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# EUCAST Technical Note on fluconazole

*The European Committee on Antimicrobial Susceptibility Testing—Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST)**

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## INTRODUCTION

Fluconazole is an azole antifungal agent active against *Candida* spp. and *Cryptococcus* spp. It can be administered orally or intravenously. It has been used for treating *Candida* infections, and is effective in treating infections caused by strains of *Candida albicans*, *Candida tropicalis* and *Candida parapsilosis* without acquired resistance mechanisms. The drug is ineffective for treating infections caused by *Candida krusei*, which is naturally resistant. The response of infections caused by *Candida glabrata* is variable, as the wild-type MIC distribution straddles most reasonable MIC breakpoints. Every attempt should be made to identify *Candida* isolates to the species level before or in conjunction with antimicrobial susceptibility testing.

The EUCAST-AFST (European Committee on Antimicrobial Susceptibility Testing—Subcommittee on Antifungal Susceptibility Testing) has determined breakpoints of fluconazole for *Candida* spp. This Technical Note is based on the EUCAST fluconazole rationale document (available on the EUCAST website: http://www.eucast.org). The rationale document includes more detail and published references related to the selection of EUCAST-AFST breakpoints.

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## DOSAGE

The EUCAST-AFST has determined clinical breakpoints for a fluconazole dose of 400–800 mg/day, given orally or parenterally.

## MIC DISTRIBUTIONS

The MIC values for wild-type *Candida* spp. are shown in Table 1. The MIC distributions are based on large collections of MIC values from several investigators, obtained using the EUCAST-AFST, CLSI and Etest methods. Wild-type isolates of *C. albicans*, *C. tropicalis* and *C. parapsilosis* exhibit MICs of ≤2 mg/L, whereas MICs for *C. glabrata* are higher at 32 mg/L, and those for *C. krusei* are higher still at up to 128 mg/L. Updates on wild-type MIC distributions can be found at http://www.eucast.org.

## ESTABLISHED BREAKPOINTS

Only Norway and Germany have established national breakpoints for fluconazole, at sensitive (S) ≤4/resistant (R) >32 mg/L and S ≤4/R >16 mg/L respectively.

## PHARMACOKINETIC DATA

The pharmacokinetic data used to evaluate fluconazole were based on standard doses of 400 and 800 mg (Table 2).

## PHARMACODYNAMIC DATA

Fluconazole is thought to be fungistatic when given in lower doses, and fungicidal when given in higher doses. The pharmacodynamic index best related to outcome is the fAUC/MIC. This is virtually the same as the dose/MIC, since the AUC and the dose are highly correlated. Hence, dose provides a good surrogate for the AUC. The

**Table 1.** Fluconazole MIC distributions[a] for *Candida* spp.

| Species | 0.016 | 0.032 | 0.064 | 0.125 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | 128 | 256 | 512 | ECOFF (mg/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Candida albicans* | 14 | 57 | 275 | 4010 | 6737 | 2518 | 1081 | 439 | 136 | 154 | 107 | 88 | 247 | 92 | 35 | 1 | 1 |
| *Candida glabrata* | 2 | 7 | 5 | 14 | 11 | 48 | 110 | 323 | 888 | 1204 | 1353 | 534 | 261 | 157 | 75 | 26 | 32 |
| *Candida krusei* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 9 | 50 | 314 | 229 | 59 | 11 | 0 | 128 |
| *Candida parapsilosis* | 0 | 0 | 4 | 62 | 415 | 980 | 646 | 241 | 70 | 58 | 39 | 11 | 5 | 2 | 2 | 1 | 2 |
| *Candida tropicalis* | 0 | 0 | 2 | 119 | 443 | 743 | 513 | 269 | 60 | 24 | 27 | 10 | 9 | 10 | 0 | 0 | 2 |

ECOFF, epidemiological cut-off value (mg/L) as defined by EUCAST.
[a]MICs determined according to EUCAST, CLSI and Etest methods are included in the distributions. Separate distributions for the three methods are shown on http://www.eucast.org.

**Table 2.** Pharmacokinetic data for fluconazole

| Parameter | | |
|---|---|---|
| Dosage (mg) | 400 | 800 |
| $C_{max}$ (mg/L) | 18.9–30.6 | 34 |
| $C_{min}$ (mg/L) | 21–23 | NA |
| Total body clearance (L/h) | NA | NA |
| $T_{1/2}$ (h) | 31–37.2 | 31–37.2 |
| $AUC_{24\ h}$ (mg.h/L) | 350 | 813.27 |
| Fraction unbound (%) | 88–89 | 88–89 |
| Volume of distribution (L) | 0.7–0.8 | 0.7–0.8 |

NA, not available.

pharmacokinetic/pharmacodynamic target was explored using Monte Carlo simulations to estimate the likelihood that a target fAUC/MIC of 50–100 could be attained. Most cases of candidosis involve immunocompromised patients; hence, fungicidal levels are considered to be a prerequisite for success. Therefore, an fAUC/MIC target of at least 100 is desirable. Classification and regression tree (CART) analysis supports this target, since >90% of patients given at least 100 mg of fluconazole daily are likely to respond.

## CLINICAL EFFICACY

There is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct, albeit imperfect, relationship between the AUC (or dose) and a successful clinical response in cases of oral candidosis and, to a lesser extent, in cases of candidaemia. Similarly, cure is less likely for infections caused by strains with higher MICs.

The EUCAST-AFST considers that fluconazole is appropriate therapy for candidaemia in neutropenic and non-neutropenic patients, chronic disseminated candidosis, disseminated cutaneous neonatal candidosis, urinary tract infections, lower respiratory tract infections, osteomyelitis, arthritis, infections of the gallbladder, pancreas and peritoneum, endocarditis, pericarditis, suppurative phlebitis, myocarditis, meningitis and endophthalmitis caused by *Candida* spp., non-genital mucocutaneous candidosis and genital candidosis.

The EUCAST-AFST considers that fluconazole is appropriate prophylaxis for neutropenic patients, particularly those colonised with *C. tropicalis*, as well as for allogeneic haematopoietic stem-cell transplant recipients and recipients of liver transplants, who are considered to be at high risk for infection.

## BREAKPOINTS

Breakpoints are summarised in Table 3.

### Non-species-related breakpoints

These have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data, and are independent of the MIC distributions for specific species. The column 'non-species-related breakpoints' is reserved for those species not indicated separately in Table 3. These breakpoints

**Table 3.** EUCAST clinical MIC breakpoints for fluconazole, 17 April 2007

| | Species-related breakpoints (S[redacted]R>) | | | | | |
|---|---|---|---|---|---|---|
| | *Candida albicans* | *Candida tropicalis* | *Candida parapsilosis* | *Candida glabrata* | *Candida krusei* | Non-species-related breakpoints (S[redacted]R>) |
| Fluconazole | 2/4 | 2/4 | 2/4 | IE | – | 2/4 |

IE, there is insufficient evidence that the species in question is a good target for therapy with fluconazole; –, susceptibility testing not recommended, as this species is a poor target for therapy with fluconazole.

should not be applied to species for which susceptibility testing is not recommended (marked with '–' or 'IE' in EUCAST breakpoint tables).

### Species-related breakpoints

The in-vitro activity of fluconazole against *Candida* spp. is not uniform. The species associated most frequently with human infections include *C. albicans*, *C. parapsilosis* and *C. tropicalis*, and these exhibit MIC values of ≤2 mg/L when mechanisms of resistance to fluconazole are absent.

### Species without breakpoints

*C. krusei* is considered to be inherently resistant, exhibiting high MIC values. A significant number of infections involve *C. glabrata*, which exhibits fluconazole MICs of 2–32 mg/L. Any reasonable breakpoint would divide wild-type *C. glabrata* isolates, thereby frustrating reliable and reproducible susceptibility testing. For these reasons, the EUCAST-AFST has refrained from assigning breakpoints for fluconazole to *C. krusei* and *C. glabrata*, and advises that alternative drugs be employed to manage infections caused by these species. One exception would be urinary tract infections caused by *C. glabrata*, since fluconazole is concentrated in the urine to levels that are likely to exceed the MIC for this species. This fact also serves to emphasise the need to correctly identify yeast isolates recovered from urine and other clinical specimens.