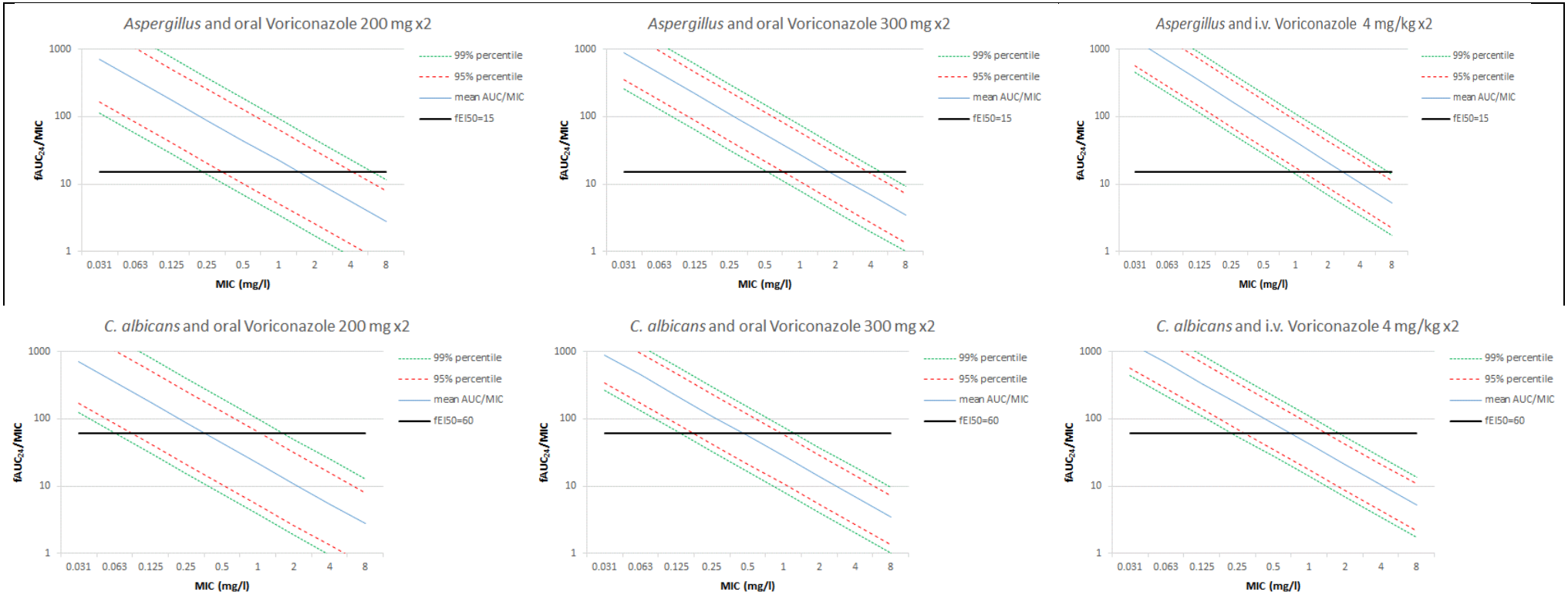


**Figure 1.** Probabilities of target attainment for different dosing regimens of voriconazole against *Candida* and *Aspergillus*.

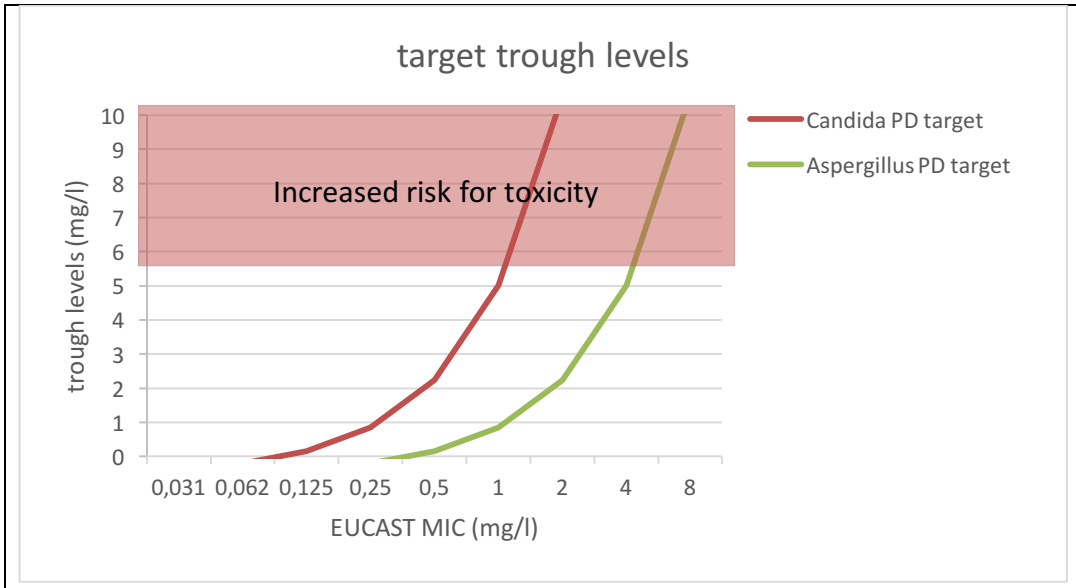


**Figure 2.**
Serum trough levels of voriconazole required to attain the pharmacodynamic target for *Candida* ($fAUC_{24}$/MIC= 60) and for *Aspergillus* ($fAUC_{24}$/MIC= 15). The AUC was correlated with trough levels with the following equation $AUC_{12}$= 7.011 + 12.687 * trough concentrations (2, 15). The recommended trough level during treatment for aspergillosis is >1-2 mg/L. Isolates with MICs >1 mg/L for *Candida albicans* and >4 mg/L for *Aspergillus* spp would require voriconazole trough levels ≥5.5 mg/L which are associated with increased risk of toxicity (19). These align with the selected EUCAST breakpoint for *A. fumigatus* of 1 mg/L (15).

## *Cryptococcus*

Monte Carlo simulations are not available for EUCAST data because there is not a clear Pk/Pd target defined and voriconazole is not approved for the treatment of *Cryptococcus* infections.

## 8. Clinical data

***Aspergillus***

Voriconazole is a first-line agent for the treatment of invasive aspergillosis. Use of the currently licensed regimen with at least 1 week of i.v. dosing results in better clinical responses and overall mortality at the end of 12 weeks compared with amphotericin B deoxycholate (20). Voriconazole is the drug of choice for treatment of aspergillosis of the central nervous system (21). Efficacy and safety of voriconazole was compared to voriconazole and anidulafungin combination therapy for invasive aspergillosis in a randomized, double-blind multi-center trial conducted in patients with hematologic malignancies and hematopoietic cell transplantation. Efficacy and safety between both regimens were not statistically significantly different (six week all-cause mortality was 27.5% for voriconazole and 19.3% for combination therapy) (22). In a randomized, double-blind multicenter trial (SECURE trial) for the primary treatment of invasive mould disease, the efficacy and safety of voriconazole was compared to isavuconazole revealing a similar efficacy of both drugs (six week all-cause mortality was 20% with voriconazole) but a higher rate of drug-related events with voriconazole (23).

The frequency of voriconazole resistance is largely undefined, as many centres do not routinely test the susceptibility of their *Aspergillus* isolates. Itraconazole resistance and cross resistance to other triazoles have currently been reported in most European countries, India, Iran, Taiwan, China, Australia, S-America, Africa and the USA (24-30). Most commonly the resistance is linked to point mutations in the target gene *cyp51A* (31-33). However, at some centres a significant proportion of the isolates with elevated voriconazole MICs lack these mutations, suggesting that other mechanisms including upregulated efflux pumps or up-regulation of target production may also play a role (34). 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 (35, 36). 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 voriconazole MICs obtained by EUCAST for isolates with different *cyp51A* point mutations vary according to the underlying mechanism but they are >1 mg/L for the most commonly identified mutants (alterations at G54, G138, M220, and the environmental phenotypes $TR_{34}$/L98H and $TR_{46}$/Y121F/T289A).

Correlation of *in vitro* voriconazole EUCAST MIC data with clinical outcome has been shown in studies comparing outcome between susceptible and molecularly confirmed resistant isolates (37, 38). If the MIC suggests the isolate may not belong to the wild-type population, voriconazole should not be used.

***Candida***

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

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

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

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

The response was above 72% for infections caused by every species except *C. glabrata* where the percentage response was 55%. Geometric mean MICs were below 0.25 mg/L except for *C. glabrata* and *C. krusei.* CART analysis of response versus MIC or $Log_2$MIC yielded an MIC value that allowed discrimination between successes and failures. However, the statistical support for this classification tree was limited as the relative error for the best tree was 0.78, the relative risk was 1.09 and the area under ROC curve was 0.6 with a true positive rate of 78% but a false positive rate exceeding 50%.

CART analysis was made separately for infections due to *C. glabrata* because of the lower response rate. CART analysis of outcome versus MIC was unable to produce an interpretable classification tree of MIC values versus successes and failures (39).

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

***Cryptococcus***
There is no clinical data regarding efficacy against *Cryptococcus* infections.

## 9. *Aspergillus* and *Candida* Clinical breakpoints

**Non-species-related breakpoints**

Non-species related breakpoints are determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes. In the case of voriconazole, the pharmacokinetics are variable and clinical data for species other than *C. albicans, C. parapsilosis* and *C. tropicalis* and for isolates with higher MICs are scarce.

EUCAST has therefore refrained from determining non-species related breakpoints for voriconazole.
There is insufficient evidence to set non-species-related breakpoints against *Aspergillus* spp.

**Species-related breakpoints**

| Organism group | MIC breakpoints (mg/L) | | Notes |
|---|---|---|---|
| | S ≤ | R > | |
| *A. fumigatus* | 1* | 2* | *Provided adequate drug exposure (>1 mg/L) has been confirmed using TDM (Fig. 2 above). The intermediate category is introduced to acknowledge that in some clinical situations voriconazole can be considered for treatment if a trough level of ≥ 2 mg/L is confirmed by TDM. |
| *C. albicans* | 0.06 | 0.25 | A clinical response of 76% was achieved in infections caused by the species listed below when MICs were lower than or equal to the epidemiological cut-offs. Therefore, wild type populations of *C. albicans, C. dubliniensis, C. parapsilosis* and *C. tropicalis* are considered susceptible.<br>For *Candida* the intermediate category is introduced to acknowledge that the increased exposure obtained by iv dosing is sufficient (potentially confirmed by TDM).<br>There is not enough information available for the response to voriconazole of infections caused by *Candida* isolates with higher MICs or infections caused by *Cryptococcus* species. |
| *C. dubliniensis* | 0.06 | 0.25 | |
| *C. parapsilosis* | 0.125 | 0.25 | |
| *C. tropicalis* | 0.125 | 0.25 | |

Breakpoints 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 voriconazole. 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 population of *A. flavus, A. nidulans, A. terreus*, the MIC distribution for *A. nidulans* is similar to those obtained for *A. fumigatus* but those for *A. flavus* and *A. terreus* are slightly higher. Moreover the fAUC/MIC ratio required for success in animal models is higher for *A. flavus* than for *A. fumigatus* (Table 6). Whether that translates into differential clinical outcome remains to be understood. However, for this reason EUCAST has abstained from setting breakpoints for these non-*A. fumigatus* species (9, 16-18, 40, 41).

Increasing data suggest that TDM is an important adjunct for the optimal clinical use of voriconazole against aspergillosis. Most accept that a trough concentration of >1-2 mg/L is a reasonable target. This was originally based on the $MIC_{90}$ of medically important fungal

| | |
|---|---|
| | pathogens, but several recent studies suggest that patients who attain this target have better clinical outcomes and survival. Isolates with a higher MIC require proportionally higher drug exposure to achieve the same effect (Figure 2). While there are no clinical data available that have specifically used EUCAST MIC methodology, preclinical models suggest that a trough:CLSI MIC ratio value of >2-5 is a potential target for therapeutic drug monitoring for treatment of non-wild-type isolates (e.g. MIC 2 mg/L). If the MIC is used in this manner to individualise dosing, the MIC should be repeated to ensure robust estimates are obtained.<br><br>*Candida* strains with MIC values above the S/I breakpoint are rare among the species that are normally susceptible. 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 | There is inadequate clinical information on the clinical outcome for patients infected with wild type isolates of non-*fumigatus Aspergillus* species. If the voriconazole exposure-response relationships for these organisms are similar to those for *A. fumigatus*, the breakpoints for *A. fumigatus* could be applied to these species. Until these data are available, EUCAST has refrained from setting breakpoints for these species.<br><br>A 21% lower response to voriconazole in invasive candidosis caused by *C. glabrata* has been shown in clinical studies when compared to the response in infections caused by *C. albicans, C. parapsilosis* and *C. tropicalis.* CART analysis of outcome versus MIC did not find higher MICs to be the variable causing this reduced response so higher MICs were not the explanation for the lower response. Consequently, there is currently insufficient evidence to set clinical breakpoints for *C. glabrata.*<br><br>The apparent clinical response in infections caused by *C. krusei* is similar to that in infections caused by *C. albicans, C. parapsilosis* and *C. tropicalis.* However, as there were only 9 cases available for analysis, there is currently insufficient evidence to set clinical breakpoints for *C. krusei*. |
| Clinical qualifications | The EUCAST AFST considers voriconazole appropriate therapy for the following *Aspergillus* infections when caused by wild type *A. fumigatus* isolates:<br>• Primary treatment of invasive aspergillosis including *Aspergillus* infections of the central nervous system<br>• Treatment of chronic pulmonary aspergillosis<br><br>The EUCAST AFST considers voriconazole appropriate therapy for the following *Candida* infections when caused by wild type *C. albicans*, *C. dubliniensis, C. parapsilosis* and *C. tropicalis*:<br>• Candidaemia in non-neutropenic patients<br>• Invasive candidosis<br>• Oesophageal candidosis |
| Dosage | The EUCAST breakpoints apply to licensed dosing of voriconazole. Dosage escalation may be considered if clinically indicated, and may |

| | |
|---|---|
| | be guided by therapeutic drug monitoring. |
| Additional comment | The pharmacokinetics of voriconazole are highly variable. It has been shown that there is a decrease in the response of patients with invasive fungal infections when voriconazole trough blood levels are below 1 mg/L (16, 17, 42). Conversely, voriconazole trough blood levels above 5.5 mg/L have been associated with an increase in toxicity (16). Others report a favourable response when random voriconazole blood concentrations exceed 2.05 mg/L (43). Voriconazole therapeutic drug monitoring is highly recommended to ensure optimal drug exposure. Voriconazole exhibits (pseudo) linear pharmacokinetics in younger children and transitions in adolescence to classical non-linear pharmacokinetics. The probability of elevated liver function tests and central nervous system toxicity is higher with higher drug exposures.<br><br>Of note, most experience rests with *Aspergillus* infections and none with invasive cryptococcosis.<br><br>The EUCAST AFST will review breakpoints for voriconazole when there are more data available for species which were not assigned breakpoints during the present review, when there are clinical data for *Candida* isolates with MIC values outside the wild type distribution or when there are data to more closely define therapeutic and toxic levels of voriconazole. |

## 10. Exceptions noted for individual national committees

None.

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