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## Isavuconazole MIC distribution of 29 yeast species responsible for invasive infections (2015–2017)

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1 **Isavuconazole MICs distribution of 29 yeast species responsible for invasive infections**  
2 **(2015-2017)**

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## 22 **Abstract**

### 23 **Objectives**

24 Isavuconazole is a recent extended-spectrum triazole with activity against yeasts. However,  
25 few data are available on the *in vitro* activity on rare yeast species. We report minimum  
26 inhibitory concentration (MIC) distribution of isavuconazole compared to fluconazole for a  
27 large collection of common or rare yeasts.

### 28 **Methods**

29 Isavuconazole and fluconazole MICs were determined using the EUCAST method for 1457  
30 clinical isolates, mainly recovered from invasive infections, belonging to 29 species. They  
31 were sent to the National Reference Center for Invasive Mycoses & Antifungals between  
32 January 2015 and October 2017 and species identification was performed by polyphasic  
33 approach (MALDI-TOF and molecular method).

### 34 **Results**

35 Isavuconazole had effective *in vitro* activity against *Cryptococcus neoformans*  
36 (MIC<sub>90</sub><0.25mg/L), the five most common *Candida* spp. (MIC<sub>90</sub>≤0.5mg/L for *Candida*  
37 *albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis* and, *Candida krusei*)  
38 and also against the majority of rare species, including *Candida kefyr* and *Candida lusitanae*.  
39 A few isolates of *C. albicans* (0.7%, 3/404), *C. glabrata* (2.7%, 5/184), *C. tropicalis* (1.0%,  
40 1/96) and *C. parapsilosis* (0.8%, 1/127) exhibited MIC ≥4 mg/L. All were also resistant to  
41 fluconazole according to the EUCAST breakpoints. Some isolates with isavuconazole MIC  
42 ≥4 mg/L were also observed among rarer species: *Meyerozyma guilliermondii* (8.7%, 2/23),  
43 *Wickerhamomyces anomalus* (10.0%, 1/10). Other rare species *Saprochaete clavata*,  
44 *Magnusiomyces capitatus* and *Rhodotorula mucilaginosa* had high MIC<sub>50</sub> (≥1mg/L) and  
45 MIC<sub>90</sub> (≥4mg/L) and could be considered as resistant to isavuconazole.

### 46 **Conclusions**

47 We confirmed the good *in vitro* activity of isavuconazole against common *Candida*,  
48 *Cryptococcus* species and majority of the rare yeast species studied.

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## 72 **Introduction**

73 Isavuconazole is part of the triazoles antifungal agents which exert antifungal activity through  
74 the inhibition of sterol 14- $\alpha$ -demethylase. It is currently approved as one of the first line  
75 therapy for human invasive aspergillosis and mucormycosis (1-4). *In vitro* activity of  
76 isavuconazole against *Cryptococcus* spp. is also reported (5) and a prospective clinical trial  
77 enrolling patients with candidemia or invasive candidiasis failed to demonstrate the non-  
78 inferiority with caspofungin (6). *In vitro*, isavuconazole is active against common *Candida*  
79 species with higher MIC value for *Candida glabrata* and *Candida krusei* than for *Candida*  
80 *albicans* (7-9). Few data are available for rare yeast species.

81 We here reported minimal inhibitory concentrations (MICs) of isavuconazole using EUCAST  
82 method for a large collection of yeast species recovered mainly from blood culture during a  
83 prospective multicenter surveillance program. We compared the results with those of  
84 fluconazole for which breakpoints (BP) exist for several *Candida* species and given that  
85 fluconazole is one of the first option for treating invasive yeast infections. The objective was  
86 to know whether isavuconazole could be proposed as an option for also treating yeast  
87 infection in case of concomitant mold infection, justifying using an extended spectrum azole.

## 88 **Methods**

### 89 **Isolates and species identification**

90 As part of its missions of expertise and surveillance, the National Reference Center for  
91 Invasive Mycoses & Antifungals (NRCMA) received clinical isolates involved in invasive  
92 infections from hospitals in France. Yeast isolates received between January 2015 and  
93 October 2017 were checked for purity on chromogenic medium BBL Chromagar™ *Candida*  
94 (BD) or Niger seed medium for *Cryptococcus* species and identified at the species level by  
95 phenotypic method and mass spectrometry (MALDI-TOF, Bruker Biotyper, Bruker Daltonic,  
96 Germany). For *C. albicans* and *Candida dubliniensis*, a duplex PCR was performed (10). For

97 rare species, D1D2 and ITS regions of ribosomal DNA were amplified and sequenced with  
98 panfungal primers (NL1/NL4 and V9D/LS266, respectively). In addition, actin gene (for  
99 *Candida lusitanae*), *RPBI* gene (for *Meyerozyma guilliermondii*, *Meyerozyma caribbica*,  
100 primer forward 5'-AGGGTTTGCGAGTGTGTTTGT-3', primer reverse 5'-  
101 CGTCAAGCTCCAATCTCTGC-3') and IGS1 region (for *Trichosporon* spp.) were  
102 sequenced (11). *Cryptococcus neoformans* serotypes were determined by amplification of  
103 *PAK1* and *GPA1* genes with serotype-specific primers and ploidy by flow cytometry (12).

#### 104 **Minimal Inhibitory Concentration (MIC) determination**

105 Isavuconazole and fluconazole MICs were determined in parallel according to the EUCAST  
106 standardized broth microdilution method (13). The concentrations tested ranged between  
107 0.007 mg/L to 4 mg/L and between 0.125 mg/L to 64 mg/L for isavuconazole and  
108 fluconazole, respectively. For MIC determination, tissue culture testplate with F-bottom,  
109 sterilized by radiation, were used (TPP®, Switzerland, Ref 92096). Quality control strains  
110 (ATCC22019, ATCC6258) were included in each set. The concentrations that inhibited 50%  
111 (MIC<sub>50</sub>) and 90% (MIC<sub>90</sub>) of the isolates were determined for isavuconazole and  
112 fluconazole for each species represented by at least 10 isolates. Results were analysed using  
113 EUCAST BP (resistance when MIC >4mg/L for *C. albicans*, *Candida tropicalis*, *Candida*  
114 *parapsilosis* >32mg/L for *C. glabrata*) (14). Rare species without defined BP and exhibiting  
115 fluconazole MIC<sub>50</sub>>4mg/L (non-species related BP determined by EUCAST is R>4mg/L)  
116 were considered as intrinsically resistant to fluconazole or at least less susceptible.

#### 117 **Results**

118 The 1457 isolates analysed belonged to 29 species (23 ascomycetous and 6 basidiomycetous)  
119 including the five most frequent species involved in candidemia (*C. albicans*, *C. glabrata*, *C.*  
120 *tropicalis*, *C. parapsilosis*, and *C. krusei*) and three serotypes of *Cryptococcus neoformans*  
121 (Table 1). Isolates were mostly (93%, 1351/1457) recovered from blood cultures (n=1133),

122 cerebrospinal fluids (n=89) or other site of invasive infections (n=129). Isolates were sent  
123 mainly (52.5%, 765/1457) in the context of the active surveillance of all yeasts fungemia in  
124 the Paris area (YEASTS program). Other isolates were sent in the context of the French  
125 Surveillance Network of Invasive Fungal Infections (RESSIF) but only in case of abnormal  
126 antifungal susceptibility profiles and/or rare species.

127 For 17 species among the 29 studied here, isavuconazole MIC<sub>90</sub> varied between <0.007 and 2  
128 mg/L with 14/17 having an MIC<sub>90</sub> <0.5 mg/L. Of note, *C. neoformans* serotype D exhibited  
129 lower MIC<sub>50</sub> and MIC<sub>90</sub> for isavuconazole and fluconazole than serotype A and hybrid AD  
130 isolates. Three species exhibited an MIC<sub>90</sub> of 0.5 mg/L (*C. glabrata*, *Saccharomyces*  
131 *cerevisiae*) and 2 mg/L (*Meyerozyma guilliermondii*). Finally, *Saprochaete clavata*,  
132 *Magnusiomyces capitatus* and *Rhodotorula mucilaginosa* had high MIC<sub>90</sub> ( $\geq 4$ mg/L).

133 MICs were also determined for 9 rare yeast species (7 Ascomycetous and 2 Basidiomycetous)  
134 (Table 1) for which less than ten isolates were studied. For four species, the MIC values were  
135 low (<0.25mg/L) whereas MIC distribution was heterogeneous for the others (Table S1).

136 Analysis of the MIC distributions showed that for 11 species, some isolates (2.5%-10.0%) had  
137 a MIC above the MIC<sub>90</sub> (Table 1 and Table S1). Of those with MICs  $\geq 4$  mg/L were found  
138 isolates of *C. albicans* (n=3), *C. glabrata* (n=5), *C. tropicalis* (n=1), *C. parapsilosis* (n=1), *M.*  
139 *guilliermondii* (n=2), and *Wickerhamomyces anomalus* (n=1). All these isolates were  
140 considered resistant to fluconazole according to the EUCAST BP.

141 In the absence of BP and epidemiological cut-off values defined for isavuconazole, Astvad *et*  
142 *al* (17) categorized isolates as wild-type (wt) and non-wild-type (non-wt) based on a wild-type  
143 upper limit value (wtUL). The wtUL corresponds to two dilutions above the MIC<sub>50</sub>, or to the  
144 lowest concentration tested in case all the isolates of a given species exhibit MICs less than or  
145 equal to the lowest concentration tested (*C. dubliniensis* in our study). In case of species  
146 exhibiting an MIC<sub>50</sub> equal to the highest concentration tested (*S. clavata* and *M. capitatus* in

147 our study), the wtUL is impossible to determine. Comparable to the published wtUL values,  
148 only minor differences (maximum two-fold dilutions) were detected here for some species.  
149 The percentage of isolates with MIC>wtUL ranged from 1.3% to 5.2% for common *Candida*  
150 species, a proportion similar to that of the fluconazole-resistant isolates (2.72% to 6.3%, Table  
151 1). This proportion ranged between 0 and 13% for rare species, except for *S. cerevisiae* that  
152 reached almost 44% (7/16) of non-wt with a very heterogeneous MIC distribution (Table S1).  
153 Looking at cross-resistance (9), among the 12 non-wt isolates of *C. albicans*, 11 were resistant  
154 to fluconazole (MIC>4mg/L). For the 5 non-wt isolates of *C. tropicalis*, 3 were resistant to  
155 fluconazole (MIC>4mg/L). All the 6 non-wt isolates of *C. parapsilosis* and the 7 non-wt  
156 isolates of *C. glabrata* were also resistant to fluconazole (MIC>4mg/L and MIC>32mg/L,  
157 respectively). Similarly, all isolates of *C. albicans* (11/404, 2.7%) resistant to fluconazole  
158 were non-wt for isavuconazole. For *C. glabrata* (11/184, 5.9%), *C. tropicalis* (3/96, 3.1%)  
159 and *C. parapsilosis* (8/127, 6.3%) resistant to fluconazole, the majority (7/11, 2/3 and 6/8,  
160 respectively) were non-wt for isavuconazole.

## 161 **Discussion**

162 We here confirmed that isavuconazole is active *in vitro* against *C. neoformans* and the most  
163 common *Candida* species (7, 8). Of note, *C. glabrata* and *C. krusei* which are considered as  
164 less susceptible or intrinsically resistant to fluconazole, respectively, had isavuconazole  
165 MIC<sub>90</sub>≤0.5 mg/L which is higher than for *C. albicans* but suggest a good *in vitro* activity (7,  
166 9). We also observed a low percentage of isolates of common *Candida* species categorized as  
167 fluconazole resistant or with high MIC for isavuconazole. But mainly, isolates resistant to  
168 fluconazole were also nonwt for isavuconazole. The proportion of isavuconazole non-wt  
169 isolates was comparable to that obtained by Marcos-Zambrano *et al.* for *C. albicans* [2.97%  
170 (12/404) vs. 2.3%] but higher for *C. glabrata* [3.8% (7/184) vs. 1.1%], *C. parapsilosis* [4.7%  
171 (6/127) vs. 1.5%] and *C. tropicalis* [5.2% (5/96) vs. 0%] (19). Our data suggest that



172 isavuconazole is also active *in vitro* against the majority of rare yeast species studied, except  
173 for species already considered as intrinsically resistant to fluconazole such as *S. cerevisiae*, *M.*  
174 *guilliermondii*, *S. clavata*, *M. capitatus* and *R. mucilaginosa* (11, 15, 16). These results are in  
175 accordance with data reviewed by Miceli *et al.* and Astvad *et al.*, except for *M. capitatus* and  
176 *R. mucilaginosa* previously reported with low MICs (17, 18). In conclusion, except for *C.*  
177 *krusei*, MIC distributions of isavuconazole and fluconazole were comparable for common and  
178 rare yeast species. .

179 Preliminary results were presented at the 28<sup>th</sup> European Congress of Clinical Microbiology  
180 and Infectious Diseases, (21-24 April 2018, Madrid, Spain; abstract number 7965).

#### 181 **Conflict of interests**

182 SB: consultancy (Gilead), honorarium for educational programs (Astellas), congress  
183 symposium (Gilead, Bio-Rad), and travel grants (Pfizer).

184 OL: member of speaker's bureau Merck, Pfizer, Astellas, Gilead; consultant for Gilead

185 MDO, AB, CG and FD: nothing to declare

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**Table 1: Isavuconazole and Fluconazole susceptibility of the 20 yeast species with more than 10 isolates studied (France, 2015-2017)**

| Species (current name)   | n   | % of isolates from blood culture or CSF (nb of isolates) | Isavuconazole |              |                  |  |             |   | Fluconazole  |              |                  |  |
|--|-----|--|---------------|--------------|------------------|--|-------------|---|--------------|--------------|------------------|--|
|  |     |  | MIC50 (mg/L)  | MIC90 (mg/L) | MIC range (mg/L) | % isolates with MIC > MIC90 (nb of isolates) | wtUL (mg/L) | % isolates with MIC > wtUL (nb of isolates) | MIC50 (mg/L) | MIC90 (mg/L) | MIC range (mg/L) | % of isolates Resistant*(nb of isolates) |
| <i>Candida albicans</i>  | 404 | 91.8% (371)  | ≤0.007        | ≤0.007       | ≤0.007-≥4        | 4.95 (20)                                    | 0.03        | 2.97 (12)                                   | ≤0.125       | 0.25         | ≤0.125 -≥64      | 2.72 (11)                                |
| <i>Candida dubliniensis</i>  | 34  | 97.1 (33)  | ≤0.007        | ≤0.007       | ≤0.007-≤0.007    | 0 (0)  | ≤0.007      | 0   | ≤0.125       | 0.25         | ≤0.125 -0.5      | NA                                       |
| <i>Candida tropicalis</i>  | 96  | 89.6% (86)   | ≤0.007        | 0.03         | ≤0.007-≥4        | 5.21 (5)                                     | 0.03        | 5.21 (5)                                    | 0.25         | 1            | ≤0.125 -≥64      | 3.16 (2)                                 |
| <i>Candida parapsilosis</i>  | 127 | 85.8% (109)  | 0.015         | 0.03         | ≤0.007-≥4        | 5.51 (7)                                     | 0.06        | 4.72 (6)                                    | 0.5          | 2            | ≤0.125 -≥64      | 6.3 (8)                                  |
| <i>Candida orthopsilosis</i>   | 10  | 100% (10)  | 0.015         | 0.06         | ≤0.007-0.25      | 10 (1)                                       | 0.06        | 10.0 (1)                                    | 0.5          | 16           | 0.25 - 16        | 20 (2)                                   |
| <i>Candida metapsilosis</i>  | 11  | 72.7% (8)  | 0.015         | 0.015        | ≤0.007-0.015     | 0 (0)  | 0.06        | 0   | 1            | 1            | 1 - 2            | 0  |
| <i>Candida glabrata</i>  | 184 | 91.3% (168)  | 0.25          | 0.5          | 0.03-≥4          | 7.07 (13)                                    | 1           | 3.80 (7)                                    | 8            | 16           | 1 - ≥64          | 5.98 (11)                                |
| <i>Saccharomyces cerevisiae</i>                                      | 16  | 100% (16)  | ≤0.007        | 0.5          | 0.03-0.5         | 0 (0)  | 0.03        | 43.75 (7)                                   | 8            | 32           | ≤0.125 -32       | 56.25 (9)                                |
| <i>Candida lusitanae</i> ( <i>Clavispora lusitanae</i> )             | 55  | 96.4% (53)   | ≤0.007        | 0.015        | ≤0.007-0.5       | 5.45 (3)                                     | 0.03        | 3.64 (2)                                    | 0.25         | 0.5          | ≤0.125 -16       | 3.64 (2)                                 |
| <i>Candida guilliermondii</i> ( <i>Meyerozyma guilliermondii</i> )   | 23  | 91.3% (21)   | 0.25          | 2            | 0.03-≥4          | 8.7 (2)                                      | 1           | 13.04 (3)                                   | 4            | 16           | 1 -≥64           | NA                                       |
| <i>Candida krusei</i> ( <i>Pichia kudriavzevii</i> )                 | 76  | 90.8% (69)   | 0.125         | 0.25         | 0.015-1          | 6.58 (5)                                     | 0.5         | 1.32 (1)                                    | 32           | 64           | 16 -≥64          | NA                                       |
| <i>Candida kefyr</i> ( <i>Kluyveromyces marxianus</i> )              | 41  | 80.5%(33)  | ≤0.007        | ≤0.007       | ≤0.007-0.015     | 4.88 (2)                                     | 0.03        | 0   | 0.25         | 0.5          | ≤0.125 -1        | 0  |
| <i>Candida pelliculosa</i> ( <i>Wickerhamomyces anomalus</i> )       | 10  | 60% (6)  | 0.06          | 0.06         | 0.03-4           | 10 (1)                                       | 0.25        | 10.0 (1)                                    | 2            | 4            | 1-8              | 20 (2)                                   |
| <i>Pichia ohmeri</i> ( <i>Kodamaea ohmeri</i> )                      | 11  | 100%(11)   | 0.015         | 0.03         | ≤0.007-0.25      | 9.09 (1)                                     | 0.06        | 9.09 (1)                                    | 4            | 4            | 2-64             | 9.09 (1)                                 |
| <i>Geotrichum clavatum</i> ( <i>Saprochaete clavata</i> )            | 64  | 45.3%(29)  | 4             | ≥4           | 0.25-≥4          | 0 (0)  | NA          | NA  | 16           | 32           | 0.25-32          | 81.25 (52)                               |
| <i>Geotrichum capitatum</i> ( <i>Magnusiomyces capitatus</i> )       | 25  | 48% (12)   | 4             | ≥4           | 0.125-≥4         | 0 (0)  | NA          | NA  | 4            | 16           | 0.25-32          | 48 (12)                                  |
| <i>Cryptococcus neoformans</i> var. <i>grubii</i> (A)                | 158 | 70.9% (112)  | 0.06          | 0.25         | ≤0.007-0.5       | 2.53 (4)                                     | 0.25        | 2.53 (4)                                    | 2            | 8            | ≤0.125 -16       | 11.39 (18)                               |
| <i>Cryptococcus neoformans</i> var. <i>neoformans</i> (D)            | 25  | 60% (15)   | 0.015         | 0.03         | ≤0.007-0.125     | 8 (2)  | 0.06        | 4.0 (1)                                     | 1            | 2            | 0.25-2           | 0  |
| <i>Cryptococcus neoformans</i> AD hybrid                             | 26  | 73.1% (19)   | 0.03          | 0.125        | ≤0.007-0.25      | 7.69 (2)                                     | 0.125       | 7.69 (2)                                    | 2            | 8            | ≤0.125 -16       | 15.38 (4)                                |
| <i>Rhodotorula mucilaginosa</i>                                      | 16  | 93.8% (15)   | 1             | 4            | 0.125-4          | 0 (0)  | 4           | 25.0 (4)                                    | ≥64          | ≥64          | 1-≥64            | 93.75 (15)                               |
| <i>Candida auris</i>   | 2   | 50% (1)  | NA            | NA           | 0.015            | NA   | NA          | NA  | NA           | NA           | 16-64            | 100 (2)                                  |
| <i>Candida inconspicua</i>   | 8   | 75%(6)   | 0.06          | NA           | 0.06-0.25        | NA   | NA          | NA  | 16           | NA           | 4-32             | 87.5 (7)                                 |
| <i>Candida nivariensis</i>   | 3   | 100%(3)  | NA            | NA           | ≤0.007-0.5       | NA   | NA          | NA  | NA           | NA           | 2-4              | 0  |
| <i>Candida utilis</i> ( <i>Cyberlindnera jadinii</i> )               | 5   | 80%(4)   | 0.03          | NA           | 0.015-0.03       | NA   | NA          | NA  | 1            | NA           | 1-2              | 0  |
| <i>Geotrichum candidum</i> ( <i>Galactomyces candidus</i> )          | 7   | 0% (0)   | 0.25          | NA           | ≤0.007-2         | NA   | NA          | NA  | 16           | NA           | 0.5-≥64          | 85.71 (6)                                |
| <i>Candida fermentati</i> ( <i>Meyerozyma caribbica</i> )            | 3   | 66.7%(2)   | NA            | NA           | 0.06-≥ 4         | NA   | NA          | NA  | NA           | NA           | 4-≥64            | 66.67 (2)                                |
| <i>Yarrowia lipolytica</i>   | 5   | 40% (2)  | 0.125         | NA           | 0.125-0.25       | NA   | NA          | NA  | 2            | NA           | ≤0.124-16        | 20 (1)                                   |
| <i>Trichosporon asahii</i>   | 9   | 66.7% (6)  | 0.25          | NA           | 0.06-1           | NA   | NA          | NA  | 2            | NA           | 0.25-8           | 11.11 (1)                                |
| <i>Trichosporon dermatis</i> ( <i>Cutaneotrichosporon dermatis</i> ) | 3   | 66.7%(2)   | NA            | NA           | 0.06-2           | NA   | NA          | NA  | NA           | NA           | 2-4              | 0  |

\*EUCAST BP were used for categorized isolates as resistant. Non-species related BP (R>4mg/L) was used for all species without any BP.