

Isavuconazole: A Comprehensive Review of Spectrum of Activity of a New Triazole

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Abstract Isavuconazole is a new triazole currently undergoing phase III clinical trials. This compound has shown in vitro activity against a large number of clinically important yeasts and moulds including *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., *Candida* spp., the Zygomycetes and *Cryptococcus*

spp. Similar to voriconazole, reduced in vitro activity is seen against *Histoplasma capsulatum*. In vivo efficacy has been demonstrated in murine models of invasive aspergillosis and candidiasis. Additionally, there are several potential pharmacokinetic and drug–drug interaction advantages of this compound over existing antifungal agents. This review summarizes existing data that has been either published or presented at international symposia.

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Introduction

The clinical availability of the second generation extended spectrum triazoles voriconazole and posaconazole have been significant advances to the antifungal armamentarium. These agents have a broader spectrum of activity than fluconazole while also being available for oral administration, which is an advantage over the echinocandins and amphotericin B. However, studies have demonstrated significant variations in bioavailability and pharmacokinetics among patients administered these agents, which may limit their clinical efficacy. Isavuconazole (formerly BAL4815) is a new water-soluble extended spectrum triazole currently being codeveloped by Basilea Pharmaceutica (Basel, Switzerland) and Astellas (Tokyo,

Japan) with activity against both yeast and moulds. This compound has shown promise with excellent in vitro potency against a large number of clinically important invasive fungal pathogens including *Aspergillus*, *Fusarium*, *Scedosporium*, *Candida* spp., the Zygomycetes and *Cryptococcus* [1–4]. In vivo efficacy has also been demonstrated in murine models of invasive aspergillosis and candidiasis [3, 5]. This triazole is available as isavuconazonium (BAL-8557, formerly RO-0098557), a water-soluble prodrug consisting of a tetrazolium salt (an [N-(3-acetoxypropyl)-N-methylamino]-carboxymethyl group) linked to an aminocarboxy moiety (Figure 1) [6]. Both oral and intravenous formulations have been developed, providing advantages over posaconazole, which is currently available only in oral suspension, and voriconazole which is not active against the Zygomycetes [7]. The intravenous formulation of isavuconazole does not require the addition of cyclodextrin to achieve solubility, as is required for voriconazole, thereby eliminating concerns for nephrotoxicity due to the sulfobutylether- β -cyclodextrin component of its formulation [8]. These factors make isavuconazole a potentially attractive choice during the care of invasive mycoses, and phase III clinical trials are ongoing.

Literature Review

A careful search of entries in the Medline database revealed 26 citations containing original data on the pharmacodynamics, pharmacokinetics or the activity of isavuconazole against a number of fungal pathogens. We additionally contacted the drug manufacturer to ensure all information presented at international symposia or published in non-Medline indexed journals was available for inclusion in our review. Four additional publications and 74 abstracts were provided by the manufacturer. Abstracts that conveyed no new information to other abstracts or that have been published were excluded from inclusion in this review.

In Vitro Studies

In vitro findings have illustrated the potent activity of isavuconazole against numerous pathogens [8]. Tables 1, 2, 3, 4, 5, 6, and 7 summarize the in vitro fungistatic and fungicidal activity against a large number of clinically important yeasts and moulds.

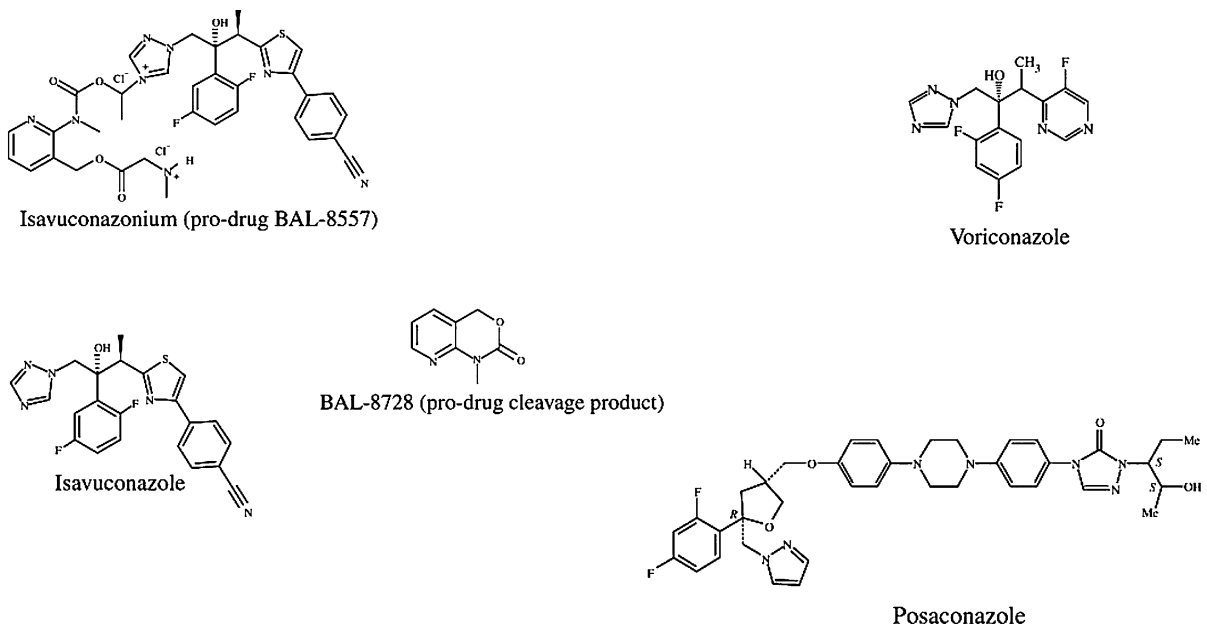


Fig. 1 Structure of isavuconazole, voriconazole, and posaconazole

Table 1 In vitro activity of isavuconazole against *Candida* spp

Fungus	No. isolates	Antifungal agent	MIC range ($\mu\text{g/ml}$)	MIC ₅₀ range ($\mu\text{g/ml}$)	MIC ₉₀ range ($\mu\text{g/ml}$)	MFC range ($\mu\text{g/ml}$)	References
<i>Candida albicans</i>	457	Isavuconazole	<0.002–>8	<0.002–0.03	<0.002–0.03	0.03–>16	[1, 4, 9–12]
	384	Amphotericin B	0.125–2	0.25–0.5	0.5–1		[4, 9, 10]
	362	Itraconazole	0.002–0.016	0.008–0.03	0.016–0.06		[4, 10]
	385	Fluconazole	0.03–>128	0.125–0.5	0.25–16		[4, 9, 10, 12]
	455	Voriconazole	<0.015–>8	<0.016–0.03	0.03–0.06		[1, 4, 9, 10, 12]
	218	Posaconazole	<0.016–0.5	<0.016–0.03	<0.016–0.25		[9, 10]
	218	Caspofungin	0.016–2	0.03–0.5	0.03–1		[9, 10]
	22	Micafungin	0.015–0.3	0.015	0.015		[9]
	22	Anidulafungin	0.015–0.125	0.015	0.015		[9]
	384	Flucytosine	<0.06–>128	<0.06–0.25	0.06–1		[4, 9, 10]
	3	Isavuconazole	0.03				[9]
	3	Amphotericin B	0.125–0.5				[9]
	3	Fluconazole	0.125				[9]
	3	Voriconazole	0.03–0.06				[9]
3	Posaconazole	0.03				[9]	
3	Caspofungin	0.015–0.125				[9]	
3	Micafungin	0.015–0.125				[9]	
3	Anidulafungin	0.015–0.03				[9]	
3	Flucytosine	0.125				[9]	
<i>Candida glabrata</i>	108	Isavuconazole	<0.015–16	0.25–2	0.5–8	0.03–>16	[1, 4, 9, 11, 12]
	68	Amphotericin B	0.25–2	0.5–2	0.5–2		[4, 9]
	46	Itraconazole	0.125–8	0.5	1		[4]
	70	Fluconazole	0.25–>128	8–32	32–>64		[4, 9, 12]
	107	Voriconazole	<0.015–8	0.125–1	1–4		[1, 4, 9, 12]
	22	Posaconazole	0.03–>16	0.5–1	2–4		[9]
	22	Caspofungin	0.06–0.5	0.125	0.125–0.25		[9]
	22	Micafungin	0.015–0.03	0.015	0.015		[9]
	22	Anidulafungin	0.015–0.125	0.06	0.06–0.125		[9]
	68	Flucytosine	0.016–>128	0.06–0.125	0.06–0.25		[4, 9]
<i>Candida guilliermondii</i>	2	Isavuconazole	0.03–0.125				[9]
	2	Amphotericin B	0.125–1				[9]
	2	Fluconazole	2–32				[9]

Table 1 continued

Fungus	No. isolates	Antifungal agent	MIC range ($\mu\text{g/ml}$)	MIC ₅₀ range ($\mu\text{g/ml}$)	MIC ₉₀ range ($\mu\text{g/ml}$)	MFC range ($\mu\text{g/ml}$)	References
<i>Candida kefyr</i>	2	Voriconazole	0.06–0.5				[9]
	2	Posaconazole	0.125–0.5				[9]
	2	Caspofungin	0.125–1				[9]
	2	Micafungin	1				[9]
	2	Anidulafungin	0.5–4				[9]
	2	Flucytosine	0.06–0.5				[9]
	3	Isavuconazole	0.03–>16				[9]
	3	Amphotericin B	0.5–2				[9]
	3	Fluconazole	0.25–>64				[9]
	3	Voriconazole	0.03–16				[9]
	3	Posaconazole	0.03–>16				[9]
	3	Caspofungin	0.03–0.5				[9]
	3	Micafungin	0.06–2				[9]
<i>Candida krusei</i>	3	Anidulafungin	0.03–1				[9]
	3	Flucytosine	0.125				[9]
	40	Isavuconazole	0.03–2	0.125–0.5	0.25–1	0.5–4	[1, 4, 9, 11, 12]
	32	Amphotericin B	0.5–4	0.5–2	0.5–4		[4, 9]
	11	Itraconazole	0.125–0.5	0.5	0.5		[4]
	34	Fluconazole	2–>64	32–64	64–>64		[4, 9, 12]
	39	Voriconazole	0.06–8	0.25–5	1*4		[1, 4, 9, 12]
	21	Posaconazole	0.03–2	0.25–0.5	1		[9]
	21	Caspofungin	0.06–1	0.25	0.25–0.5		[9]
	21	Micafungin	0.015–0.25	0.125	0.125		[9]
	21	Anidulafungin	0.03–0.5	0.03–0.06	0.125		[9]
	32	Flucytosine	0.125–64	16	16–32		[4, 9]
	<i>Candida lusitanae</i>	4	Isavuconazole	<0.015–0.125			
3		Amphotericin B	0.125–0.5				[9]
3		Fluconazole	0.25–2				[9]
3		Voriconazole	0.03				[9]
3		Posaconazole	0.03				[9]
3		Caspofungin	0.125–0.5				[9]
3		Micafungin	0.125–0.25				[9]

Table 1 continued

Fungus	No. isolates	Antifungal agent	MIC range ($\mu\text{g/ml}$)	MIC ₅₀ range ($\mu\text{g/ml}$)	MIC ₉₀ range ($\mu\text{g/ml}$)	MFC range ($\mu\text{g/ml}$)	References
<i>Candida parapsilosis</i>	3	Anidulafungin	0.03–0.5				[9]
	3	Flucytosine	0.125				[9]
	130	Isavuconazole	0.004–0.25	<0.015–0.03	0.03–0.125	0.03–>16	[1, 4, 9, 11, 12]
	43	Amphotericin B	0.25–2	0.25–1	0.5–2		[4, 9]
	23	Itraconazole	0.008–0.5	0.016	0.063		[4]
	45	Fluconazole	0.25–32	0.5–2	1–8		[4, 9, 12]
	129	Voriconazole	<0.015–0.5	<0.015–0.06	0.06–0.125		[1, 4, 9, 12]
	20	Posaconazole	0.03–0.25	0.03	0.125		[9]
	20	Caspofungin	0.06–2	0.25	1–2		[9]
	20	Micafungin	0.25–2	1–2	2		[9]
	20	Anidulafungin	0.125–>8	1	4–8		[9]
	43	Flucytosine	0.06–1	0.125	0.125–0.5		[4, 9]
<i>Candida tropicalis</i>	64	Isavuconazole	<0.015–>8	<0.015–0.03	0.03–0.125	2–>16	[1, 4, 9, 11, 12]
	47	Amphotericin B	0.25–2	0.5–2	0.5–2		[4, 9]
	25	Itraconazole	0.008–0.063	0.03	0.03		[4]
	63	Fluconazole	0.125–>64	0.25–1	1–8		[4, 9, 12]
	63	Voriconazole	<0.015–16	0.03–0.125	0.06–2		[1, 4, 9, 12]
	22	Posaconazole	0.003–>16	0.03–0.06	0.25–1		[9]
	22	Caspofungin	0.125–0.5	0.125–0.25	0.5		[9]
	22	Micafungin	0.015–0.125	0.03	0.06		[9]
	22	Anidulafungin	0.03–0.125	0.03	0.125		[9]
	47	Flucytosine	0.063–>128	0.125–0.5	0.25–128		[4, 9]
	33	Isavuconazole	<0.0005–0.5	0.004–0.016	0.016–0.5	0.003–>16	[1, 4, 48]
	<i>Candida</i> spp.	26	Amphotericin B	0.06–1	0.25–0.5	0.5–1	
26		Itraconazole	<0.016–0.5	0.016–0.25	0.25–0.5		[4, 48]
26		Fluconazole	0.125–64	1–32	4–64		[4, 48]
33		Voriconazole	0.008–1	0.03–0.25	0.125–1		[1, 4, 48]
26		Flucytosine	<0.015–>128	<0.06–1	0.06–4		[4, 48]

Table 2 In vitro activity of isavuconazole against non-*Candida* yeasts

Fungus	No. isolates	Antifungal agent	MIC range ($\mu\text{g/ml}$)	MIC ₅₀ range ($\mu\text{g/ml}$)	MIC ₉₀ range ($\mu\text{g/ml}$)	MFC range ($\mu\text{g/mL}$)	References
<i>Cryptococcus gattii</i>	77	Isavuconazole	<0.015–0.25	0.03–0.32	0.06–0.125		[14, 15]
	42	Amphotericin B	0.125–1	0.25	0.25		[14]
	42	Fluconazole	0.5–32	2	8		[14]
	42	Voriconazole	<0.015–0.5	0.125	0.25		[14]
	42	Posaconazole	<0.015–0.5	0.03	0.125		[14]
	42	Flucytosine	0.06–16	2	8		[14]
	595	Isavuconazole	0.002–0.5	0.004–0.03	0.016–0.125		[2, 9, 14–17]
<i>Cryptococcus neoformans</i>	538	Amphotericin B	0.016–>16	0.25–1	0.25–1		[2, 9, 14, 16, 17]
	342	Itraconazole	0.016–1	0.03–0.06	0.125–0.25		[2, 17]
	538	Fluconazole	0.125–64	1–4	8–4		[2, 9, 14, 16, 17]
	538	Voriconazole	<0.015–0.5	0.03–0.06	0.06–0.25		[2, 9, 14, 16, 17]
	538	Posaconazole	0.002–0.25	0.004–0.06	0.016–0.125		[2, 9, 14, 16, 17]
	110	Caspofungin	2–>8	8–16	>8		[9, 16]
	110	Micafungin	4–>128	>8	>8		[9, 16]
	110	Anidulafungin	1–>128	>8	>8		[9, 16]
	93	Terbinafine	<0.3–2	0.25	1		[16]
	445	Flucytosine	0.03–>64	1–4	2–8		[2, 9, 14, 17]
<i>Geotrichum capitatum</i>	7	Isavuconazole	0.03–0.5			1–>16	[18]
	7	Amphotericin B	0.25–1			0.5–2	[18]
	7	Fluconazole	1–4			8–>64	[18]
	7	Voriconazole	0.03–0.25			0.25–>16	[18]
	7	Posaconazole	0.06–0.5			0.5–>16	[18]
	7	Flucytosine	0.125–8			0.25–>64	[18]
	11	Isavuconazole	0.03–0.25	0.03	0.03	0.06–8	[18]
<i>Pichia</i> spp.	11	Amphotericin B	0.03–1	0.25	0.5	0.125–1	[18]
	11	Fluconazole	0.25–8	64	>64	1–>64	[18]
	11	Voriconazole	0.03–0.125	0.03	0.25	0.03–4	[18]
	11	Posaconazole	0.03–0.5	0.25	0.5	0.25–>16	[18]
	11	Flucytosine	0.125–>64	0.125	0.125	0.25–>64	[18]
	14	Isavuconazole	0.03–0.125	0.03	0.03	0.5–16	[18]
	14	Amphotericin B	0.25–0.5	0.25	0.5	0.25–2	[18]
<i>Rhodotorula</i> spp.	14	Fluconazole	0.125–>64	64	>64	64–>64	[18]

Table 2 continued

Fungus	No. isolates	Antifungal agent	MIC range ($\mu\text{g/ml}$)	MIC ₅₀ range ($\mu\text{g/ml}$)	MIC ₉₀ range ($\mu\text{g/ml}$)	MFC range ($\mu\text{g/ml}$)	References
<i>Saccharomyces cerevisiae</i>	14	Voriconazole	0.03–0.25	0.03	0.25	0.5–>16	[18]
	14	Posaconazole	0.03–1	0.25	0.5	1–>16	[18]
	14	Flucytosine	0.125–0.125	0.125	0.125	0.25–0.25	[18]
	20	Isavuconazole	0.03–1	0.06	0.25	0.5–>16	[11, 18]
	18	Fluconazole	0.125–16	2	4	32–>64	[18]
	18	Voriconazole	0.03–0.25	0.03	0.125	1–>16	[18]
<i>Trichosporon</i> spp.	18	Posaconazole	0.125–1	0.125	0.5	1–>16	[18]
	18	Flucytosine	0.125–2	0.125	2	0.25–>64	[18]
	99	Isavuconazole	0.002–0.5	0.06–0.125	0.125–0.25	0.06–>16	[9, 18, 49]
	99	Amphotericin B	0.125–>16	0.125–8	0.5–>16	0.06–>16	[9, 18, 49]
	25	Itraconazole	0.03–1	0.25	0.5		
	99	Fluconazole	0.125–>64	0.125–4	1–8		[9, 18, 49]
	99	Voriconazole	0.016–2	0.03–0.125	0.06–0.25	0.03–>16	[9, 18, 49]
	99	Posaconazole	0.03–0.5	0.03–0.25	0.25	0.06–8	[9, 18, 49]
	20	Caspofungin	4–>8	8	8		[9]
	20	Micafungin	8–>8	>8	>8		[9]
20	Anidulafungin	2–>8	4–>8	>8		[9]	
74	Flucytosine	0.5–16	2–8	4–16		[9, 18]	

Table 3 In vitro activity of isavuconazole against *Aspergillus* spp.

Fungus	No. isolates	Antifungal agent	MIC range (µg/ml)	MIC ₅₀ range (µg/ml)	MIC ₉₀ range (µg/ml)	MFC range (µg/ml)	References
<i>Aspergillus flavus</i>	97	Isavuconazole	0.25–16	0.5–2	1–16	0.5–4	[1, 3, 9, 11, 19]
	45	Amphotericin B	0.5–16	1–2	1–4		[3, 9]
	20	Itraconazole	0.06–0.5	0.125	0.5		[3]
	25	Fluconazole	>64	>64	>64		[9]
	95	Voriconazole	0.125–4	0.5–1	0.5–2	1–4	[1, 3, 9, 19]
	41	Posaconazole	0.125–2	0.125–0.25	0.5	1–2	[9, 19]
	45	Caspofungin	0.015–>8	0.03–0.25	0.03–0.25		[3, 9]
	25	Micafungin	0.015–>8	0.015	0.03		[9]
	25	Anidulafungin	0.015–>8	0.015	0.015–>8		[9]
	25	Flucytosine	2–>64	>64	>64		[9]
	939	Isavuconazole	0.06–4	0.25–1	0.5–2	0.125–4	[1, 3, 9, 11, 19, 50]
	302	Amphotericin B	0.06–8	0.25–4	0.5–8		[3, 9, 50]
	<i>Aspergillus fumigatus</i>	279	Itraconazole	0.125–>8	0.25–0.5	1–>8	
23		Fluconazole	>64	>64	>64		[9]
936		Voriconazole	0.125–16	0.25–1	0.5–2	1–4	[1, 3, 9, 19, 50]
272		Posaconazole	<0.016–>16	0.125–0.5	0.25–1	1–2	[9, 19, 50]
302		Caspofungin	0.015–4	0.06–0.5	0.06–0.5		[3, 9, 50]
23		Micafungin	0.015–0.03	0.015	0.015		[9]
23		Anidulafungin	0.015	0.015	0.015		[9]
240		Flucytosine	0.5–>64	>64	>64		[9, 50]
1		Isavuconazole	1				[9]
1		Amphotericin B	1				[9]
1		Fluconazole	>64				[9]
1		Voriconazole	2				[9]
1		Posaconazole	0.5				[9]
1	Caspofungin	0.03				[9]	
1	Micafungin	0.015				[9]	
1	Anidulafungin	0.015				[9]	
1	Flucytosine	>64				[9]	
<i>Aspergillus nidulans</i>	70	Isavuconazole	0.06–2	0.25	1		[9, 51]
	70	Amphotericin B	1–8	4	4		[9, 51]
	63	Itraconazole	0.25–4	1	1		[51]

Table 3 continued

Fungus	No. isolates	Antifungal agent	MIC range ($\mu\text{g/ml}$)	MIC ₅₀ range ($\mu\text{g/ml}$)	MIC ₉₀ range ($\mu\text{g/ml}$)	MFC range ($\mu\text{g/ml}$)	References
<i>Aspergillus niger</i>	7	Fluconazole	>64				[9]
	70	Voriconazole	0.06–2	0.5	2		[9, 51]
	70	Posaconazole	0.25–1	0.5	1		[9, 51]
	70	Caspofungin	0.03–8	0.125	0.25		[9, 51]
	70	Micafungin	0.015–0.125	0.06	0.06		[9, 51]
	7	Anidulafungin	0.015				[9]
	63	Terbinafine	0.03–1	0.06	0.125		[51]
	7	Flucytosine	2–>64				[9]
	84	Isavuconazole	0.125–>16	0.5–2	2–4	0.25–>8	[1, 3, 9, 19]
	39	Amphotericin B	0.25–2	0.5–1	0.5–2		[3, 9]
	18	Itraconazole	0.25–4	0.5	2		[3]
	21	Fluconazole	>64	>64	>64		[9]
	84	Voriconazole	0.125–4	0.25–2	1–2	2–8	[1, 3, 9, 19]
	34	Posaconazole	0.125–2	0.25–0.5	0.5–1	1–4	[9, 19]
	39	Caspofungin	0.015–8	0.06–0.25	0.125–0.25		[3, 9]
<i>Aspergillus terreus</i>	21	Micafungin	0.015–0.06	0.015	0.015		[9]
	21	Anidulafungin	0.015–0.03	0.015	0.015		[9]
	21	Flucytosine	4–>64	>64	>64		[9]
	222	Isavuconazole	0.125–>16	0.5–1	0.5–4	0.25–2	[1, 3, 9, 11, 19, 52]
	161	Amphotericin B	0.25–16	1–4	1–8		[3, 9, 52]
	150	Itraconazole	0.06–1	0.125–0.5	0.25–1		[3, 52]
	11	Fluconazole	>64	>64	>64		[9]
	221	Voriconazole	0.125–4	0.25–1	0.5–2	1–2	[1, 3, 9, 19, 52]
	178	Posaconazole	0.06–1	0.125–0.25	0.5	1–2	[9, 19, 52]
	161	Caspofungin	0.03–>8	0.03–0.5	0.06–0.5		[3, 9, 52]
	143	Micafungin	0.015–>8	0.015–0.06	0.015–0.06		[9, 52]
	11	Anidulafungin	0.015–8	0.015	0.015		[9]
	132	Terbinafine	0.06–0.25	0.03	0.03		[52]
	11	Flucytosine	4–>64	>64	>64		[9]
	<i>Aspergillus</i> spp.	31	Isavuconazole	0.06–4	1	2	0.25–16
22		Amphotericin B	0.25–>16	1	4		[50]
22		Itraconazole	0.25–>16	0.5	4		[50]

Table 3 continued

Fungus	No. isolates	Antifungal agent	MIC range ($\mu\text{g/ml}$)	MIC ₅₀ range ($\mu\text{g/ml}$)	MIC ₉₀ range ($\mu\text{g/ml}$)	MFC range ($\mu\text{g/ml}$)	References
	31	Voriconazole	0.125–>16	2	8		[1, 50]
	22	Posaconazole	0.06–>16	0.25	2		[50]
	22	Caspofungin	0.125–1	0.5	1		[50]
	22	Flucytosine	0.5–>64	8	>64		[50]

Candida spp.

Isavuconazole has in vitro activity (MIC < 2 $\mu\text{g/ml}$) against most *Candida* spp. with potency similar to voriconazole and posaconazole, and superior to that of fluconazole, itraconazole, and amphotericin B (Table 1) [1, 4, 9–12]. However, isavuconazole MICs of >2 $\mu\text{g/ml}$ were observed in *C. albicans* isolates with fluconazole MICs > 64 $\mu\text{g/ml}$ [13]. Against *C. glabrata*, *C. krusei*, and *C. tropicalis*, three non-*albicans* *Candida* spp. that may be resistant to fluconazole or require higher fluconazole doses, the isavuconazole MIC ranges were ≤ 0.015 –16 $\mu\text{g/ml}$, 0.03–2 $\mu\text{g/ml}$, and ≤ 0.015 to >8 $\mu\text{g/ml}$, respectively. However, the isavuconazole MIC₅₀ values against these species remained low ranging from 0.25 to 2 $\mu\text{g/ml}$ in *C. glabrata*, 0.125 to 0.5 $\mu\text{g/ml}$ in *C. krusei*, and ≤ 0.015 to 0.03 $\mu\text{g/ml}$ in *C. tropicalis*. Although elevated fluconazole MICs have also been reported with *C. dublinensis*, isavuconazole activity has only been reported against three isolates of this species, each with MICs of 0.03 $\mu\text{g/ml}$ and comparably low fluconazole MICs (0.125 $\mu\text{g/ml}$). *C. lusitanae*, which in some cases may be resistant to amphotericin B, and *C. parapsilosis* and *C. guilliermondii*, which may have elevated echinocandin MICs, exhibited isavuconazole MIC ranges lower than all other antifungals tested. The mean fungicidal concentration (MFC) of isavuconazole was determined against very few *Candida* isolates, and no comparative data are currently available. MFC ranges varied widely (0.03 to >16 $\mu\text{g/ml}$) for all species; however, MFC₅₀s of 4 $\mu\text{g/ml}$ were seen in *C. parapsilosis*; while *C. albicans*, *C. glabrata*, and *C. tropicalis* all exhibited MFC₅₀s of ≥ 16 $\mu\text{g/ml}$ [1].

Non-*Candida* Yeasts

Isavuconazole has excellent in vitro activity against *Cryptococcus* spp. (Table 2). Although MIC ranges were similar between isavuconazole, posaconazole, and voriconazole, the isavuconazole MIC₅₀ and MIC₉₀ values were lower than or equal to other antifungal agents [2, 9, 14–17]. In addition, excellent activity against isolates with intermediate fluconazole susceptibility (MIC, 16–64 $\mu\text{g/ml}$) was maintained for isavuconazole (0.06–0.5 $\mu\text{g/ml}$), posaconazole (0.125–0.5 $\mu\text{g/ml}$) and voriconazole (0.25–0.5 $\mu\text{g/ml}$) [14].

Table 4 In vitro activity of isavuconazole against Zygomycetes

Fungus	No. isolates	Antifungal agent	MIC range (µg/ml)	MIC ₅₀ range (µg/ml)	MIC ₉₀ range (µg/ml)	MFC range (µg/ml)	References
<i>Lichtheimia</i> spp. (formerly <i>Absidia</i>)	111	Isavuconazole	0.03–>8	0.5–4	1–>8	4–>16	[1, 19, 26, 53]
	17	Amphotericin B	0.25–1	0.5	1		[26]
	17	Itraconazole	0.5–2	1	2		[26]
	17	Fluconazole	8–32	16	32		[26]
	31	Voriconazole	4–>16	8–>8	>8	>8	[1, 19, 26]
	85	Posaconazole	0.03–>8	0.12–1	0.12–2	4–8	[19, 26, 53]
	59	Ravuconazole	0.03–8	0.25–4	1–8		[26, 53]
<i>Cunninghamella</i> spp.	25	Isavuconazole	0.12–>8	2–16	>8	2–>16	[1, 19, 53]
	7	Voriconazole	8–16	>8	>8	>8	[1, 19]
	21	Posaconazole	0.12–1	1	1	>8	[19, 53]
	4	Ravuconazole	0.12–1				[53]
<i>Mucor</i> spp.	107	Isavuconazole	<0.015–>8	1–>8	2–>8	2–>16	[1, 19, 53]
	30	Voriconazole	2–>16	>8	>16	>8	[1, 19]
	51	Posaconazole	0.06–>16	0.25–1	0.5–2	4–>8	[19, 53]
	22	Ravuconazole	0.5–>128	4	8		[53]
<i>Mucorales circinelloides</i>	16	Isavuconazole	2–8	4	8		[26]
	16	Amphotericin B	0.25–1	0.5	1		[26]
	16	Itraconazole	0.5–2	1	1		[26]
	16	Fluconazole	8–64	16	32		[26]
	16	Voriconazole	4–8	8	8		[26]
	16	Posaconazole	0.5–2	1	2		[26]
	16	Ravuconazole	2–8	4	8		[26]
<i>Rhizomucor</i> spp.	38	Isavuconazole	<0.015–>8	2–>8	>8	2–>8	[19, 53]
	9	Voriconazole	>8	>8	>8	>8	[19]
	26	Posaconazole	0.03–4	0.25–1	0.5–4	2–>8	[19, 53]
	8	Ravuconazole	0.015–1				[53]
<i>Rhizopus</i> spp.	189	Isavuconazole	0.12–>8	0.25–4	1–>8	1–>16	[1, 9, 19, 26, 53]
	30	Amphotericin B	0.25–2	0.5	1		[9, 26]
	27	Itraconazole	0.25–4	0.5	2		[26]
	30	Fluconazole	4–>64	8	16		[9, 26]
	49	Voriconazole	1–>16	2–>8	2–>16	>8	[1, 9, 19, 26]
	149	Posaconazole	0.03–>16	0.25–2	0.5–4	4–>8	[9, 19, 26, 53]
	64	Ravuconazole	0.06–8	2	4		[26, 53]
<i>Syncephalastrum</i> spp.	2	Isavuconazole	0.125–4			1–16	[1]
	2	Voriconazole	2–16				[1]

Potent activity was also observed for each of the azoles tested against *Trichosporon* isolates. Isavuconazole MIC₅₀ and MIC₉₀ values were lower than those of amphotericin B and flucytosine, and lower than or equivalent to the corresponding values of other azoles except for voriconazole for which the

MIC₅₀ and MIC₉₀ values were 2 to fourfold lower [18]. Similar results were seen in the other rare yeasts tested. For *Geotrichum capitatum*, and *Pichia* spp., isavuconazole, voriconazole, and posaconazole had similar activity with MIC₅₀ and MIC₉₀ values ranging from 0.03 to 0.5 µg/ml. Against *Rhodotorula* and

Table 5 In vitro activity of isavuconazole against other moulds

Fungus	No. isolates	Antifungal agent	MIC range ($\mu\text{g/ml}$)	MIC ₅₀ range ($\mu\text{g/ml}$)	MIC ₉₀ range ($\mu\text{g/ml}$)	MFC range ($\mu\text{g/ml}$)	References
<i>Alternaria alternata</i>	30	Isavuconazole	0.5–2	1	1	1	[26]
	30	Amphotericin B	0.5–4	1	2	2	[26]
	30	Itraconazole	0.5–2	0.5	1	1	[26]
	30	Fluconazole	8–64	16	64	64	[26]
	30	Voriconazole	0.125–1	0.5	0.5	0.5	[26]
	30	Posaconazole	0.125–1	0.5	0.5	0.5	[26]
	30	Ravuconazole	0.5–2	1	1	1	[26]
	50	Isavuconazole	2–4	4	4	4	[24]
	50	Amphotericin B	0.125–1	0.25	0.5–1	0.5–1	[24]
	50	Itraconazole	0.125–2	0.5	1	1	[24]
<i>Alternaria infectoria</i>	50	Fluconazole	16–32	32	32	32	[24]
	50	Voriconazole	1–16	2	4–8	4–8	[24]
	50	Posaconazole	0.06–0.5	0.125	0.125–0.25	0.125–0.25	[24]
	50	Caspofungin	0.5–2	1	1	1	[24]
	50	Anidulafungin	0.008–0.3	0.008	0.008–0.16	0.008–0.16	[24]
	35	Isavuconazole	0.06–4	0.125–2	0.25–4	0.25–4	[25, 26]
	35	Amphotericin B	0.25–4	0.25–0.5	0.5–4	0.5–4	[25, 26]
	30	Itraconazole	0.5–8	2	4	4	[26]
	30	Fluconazole	8–64	16	64	64	[26]
	30	Voriconazole	0.5–4	1	2	2	[26]
<i>Bipolaris spicifera</i>	30	Posaconazole	0.5–2	1	2	2	[26]
	30	Ravuconazole	0.5–4	2	4	4	[26]
	5	Isavuconazole	0.06	0.06	0.06	0.06	[25]
	5	Amphotericin B	0.125–1	0.5	1	1	[25]
	29	Isavuconazole	0.25–4	0.5–2	0.5–4	0.5–4	[25, 26]
	29	Amphotericin B	0.5–2	1	1–2	1–2	[25, 26]
	24	Itraconazole	0.5–4	2	4	4	[26]
	24	Fluconazole	8–64	32	64	64	[26]
	24	Voriconazole	0.5–2	1	2	2	[26]
	24	Posaconazole	0.5–2	1	2	2	[26]
<i>Cladosporium</i> spp.	24	Ravuconazole	0.5–4	2	4	4	[26]
	5	Amphotericin B	0.125–1	0.5	1	1	[25]
	29	Isavuconazole	0.25–4	0.5–2	0.5–4	0.5–4	[25, 26]
	29	Amphotericin B	0.5–2	1	1–2	1–2	[25, 26]
<i>Curvularia lunata</i>	24	Itraconazole	0.5–4	2	4	4	[26]
	24	Fluconazole	8–64	32	64	64	[26]
	24	Voriconazole	0.5–2	1	2	2	[26]
	24	Posaconazole	0.5–2	1	2	2	[26]
24	Ravuconazole	0.5–4	2	4	4	[26]	

Table 5 continued

Fungus	No. isolates	Antifungal agent	MIC range ($\mu\text{g/ml}$)	MIC ₅₀ range ($\mu\text{g/ml}$)	MIC ₉₀ range ($\mu\text{g/ml}$)	MFC range ($\mu\text{g/ml}$)	References
<i>Exophiala</i> spp.	112	Isavuconazole	0.03–>4	0.06–0.5	0.06–0.5		[25, 26, 54]
	112	Amphotericin B	0.03–4	0.125–2	0.25–2		[25, 26, 54]
	107	Itraconazole	0.03–>16	0.25	0.25–0.5		[26, 54]
	107	Fluconazole	0.125–>64	4	8–16		[26, 54]
	107	Voriconazole	0.06–>16	0.125–0.5	0.25–1		[26, 54]
	107	Posaconazole	0.016–0.25	0.06–0.125	0.125–0.25		[26, 54]
	12	Ravuconazole	0.125–0.5	0.5	0.5		[26]
	95	Caspofungin	0.016–8	2	4–8		[54]
	95	Flucytosine	0.06–4	0.125–0.25	2		[54]
	5	Isavuconazole	0.06	0.06	0.06		[25]
<i>Fonsecaea</i> spp.	5	Amphotericin B	0.03–0.5	0.5	0.5		[25]
	85	Isavuconazole	0.25–>16	8–>16	>8–>16	4–>16	[1, 9, 25, 26]
	65	Amphotericin B	1–8	2–4	2–8		[9, 25, 26]
	30	Itraconazole	4–>16	8	>16		[26]
	60	Fluconazole	>64	>64	>64		[9, 26]
	80	Voriconazole	1–>16	2–>16	4–>16		[1, 9, 26]
	60	Posaconazole	1–>16	2–>16	4–>16		[9, 26]
	30	Ravuconazole	2–>8	8	>8		[26]
	30	Caspofungin	>8	>8	>8		[9]
	30	Micafungin	>8	>8	>8		[9]
<i>Paecilomyces lilacinus</i>	30	Anidulafungin	>8	>8	>8		[9]
	30	Flucytosine	>64	>64	>64		[9]
	22	Isavuconazole	0.2–2	1	2		[26]
	22	Amphotericin B	4–>16	4	>16		[26]
	22	Itraconazole	1–>16	2	>16		[26]
	22	Fluconazole	16–>64	32	>64		[26]
	22	Voriconazole	0.5–4	1	4		[26]
	22	Posaconazole	0.5–2	1	2		[26]
	22	Ravuconazole	0.25–2	1	2		[26]
	1	Isavuconazole	0.12–0.25 b				[11]
<i>Phialophora</i> spp.	5	Isavuconazole	0.06–0.25	0.06	0.06		[25]
	5	Amphotericin B	0.5–1	1	1		[25]

Table 5 continued

Fungus	No. isolates	Antifungal agent	MIC range ($\mu\text{g/ml}$)	MIC ₅₀ range ($\mu\text{g/ml}$)	MIC ₉₀ range ($\mu\text{g/ml}$)	MFC range ($\mu\text{g/ml}$)	References
<i>Rhinochrysiella mackenziei</i>	10	Isavuconazole	0.25–8	0.5	1		[27]
	10	Amphotericin B	2–16	8	16		[27]
	10	Itraconazole	0.06–0.25	0.125	0.25		[27]
	10	Fluconazole	16–64	32	64		[27]
	10	Voriconazole	0.25–2	1	2		[27]
	10	Posaconazole	0.016–0.06	0.06	0.125		[27]
	10	Caspofungin	4–8	8	8		[27]
	10	Anidulafungin	1–8	2	8		[27]
	50	Isavuconazole	0.5–>8	1–2	2–4	2–>16	[1, 11, 25, 26]
	33	Amphotericin B	1–8	2	4		[25, 26]
<i>Scedosporium apiospermum</i>	28	Itraconazole	0.5–8	2	4		[26]
	28	Fluconazole	4–64	16	32		[26]
	44	Voriconazole	0.125–4	0.25–2	0.5–2		[1, 26]
	28	Posaconazole	0.125–2	1	2		[26]
	28	Ravuconazole	0.5–8	2	4		[26]
	6	Isavuconazole	4–16	>16			[1]
	6	Voriconazole	4–8				[1]
	5	Isavuconazole	0.5–8	2	8		[25]
		Amphotericin B	1–>16	>16	>16		[25]
	<i>Scedosporium prolificans</i>	6					
6							
<i>Scedosporium</i> spp.	5						

Table 6 In vitro activity of isavuconazole against Dermatophytes

Fungus	No. isolates	Antifungal agent	MIC range (µg/ml)	MIC ₅₀ range (µg/ml)	MIC ₉₀ range (µg/ml)	MFC range (µg/ml)
<i>Trichophyton rubrum</i>	29	Isavuconazole	0.06–0.25	0.06–0.25	0.06	[25, 55, 56]
	9	Amphotericin B	0.5			[56]
	9	Itraconazole	0.25–0.5	0.5		[56]
	9	Fluconazole	1–16	4		[56]
	9	Voriconazole	0.25–0.5	0.25		[56]
	19	Terbinafine	0.002–16	0.004–4	0.004–4	[55, 56]
<i>Trichophyton mentagrophytes</i>	39	Isavuconazole	0.06–2	0.06–1	0.06	[25, 55, 56]
	19	Amphotericin B	2			[56]
	19	Itraconazole	0.25–16	1		[56]
	19	Fluconazole	8–64	32		[56]
	19	Voriconazole	0.5–1	0.5		[56]
	29	Terbinafine	0.008–2	0.008–0.125	0.03	[55, 56]
<i>Trichophyton tonsurans</i>	20	Isavuconazole	0.06–1	0.125	0.25	[25, 55]
	20	Terbinafine	0.004–0.015	0.015	0.015	[25, 55]
<i>Epidermophyton floccosum</i>	20	Isavuconazole	0.06	0.06	0.06	[25, 55]
	20	Terbinafine	0.002–0.03	0.008	0.015	[25, 55]
<i>Microsporum canis</i>	54	Isavuconazole	0.06–0.5	0.06–0.125	0.125	[25, 55, 56]
	32	Amphotericin B	1			[25, 55, 56]
	12	Itraconazole	0.06–1	0.5		[56]
	12	Fluconazole	2–32	8		[56]
	12	Voriconazole	0.25–0.5	0.5		[56]
	12	Terbinafine	0.015–0.25	0.015–0.125	0.03	[55, 56]

Saccharomyces spp. isavuconazole and voriconazole were the most potent tested agents with MIC₅₀ and MIC₉₀ values ranging from 0.03 to 0.25 µg/ml. MFC values were higher than the corresponding MICs for each isolate tested with MFC₉₀ values often exceeding the highest concentration tested.

Aspergillus spp.

Isavuconazole has potent in vitro activity against most *Aspergillus* isolates (Table 3). The MIC₅₀ and MIC₉₀ values of isavuconazole were lower than or equivalent to those of posaconazole or voriconazole for all species. Although the MIC₅₀s of the extended spectrum triazoles and echinocandins were all <0.5 µg/ml, the echinocandins (casposfungin, micafungin, and anidulafungin) exhibited MIC₅₀ and MIC₉₀ values 4 to eightfold below those of voriconazole and posaconazole [3]. Additionally, isavuconazole, voriconazole,

and posaconazole also showed antifungal activity against *A. terreus* (MIC₅₀ values ≤1 µg/ml), a well-known amphotericin B-resistant species. No significant differences in isavuconazole potency were found among different *Aspergillus* spp., although isavuconazole MICs tended to be higher (1–2 dilutions) against *A. niger* [1].

To further evaluate potential isavuconazole resistance, isolates in one study were preselected for itraconazole resistance (MIC > 8 µg/ml), and were additionally known to have elevated posaconazole MICs [3]. The isavuconazole geometric mean MIC and MFC of these isolates were 1.1 and 2.3 µg/ml, respectively. Isavuconazole was also fungicidal against most isolates with MFCs within 2 dilutions of the MICs [1, 19]. The isavuconazole MFCs were lower than other tested antifungal agents, including posaconazole and voriconazole, by an average of 2–3 dilutions [19].

Table 7 In vitro activity of isavuconazole against dimorphic fungi—the endemic mycoses

Fungus	No. isolates	Antifungal agent	MIC range (µg/ml)	MIC ₅₀ range (µg/ml)	MIC ₉₀ range (µg/ml)	MFC range (µg/ml)
<i>Blastomyces dermatitidis</i>	6	Isavuconazole	0.5–4	1		[26]
	6	Amphotericin B	0.06–0.5	0.25		[26]
	6	Itraconazole	0.25–4	0.5		[26]
	6	Fluconazole	4–32	8		[26]
	6	Voriconazole	0.125–2	1		[26]
	6	Posaconazole	0.25–1	0.5		[26]
	6	Ravuconazole	0.125–4	1		[26]
<i>Histoplasma capsulatum</i>	28	Isavuconazole	0.125–2	0.5	2	[26]
	28	Amphotericin B	0.06–0.25	0.125	0.25	[26]
	28	Itraconazole	0.25–2	0.5	1	[26]
	28	Fluconazole	4–32	4	16	[26]
	28	Voriconazole	0.06–2	0.25	1	[26]
	28	Posaconazole	0.03–2	0.25	2	[26]
	28	Ravuconazole	0.125–2	0.5	1	[26]
<i>Coccidioides posadasii</i>	30	Isavuconazole	0.125–1	0.25	0.5	[26]
	30	Amphotericin B	0.03–0.125	0.06	0.125	[26]
	30	Itraconazole	0.03–0.5	0.125	0.5	[26]
	30	Fluconazole	2–64	8	32	[26]
	30	Voriconazole	0.06–1	0.125	0.5	[26]
	30	Posaconazole	0.06–1	0.125	0.5	[26]
	30	Ravuconazole	0.125–1	0.25	0.5	[26]
<i>Sporothrix</i> spp.	5	Isavuconazole	2–8	4	8	[25]
	5	Amphotericin B	1–2	2	2	[25]

Zygomycetes

The Zygomycetes include several genera that cause significant disease in humans [20]. These pathogens respond poorly to existing antifungal therapy and amphotericin B formulations currently remain the standard of care given the lack of activity of voriconazole or fluconazole against these agents of infection. Posaconazole has previously shown activity against this group of organisms; however, its efficacy has thus far been studied only in salvage settings [21]. Against a large number of Zygomycetes isolates isavuconazole MIC₅₀ and MIC₉₀ values were comparable to those of posaconazole, although on average 2 to fourfold higher (Table 4). Isavuconazole MIC₅₀ values were lowest in *Lichtheimia* (formerly *Absidia*) (0.5–4 µg/ml) and *Rhizopus* spp. (0.25–4 µg/ml) compared to other species; however, even in these the posaconazole MIC₅₀s remained lower still (0.12–1 and 0.25–2 µg/ml, respectively). Posaconazole

MIC₅₀ values were similar amongst all species with the exception of *Mucor circinelloides* (isavuconazole MIC₅₀ 4 µg/ml, posaconazole MIC₅₀ 1 µg/ml) and *Cunninghamella* spp. (isavuconazole MIC₅₀ 2–16 µg/ml; posaconazole 1 µg/ml), which had the highest MIC₅₀ values of all species tested. Both posaconazole and isavuconazole exhibited higher MIC₅₀ and MIC₉₀ values than did amphotericin B for all species. Similar to previous reports [22] voriconazole and fluconazole showed little to no activity against most isolates with MIC values frequently exceeding 8 µg/ml in our review. MFC values were only available for triazoles and were typically high for all agents tested (posaconazole and isavuconazole MFC ranges 1 to >8 µg/ml).

Other Moulds

Against other medically important moulds isavuconazole has variable in vitro activity (Table 5).

Fusarium and *Scedosporium* spp. are known to frequently demonstrate reduced susceptibility to most antifungal agents. Although low MICs were seen against some *Fusarium* isolates for isavuconazole, the MIC₅₀ values were equivalent to or higher than corresponding values of posaconazole, voriconazole and the echinocandins. MFCs ranged from 4 to >16 µg/ml against *Fusarium*. Considerable differences in susceptibility were seen between *Scedosporium* spp., similar to findings previously reported by others [23]. MIC₅₀s against *S. apiospermum* were similar among the extended spectrum triazoles (isavuconazole 1–2 µg/ml, voriconazole 0.25–2 µg/ml, posaconazole 1 µg/ml). Although only a few isolates of the dematiaceous fungus *S. prolificans* have been evaluated, each azole exhibited high MIC values (≥4 µg/ml). Additionally, isavuconazole MFCs exceeded 16 µg/ml against this species. *Paecilomyces* spp. showed low MICs to all triazoles except fluconazole, and isavuconazole MIC₅₀ values (1 µg/ml) were lower than or equal to those of all other tested antifungal agents.

The other dematiaceous fungi (*Alternaria*, *Bipolaris*, *Cladosporium*, *Curvularia*, *Exophiala*, *Fonsecaea*, and *Phialophora* amongst others) typically demonstrated very low MIC's to all tested agents with the exception of fluconazole (MIC₅₀s ≥ 16 µg/ml for all species except *Exophiala*, MIC₅₀ = 4 µg/ml). Lower MIC₅₀s were observed against *Alternaria alternata* for the extended spectrum triazoles (isavuconazole MIC₅₀ 1 µg/ml, posaconazole 0.5 µg/ml, voriconazole 0.5 µg/ml) than against *Alternaria infectoria* (isavuconazole MIC₅₀ 4, posaconazole 0.125, and voriconazole 2 µg/ml) [24]. Isavuconazole MIC₅₀ values were less than or equivalent to other triazoles against *B. spicifera*, *C. lunata*, *Exophiala* spp. and *Rhinochadiella mackenziei* [25–27]. *Cladosporium* and *Phialophora* spp. isavuconazole MICs were compared only to amphotericin B. For the small number of isolates tested, isavuconazole MIC₅₀s were at least 3 dilutions lower than those of amphotericin B [25].

Dermatophytes

Against the dermatophytes (*T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *E. floccosum*, and *M. canis*), isavuconazole has shown potent in vitro activity (Table 6). Isavuconazole MIC₅₀ and MIC₉₀ values

were lower than other triazoles against all tested strains. Terbinafine showed lower MIC₅₀ and MIC₉₀ values than those of isavuconazole; however, against terbinafine-resistant *T. rubrum* strains, isavuconazole MICs remained low (0.06 µg/ml for all tested isolates) [25].

Dimorphic Fungi

Itraconazole, voriconazole, posaconazole, ravuconazole, and isavuconazole have potent in vitro activity against the dimorphic fungi (Table 7) [25, 26]. The MICs of isavuconazole were similar to all other tested agents against *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides posadasii*, and were lower than those of fluconazole. However, isavuconazole did exhibit higher MIC₅₀ and MIC₉₀ values against *Sporothrix* spp.—similar to those previously reported with voriconazole [28].

In Vivo Studies

Animal models of invasive fungal infections caused by *Aspergillus* and *Candida* species have demonstrated that the in vitro activity of isavuconazole is maintained in vivo. In a recent study by Warn et al. [5, 29] isavuconazole was effective in reducing tissue fungal burden in mice with disseminated candidiasis caused by susceptible *C. albicans* (MIC 0.004 µg/ml). In this study isavuconazole, administered by subcutaneous injection, demonstrated a near maximal effect with doses of >15 mg/kg, and concentration dependent activity was observed as the pharmacokinetic/pharmacodynamic parameter most closely associated with reductions in tissue fungal burden within the kidneys was the area under the concentration curve/MIC ratio (AUC/MIC). As this PK/PD parameter increased, the likelihood of survival also increased. In temporarily neutropenic mice, 90% survival was observed after 5 days of therapy when the AUC/MIC ratio was >270. Isavuconazole also demonstrated a modest post-antifungal effect in this model effectively preventing the growth of the infecting organism by approximately 8 h once the concentration of this drug decreased below the MIC [30]. However, isavuconazole did not demonstrate fungicidal activity but rather retarded growth, and in animals that were persistently neutropenic a much

higher AUC/MIC value (670) was required to achieve this same survival benefit. Despite these promising results, it is uncertain how well the data will translate into humans due to pharmacokinetic considerations. The concentrations of isavuconazole achieved within the kidneys of mice, the organs in which the fungal burden was measured, was 5–6 times higher than that observed in the plasma. In addition, isavuconazole was rapidly cleared from the plasma in these animals with a terminal half-life of 3.41 h, which is significantly shorter than what has been reported in humans (>50 h) [31].

Isavuconazole has also proven effective in one study against disseminated infections caused by non-*albicans Candida* species [32]. In both temporarily and persistently neutropenic mice, both isavuconazole and fluconazole were effective at reducing tissue fungal burden within the kidneys of mice infected with an isavuconazole susceptible *C. tropicalis* with isavuconazole demonstrating a maximum effect at oral doses between 60 and 120 mg/kg administered twice daily. This in vivo activity was superior to that observed in mice treated voriconazole that were also administered grapefruit juice to prevent the rapid metabolism of this azole. Isavuconazole also reduced the tissue fungal burden within the kidneys and brains of temporarily and persistently neutropenic mice infected with *C. krusei* with activity similar to that observed for voriconazole. Similar to the results described above for *C. albicans*, isavuconazole did not result in sterilization of the tissues. Interestingly, higher doses of isavuconazole were required in this study to achieve a maximum effect against disseminated candidiasis caused by *C. tropicalis* and *C. krusei* (>60 mg/kg twice daily) compared to that observed against *C. albicans* (>15 mg/kg) in the previous study. It is unknown if this is due to the reduced potency of this azole against the *C. tropicalis* and *C. krusei* isolates used in this study (MIC 0.015 and 0.25 µg/ml, respectively) compared to the *C. albicans* isolate (MIC 0.004 µg/ml), or to differences in pharmacokinetics that may have arisen secondary to different routes of administration (oral versus subcutaneous).

Isavuconazole has also been shown to be effective in an animal model of disseminated aspergillosis. In this study, oral isavuconazole was initiated either prior to inoculation (2 h), or after inoculation (4 or 24 h) of neutropenic mice with an *A. flavus* isolate

(isavuconazole MIC 1 µg/ml) via the lateral tail vein [8]. Isavuconazole was 100% effective at improving survival at all doses tested (3, 6, and 15 mg/kg) when initiated 2 h prior to inoculation; however, higher doses (15 and 30 mg/kg) were required for a similar survival benefit if therapy was initiated 4 or 24 h post-inoculation. Clearance of the organism from tissues was also demonstrated in several animals that survived to the study endpoint (14 days post-inoculation). Although these results are promising, it is unclear how effective isavuconazole would be in a pulmonary inoculation model that simulates the pathogenesis observed in humans. In a non-lethal murine model of disseminated aspergillosis caused by different *A. fumigatus* isolates, isavuconazole doses of ≥ 75 up to 250 mg/kg have been effective in reducing tissue fungal burden regardless of the initial MIC [33–35]. In these studies, divided doses of this azole were more effective; however, once daily dosing was also capable of reducing fungal burden.

Pharmacokinetics

Both oral and intravenous preparations of isavuconazole have been developed. The pro-drug, isavuconazonium (BAL-8557) is cleaved by plasma esterases to the active form of isavuconazole and an inactive metabolite (BAL-8728) [31]. In an early study, single-ascending oral doses of BAL-8557 were administered to healthy volunteers as 100, 200 or 400 mg BAL-4815 equivalents, and serum drug levels were followed for 288 h. Following administration peak concentrations observed 1.5–3 h after dosing were 1.45, 2.59 and 5.57 µg/ml, respectively, and the mean half-life ranged from 56 to 77 h with detectable drug seen in plasma up to 16 days post-dose [31]. No significant food effect has been found with oral administration of isavuconazole [36], a potential benefit over oral itraconazole, posaconazole, and voriconazole.

The pharmacokinetics of intravenous administration of isavuconazole at 50, 100, or 200 mg has also been studied in healthy volunteers [31]. Peak plasma concentrations were reached between 0.75 and 1 h after IV administration and declined in a biphasic manner thereafter. Peak levels of 0.44, 1.03, and 2.47 µg/ml, respectively, were obtained at these doses and increased disproportionately to the dose.

Similar results have been found in neutropenic patients administered isavuconazole [37] and in this study, patients were given 3 doses of intravenous isavuconazole on day 1 (400, 200, and 200 mg), followed by 200 mg twice daily on day 2, then daily therapy until resolution of neutropenia. The pharmacokinetics observed in this study were similar to those previously reported in healthy volunteers.

The disposition of isavuconazole has also been evaluated and the volume of distribution in the post-distributive phase is impressive (155–292 L) [31]. In animal models, isavuconazole also has a large volume of distribution and is highly protein bound [3]. The aqueous solubility of isavuconazonium avoids the necessity of cyclodextrin thus obviating concerns for accumulation of this excipient in patients with a reduction in renal function—a potential advantage over intravenous voriconazole. In humans, urinary concentrations are detectable in <1% of all samples and amounted to only 0.02–0.04% of the administered dose [31].

Isavuconazole is primarily metabolized by CYP3A4 raising concerns for potential interactions with drugs that either act as inhibitors or inducers of this isoenzyme [38]. In patients with underlying liver impairment secondary to alcohol use or hepatitis B or C, the half-life of isavuconazole is prolonged as this parameter increased from 123 h in the control group to 224 and 302 h in patients with average Child-Pugh scores of 5.9 and 8.4, respectively [39]. A summary table comparing pharmacokinetic data between isavuconazole and existing triazoles is provided in Table 8.

Mechanism of Resistance

The potential effectiveness of isavuconazole against isolates resistant to other azoles has been recently evaluated. In one study that compared isavuconazole, voriconazole, and fluconazole against *C. glabrata* isolates, the MIC₅₀ values for isavuconazole were significantly lower than those observed with voriconazole ($P < 0.05$), and the majority of fluconazole-resistant *Candida* isolates were inhibited by both voriconazole and isavuconazole at concentrations attainable in vivo [40]. A similar study demonstrated that isavuconazole was as potent as itraconazole and voriconazole against fluconazole-resistant *C. glabrata* isolates (MIC₅₀ = 2 µg/ml for each agent) [41].

More recently the activity of isavuconazole was evaluated against *Saccharomyces cerevisiae* and *C. albicans* isolates containing specific drug resistance genes [13]. In these isolates the potency of isavuconazole was affected by mutations in *ERG11*. However, these affects were more moderate than those observed for fluconazole and voriconazole. Isavuconazole was also shown not to be a substrate of *MDR1* or *FLU1*, in contrast to fluconazole and voriconazole. Additionally, the majority of fluconazole-resistant isolates showed comparably low isavuconazole MICs (<2 µg/ml) suggesting the potential utility of isavuconazole against fluconazole-resistant isolates. However, more studies, including data from in vivo experiments, are needed.

Therapeutic Drug Monitoring

Isavuconazole has shown low to moderate intersubject variability in serum levels (coefficient of variation (CV) < 20%), compared to voriconazole (up to 100-fold) with oral dosing, yet moderate to high variability with intravenous administration (CV < 40%) [31]. Although this early data is conflicting, the utility and necessity of therapeutic drug monitoring remains to be determined. Phase III and post-marketing studies will help to determine the utility of monitoring levels of this compound.

Adverse Effects Profile

Animal data has shown no evidence of mutagenesis, allergenicity, or phototoxicity, and initial dose escalation trials have reported no adverse effects [31]. Electrocardiographic abnormalities, including QTc interval prolongation, have not been observed [42]. Side effects of headache, rhinitis, nasopharyngitis, moderate diarrhea, nausea, and mild upper abdominal pain have been seen in healthy volunteer studies. Preliminary results of phase II studies in the treatment of esophageal candidiasis have shown comparable toxicities to those of fluconazole [43].

Drug Interactions

Similar to other medications metabolized through the hepatic CYP450 system, multiple drug interactions are predicted for isavuconazole. A 35-fold increase in isavuconazole clearance, a fourfold reduction in

Table 8 Comparative pharmacokinetics of the triazoles: fluconazole (FLU), itraconazole (ITR), voriconazole (VOR), posaconazole (POS), and isavuconazole (ISA)

	Antifungal agent				
	FLU	ITR ^a	VOR	POS	ISA
Currently available formulations	PO/IV	PO	PO/IV	PO	PO/IV
Therapeutic drug monitoring	No	Yes	Yes	Yes	ND
Routinely recommended					
Vehicle required for IV solubility	None	N/A	Cyclodextrin	N/A	None
Pharmacokinetic parameter					
Oral bioavailability, %	>90	50	96	ND	>95
Food effect	None	ES	ES	Food	None
Total C _{max} µg/ml	6.7 ^b	11 ^c	3.0 ^d	7.8 ^e	2.59 ^f
Elimination half-life (hours)	22–31	35–64	6–24	25–35	56–77
AUC, mg × h/L	356 ^b	29.2 ^c	20.3 ^d	8.9 ^e	77 ^f
Protein binding, %	11–22	99.8	58	99	98
V ^d (liters/kg)	0.7 ^b	11 ^c	4.6 ^d	25.3 ^e	4.2 ^f
CSF penetration, %	50–90	<10	60	ND	ND
Vitreous penetration, %	27 ^h	10 ^g	38 ^g	26 ^{g,h}	ND
Excreted unchanged in urine, % ⁱ	>80	1–10	<2	<2	<1
Metabolism	Hep	Hep	Hep	Hep	Hep
Elimination	Renal	Hep	Renal	Feces	ND
Half-life, h	30	24	6	25	56–77

N/A not applicable, ND no data, ES empty stomach, C_{max} peak drug concentration, AUC area under the concentration curve, V^d volume of distribution, Hep hepatic, Itr itraconazole, Vor voriconazole, Pos posaconazole

^a Data are for oral solution as intravenous form has been discontinued

^b FLU data based on a 400 mg oral dose

^c ITR data based on a 200 mg dose

^d VOR data based on a 200 mg dose

^e POS data based on a 400 mg dose

^f ISA C_{max} and AUC data based on a 200 mg oral dose

^g Human data

^h Animal data

ⁱ Percentage for active drug or metabolites

Data adapted from [31, 57–62]

C_{max}, and a 40-fold reduction in the AUC have been observed when the CYP450 inducer rifampicin was coadministered [44]. However, warfarin and cyclosporine levels were unaffected when coadministered with isavuconazole [45, 46]. When coadministered with tacrolimus, the C_{max} and AUC₀₋₈ of tacrolimus increased by 74.1 and 79.2% respectively [47].

Clinical Evidence

Clinical trials evaluating the efficacy of isavuconazole are currently underway. These include phase

III clinical trials investigating isavuconazole for the prophylaxis or treatment of invasive pulmonary aspergillosis and a non-randomized study examining the safety and efficacy of escalating doses as prophylaxis in acute myeloid leukemia patients. An additional head-to-head trial comparing isavuconazole to voriconazole in the treatment of invasive aspergillosis will also be of great interest to clinicians. The results of these trials will provide insight into the proper use of isavuconazole in the treatment and prevention of invasive mycoses [7].

Conclusions

This agent has demonstrated excellent in vitro activity against a number of clinically important yeasts and moulds and in vivo models of infection have also demonstrated the potential efficacy of this compound. Isavuconazole has a longer half-life than other currently available triazoles, and is available in both oral and a cyclodextrin-free intravenous formulation. Ongoing trials will further define the clinical use of isavuconazole and further studies investigating the potential drug–drug interactions and potential need for therapeutic drug monitoring to predict efficacy are needed. However, isavuconazole has several advantages over existing antifungal agents and thus may be a welcome and needed addition to the antifungal armamentarium.

Transparency Declaration

G. R. T has served as a consultant for Basilea, serves on the speakers bureau for Merck and has received research support from Pfizer. N. P. W. has received research support from Pfizer, Schering-Plough, CyDex, Merck, Associates of Cape Cod, and Basilea.

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