Activity of Ibrexafungerp and Comparator Antifungals Tested Against Candida and Aspergillus Isolates Collected from Invasive Infections in a Global Surveillance Program in 2023

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Introduction

- Ibrexafungerp is a novel triterpenoid antifungal agent approved by the United States Food and Drug Administration for the treatment of vulvovaginal candidiasis.
- There are ongoing clinical trials of ibrexafungerp in the treatment of invasive candidiasis.
- Rising azole resistance rates complicate the treatment of *Candida* infections and
- ibrexafungerp is the only non-azole antifungal agent with an approved oral formulation. We evaluated the *in vitro* activity of ibrexafungerp; echinocandins—micafungin and anidulafungin; azoles—fluconazole (yeast only), itraconazole, voriconazole; and amphotericin B against a global collection of Candida spp. and Aspergillus spp. isolates causing invasive infections in 2023.

Methods

- A total of 1,119 Candida spp. isolates and 203 Aspergillus spp. isolates were collected in 2023 as a part of the SENTRY global surveillance program.
- These isolates were tested for susceptibility to ibrexafungerp, micafungin, anidulafungin, fluconazole, itraconazole, voriconazole, amphotericin B (Table 1) and caspofungin and posaconazole (data not included). Isolates included the 6 most common Candida spp. including *Candida auris* and the 3 most common *Aspergillus* spp.
- Isolates were from 11 medical centers in North America, 18 medical centers in Europe, 7 medical centers in the Asia-West Pacific region, and 5 medical centers in Latin America (Figure 1).
- Only the first isolate collected per patient was submitted and tested.
- Isolate identification was performed by MALDI-TOF MS and/or molecular methods.
- Susceptibility testing was performed by broth microdilution according to CLSI standards. Minimum inhibitory concentrations (MICs) were determined for yeast with all agents and for molds with azoles and amphotericin B. Minimum effective concentrations (MECs) were determined for molds with ibrexafungerp and echinocandins.
- There are no current breakpoints for ibrexafungerp by CLSI criteria, but CLSI breakpoints were applied for comparator agents where available and CDC tentative breakpoints were used for *C. auris*.

Table 1. MIC/MEC_{50/90} (mg/L) for ibrexafungerp (IBX) and comparator agents against 5 most common *Candida* spp., *C. auris*, and 3 most common *Aspergillus* spp. in 2023 SENTRY Antifungal Surveillance Program

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Organism (#)	IBX	MFG	AND	FLC	ITC	VRC	AMB
C. albicans (395)	0.06/0.12	0.015/0.015	0.03/0.06	0.25/0.5	0.06/0.12	0.008/0.015	0.5/1
C. glabrata (246)	0.25/0.5	0.015/0.03	0.12/0.12	4/8	0.5/1	0.06/0.12	1/1
<i>C. parapsilosis</i> (181)	0.25/0.5	1/1	2/2	0.5/32	0.12/0.25	0.008/0.25	1/1
C. tropicalis (134)	0.12/0.25	0.015/0.06	0.03/0.06	0.5/1	0.12/0.25	0.03/0.06	1/1
C. krusei (33)	0.5/1	0.12/0.12	0.06/0.06	32/32	0.5/1	0.25/0.25	1/2
<i>C. auris</i> (25)	0.5/1	0.25/1	0.5/1	64/>128	0.25/1	0.25/1	2/2
A. fumigatus (141)	0.03/0.06	0.004/0.008	0.015/0.03	NT	1/1	0.5/1	1/2
A. section Nigri (29)	0.03/0.03	0.004/0.008	0.004/0.008	NT	1/>8	1/4	0.25/0.5
A. section Flavi (19)	0.03/0.06	≤0.002/0.008	0.004/0.008	NT	0.5/0.5	0.5/1	1/2

MIC, minimum inhibitory concentration; MEC, minimum effective concentration (for Aspergillus and ibrexafungerp or echinocandins); IBX, ibrexafungerp; MFG, micafungin; AND, anidulafungin; FLC, fluconazole; ITC, itraconazole; VRC, voriconazole; AMB, amphotericin B; NT, not tested

Results

Overall

- Of the 1119 *Candida* spp. isolates tested, 20 species were represented (Figure 2).
- The range of ibrexafungerp MICs for all *Candida* spp. was ≤0.004 mg/L to 2 mg/L with an overall MIC₅₀ of 0.12 mg/L and MIC₅₀ of 0.5 mg/L.
- Of the 203 Aspergillus spp. isolates tested, 8 species were represented (Figure 3).
- The range of ibrexafungerp MICs for all *Aspergillus* spp. was 0.008 mg/L to 8 mg/L with an overall MIC₅₀ of 0.03 mg/L and MIC₅₀ of 0.06 mg/L.
- Species of interest are discussed in more depth below.

Candida albicans n=395

- Ibrexafungerp MICs ranged from 0.015–0.5 mg/L with MIC₅₀ of 0.06 mg/L and MIC₉₀ of 0.12 mg/L (Figure 4, Table 1).
- The MIC₉₀ for ibrexafungerp was 2 to 8x higher than echinocandins, 4x lower than fluconazole, the same as itraconazole, 8x higher than voriconazole, and 8x lower than amphotericin B.
- One isolate was resistant to anidulafungin, two to micafungin, and one to fluconazole.

Candida glabrata n=246

- Ibrexafungerp MICs ranged from ≤0.004–2 mg/L with MIC₅₀ of 0.25 mg/L and MIC₉₀ of 0.5 mg/L (Figure 5, Table 1).
- The MIC_{on} for ibrexafungerp was 4 to 16x higher than echinocandins, 16x lower than fluconazole, 2x lower than itraconazole, 4x higher than voriconazole, and 2x lower than amphotericin B.
- There were 3 isolates resistant to anidulafungin and micafungin and 8 isolates resistant to fluconazole.

Candida parapsilosis n=181

- Ibrexafungerp MICs ranged from 0.06–1 mg/L with MIC₅₀ of 0.25 mg/L and MIC₅₀ of 0.5 mg/L (Table 1).
- The MIC₉₀ for ibrexafungerp was 2 to 4x lower than echinocandins, 64x lower than fluconazole, 2x higher than itraconazole, 2x higher than voriconazole, and 2x lower than amphotericin B.
- No isolates were resistant to anidulafungin or micafungin; 24 isolates were resistant to fluconazole.

Candida auris n=25

- Ibrexafungerp MICs ranged from 0.25–1 mg/L with MIC₅₀ of 0.5 mg/L and MIC₅₀ of 1 mg/L (Figure 6, Table 1).
- The MIC₉₀ for ibrexafungerp was the same as the echinocandins, >128x lower than fluconazole, the same as itraconazole and voriconazole, and 2x lower than amphotericin B.
- Of the 25 isolates tested, 8% (2) were resistant to anidulafungin and micafungin (both isolates from the same hospital), 100% (25) were resistant to fluconazole, and 56% (14) were resistant to amphotericin B

Aspergillus fumigatus n=141

- Ibrexafungerp MECs ranged from 0.008–0.25 mg/L with MEC₅₀ of 0.03 mg/L and MEC₉₀ of 0.06 mg/L (Figure 7, Table 1).
- MEC/MIC₉₀ for ibrexafungerp was 2 to 8x higher than that of echinocandins and \geq 16x lower than that of itraconazole, voriconazole, and amphotericin B.



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Figure 7: Aspergillus fumigatus susceptibility testing (n = 141)



Conclusions

- Ibrexafungerp is an oral non-azole agent with low MIC/MEC_{50/90} values against the predominant Candida and Aspergillus species from a worldwide contemporary surveillance collection.
- MICs were low even for organisms of critical concern like *Candida auris* where the highest observed MIC for ibrexafungerp was 1 mg/L.
- Ibrexafungerp may represent an oral option for the management of difficult-to-treat invasive fungal infections from pathogens such as C. glabrata, C. auris, and Aspergillus spp. in addition to its current indication for vulvovaginal candidiasis.

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