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Isavuconazole: A New Option for the Management of Invasive Fungal Infections

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Abstract

Objective: To review the pharmacology, chemistry, in vitro susceptibility, pharmacokinetics, clinical efficacy, safety, tolerability, dosage, and administration of isavuconazole, a triazole antifungal agent. **Data Sources:** Studies and reviews were identified through an English language MEDLINE search (1978 to March 2015) and from http://www.clinicaltrials.gov, Food and Drug Administration (FDA) briefing documents, program abstracts from international symposia, and the manufacturer's Web site. **Study Selection and Data Extraction:** All published and unpublished trials, abstracts, in vitro and preclinical studies, and FDA briefing documents were reviewed. **Data Synthesis:** Isavuconazole has activity against a number of clinically important yeasts and molds, including *Candida* spp, *Aspergillus* spp, *Cryptococcus neoformans*, and *Trichosporon* spp and variable activity against the Mucorales. Isavuconazole, available for both oral and intravenous administration, is characterized by slow elimination allowing once-daily dosing, extensive tissue distribution, and high (>99%) protein binding. The most commonly reported adverse events, which are mild and limited in nature, include nausea, diarrhea, and elevated liver function tests. Its drug interaction potential appears to be similar to other azole antifungals but less than those observed with voriconazole. Comparative trials are under way or have been recently completed for the treatment of candidemia, invasive candidiasis and aspergillosis, and rare mold infections. **Conclusions:** Isavuconazole has a broad spectrum of activity and favorable pharmacokinetic properties, providing an advantage over other currently available broad-spectrum azole antifungals and a clinically useful alternative to voriconazole for the treatment of invasive aspergillosis. It may also prove useful for the treatment of candidemia and invasive mold infections; however, these indications await the results of clinical trials.

Keywords

antifungal agents, triazole, isavuconazole, pharmacokinetics, candidiasis, aspergillosis, Mucor, mold infections, invasive fungal infections

Mortality associated with invasive fungal disease increased 3.4-fold between 1980 and 1997, with mycoses becoming the seventh-leading cause of infectious mortality.[1] Increasing numbers of cancer patients with chemotherapy-induced neutropenia and patients undergoing transplantation has led to an increased incidence of invasive fungal infections (IFIs). Mortality from IFIs is high, particularly in aspergillosis, ranging from 30% to 90%.[2] There is an urgent need for new antifungal agents with favorable pharmacokinetic and adverse effect profiles and improved efficacy against *Candida* and *Aspergillus* spp, including drug-resistant strains. Moreover, the increased incidence of previously less-common fungi, including *Fusarium* spp, *Trichosporon* spp, *Cryptococcus* spp, *Scedosporium* spp, and the Mucorales, necessitates the introduction of antifungal agents with an expanded spectrum of activity.

Currently available antifungal agents for the treatment of IFIs include polyenes, echinocandins, and azoles. The polyene antifungal amphotericin B has a broad spectrum of activity; however, use is limited by infusion-related reactions, nephrotoxicity, and lack of an oral formulation. Although echinocandin antifungals (caspofungin, micafungin, and anidulafungin) and azole antifungals offer attractive safety profiles, the echinocandins lack oral formulations, and their spectrum of activity is primarily limited to *Candida* and *Aspergillus* species; also, there is increasing resistance among certain *Candida* spp (eg, *Candida glabrata*).[3] Fluconazole has excellent oral bioavailability, but it lacks activity against filamentous fungi, and the rates of resistance of some

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Candida species (eg, *Candida glabrata)* are increasing. Although newer azoles, including itraconazole, voriconazole, and posaconazole, have expanded coverage against filamentous fungi and fluconazole-resistant organisms, they display significant pharmacokinetic variability, are associated with significant drug interactions, and rare but severe toxicities, including hepatotoxicity and QT prolongation.[4]

Isavuconazole is a second-generation triazole antifungal, that demonstrates potent in vitro activity against many opportunistic and invasive fungal organisms. It is available for oral and intravenous (IV) administration; the IV formulation does not contain the sulfobutylether β-cyclodextrin found in the IV formulation of voriconazole, which may accumulate in patients with renal dysfunction. Currently, isavuconazole is under investigation in phase III trials for the treatment of systemic candidiasis, aspergillosis, and IFIs caused by rare molds.[5] The purpose of this review is to summarize the pharmacology, chemistry, in vitro susceptibility, pharmacodynamics/pharmacokinetics, clinical efficacy, safety, tolerability, dosage, and administration of isavuconazole.

Studies and reviews were identified through a MEDLINE search, restricted to the English language (1978 to January 2015). Additional articles were identified by reviewing the bibliographies of articles identified via MEDLINE, http://www.clinicaltrials.gov, and Food and Drug Administration (FDA) briefing documents. Supplementary sources included program abstracts from international symposia from 1996 to 2014 and information available from the manufacturer's Web site. All published and unpublished trials and abstracts of in vitro and preclinical studies as well as phase II and III clinical trials of isavuconazole and FDA briefing documents were selected for review.

Chemistry

Isavuconazonium (BAL8557, Basilea and Astellas), a water soluble prodrug, is rapidly (half-life [$t_{1/2}$] < 1 minute) and almost completely (>98%) cleaved by plasma esterases to the active form of the drug, isavuconazole (BAL4815).[6,7] The structure of isavuconazole and its prodrug are shown in Figure 1.[7]

Pharmacology

Mechanism of Action

Similar to other azoles, isavuconazole inhibits fungal cell growth and replication by inhibiting the synthesis of ergosterol, an integral component of the fungal cell membrane, via inhibition of lanosterol 14-α-demethylase (CYP51), leading to an accumulation of toxic 14-α-methylsterols and a depletion of membrane-associated ergosterol.[8]

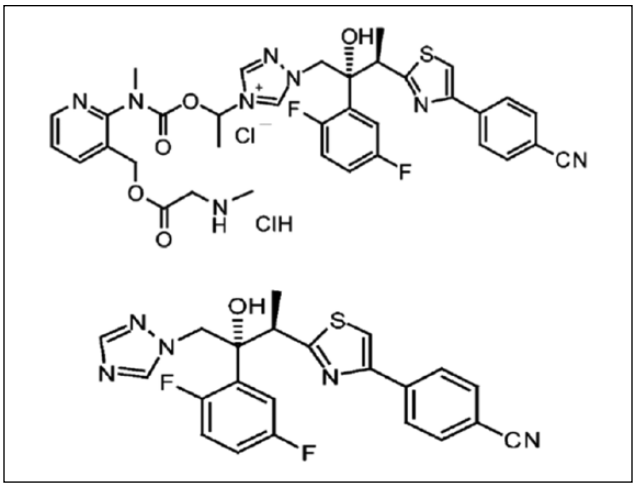

Figure 1. Isavuconazonium (BAL8557; prodrug of isavuconazole) and isavuconazole (BAL4185; active moiety).

In Vitro Antifungal Activity

Similar to the triazole antifungals voriconazole and posaconazole, isavuconazole demonstrates fungistatic activity against yeasts, with a minimum fungicidal concentration within 2 dilutions of the minimum inhibitory concentration (MIC).[9-12] The available in vitro susceptibility data for isavuconazole against common clinical pathogens is shown in Table 1.

Interpretive clinical breakpoints have not been established for isavuconazole, although wild-type MIC distributions and epidemiological cutoff values have been established for *Aspergillus* and *Cryptococcus* spp.[13-16] Of note, while essential agreement (MIC ± 2 $\log_2$ dilutions) between the 2 standardized methods of susceptibility testing for fungi (Clinical and Laboratory Standards Institute [CLSI] and the European Committee on Antimicrobial Susceptibility Testing [EUCAST]) appears to be good for most species of *Candida*, it was poor when testing a large population of *Candida glabrata* and *Candida tropicalis* isolates.[17]

Candida spp[16-24]. Isavuconazole is active against bloodstream isolates of *Candida*, with MIC_{90} values ≤1 μg/mL against most *Candida glabrata* and *Candida krusei* and ≤1 μg/mL for 99.5% of the *Candida* spp.[18,19] The intrinsic resistance of *Candida krusei* to fluconazole is attributable to the reduced affinity to CYP51.[25] However, isavuconazole, like posaconazole and voriconazole, generally inhibits *Candida krusei* at MIC values ≤1 μg/mL.[17] Cross-resistance with other azole antifungals has been observed: isavuconazole displays higher MIC_{90} values to some fluconazole-resistant strains of *Candida*, and MICs >1 μg/mL for many fluconazole-resistant *Candida glabrata*.[21]

Table 1. In Vitro Susceptibility Data.

Fungal Pathogen	n	Agent	MIC Range	MIC_{50}	MIC_{90}	MFC_{90}	Reference Numbers
Aspergillus							
Aspergillus flavus	1170	Isavuconazole	0.06-4	0.5-2	1-4	1-8	11, 12, 15, 16, 18, 20, 21, 26-29, 31
	417	Amphotericin B	0.25-16	0.5-4	1-8	—	12, 20, 28, 31
	440	Itraconazole	0.06-1	0.125-0.5	0.25-0.5	—	12, 16, 20, 21, 28, 31
	497	Voriconazole	0.125-4	0.5-1	0.5-2	—	11, 12, 16, 18, 20, 21, 27, 28, 31
	435	Posaconazole	0.062-2	0.125-1	0.25-1	—	12, 21, 28, 31
	439	Caspofungin	0.015-1	0.015-0.5	0.015-0.5	—	12, 16, 21, 28, 31
	406	Anidulafungin	≤0.008-0.03	≤0.008	≤0.008	—	21, 28, 31
	419	Micafungin	≤0.008-0.25	≤0.008-0.063	0.0015-0.125	—	16, 21, 28, 31
Aspergillus fumigatus	2250	Isavuconazole	0.06 to >16	0.2-2	0.39-2	1-8	11, 12, 15, 16, 18, 20, 21, 26, 27, 29
	130	Amphotericin B	0.06-0.5	0.25-0.39	0.39-0.5	—	12, 20
	321	Itraconazole	0.025->8.0	0.05-1	0.1 to >8.0	—	12, 16, 20, 21
	971	Voriconazole	0.1-8	0.2-1	0.2-1	—	11, 12, 16, 18, 20, 21, 27
	223	Posaconazole	0.06-1	0.25-0.5	0.5-1	—	11, 16, 21
	71	Anidulafungin	≤0.008-0.12	—	—	—	21
	309	Caspofungin	<0.008-4	0.03-0.5	0.03-0.5	—	12, 16, 21
	191	Micafungin	≤0.008-0.06	≤0.008	0.015	—	16, 21
Aspergillus niger	498	Isavuconazole	0.06-16	0.5-2	2-4	2 to >8	11, 12, 15, 18, 20, 21, 26, 27, 29
	18	Amphotericin B	0.25-1	0.5	0.5	—	12
	30	Itraconazole	0.2-4	0.5	2	—	12, 20, 21
	75	Voriconazole	0.25-4	0.25-2	1-2	—	11, 12, 18, 20, 21
	24	Posaconazole	0.25-1	0.25	0.5	—	11, 21
	11	Anidulafungin	≤0.008-0.03	—	—	—	21
	29	Caspofungin	0.015-0.25	0.25	0.25	—	12, 21
	11	Micafungin	≤0.008-0.03	—	—	—	21
Aspergillus terreus	703	Isavuconazole	0.06-8	0.2-1	0.39-4	1-8	11, 12, 15, 18, 20, 21, 26, 27, 29
	21	Amphotericin B	0.25-1	0.39-1	0.39-1	—	12, 20
	27	Itraconazole	0.05-0.5	0.05-0.125	0.1-0.25	—	12, 20, 21
	88	Voriconazole	0.125-2	0.25-1	0.39-2	—	11, 12, 18, 20, 21, 27
	6	Anidulafungin	0.015-0.12	—	—	—	21
	41	Posaconazole	0.125-1	0.125	0.5	—	11, 21
	24	Caspofungin	0.015-0.5	0.5	0.5	—	12, 21
	6	Micafungin	≤0.008-0.12	—	—	—	21
Other *Aspergillus* spp[a]	406	Isavuconazole	0.03 to >8	0.125-0.25	0.25-0.5	—	15, 20, 21, 29, 30
	19	Itraconazole	0.39-2	1	2	—	20, 21, 30
	19	Voriconazole	0.5-2	2	2	—	20, 21, 30
	3	Posaconazole	0.5-1	—	—	—	21
	3	Anidulafungin	0.015-0.06	—	—	—	21
	3	Caspofungin	0.015-0.03	—	—	—	21
	3	Micafungin	0.015-0.03	—	—	—	21
Candida spp							
Candida albicans	2303	Isavuconazole	<0.0004-16	0.0007-0.03	0.0013-0.21	>16	16-22
	1060	Amphotericin B	0.0031-2	0.05-1	0.05-1	—	17, 19, 20, 22
	926	Flucytosine	0.063 to ≥128	0.125-0.5	0.25-0.5	—	17, 19
	2329	Fluconazole	0.018 to >128	0.045-0.5	0.15-20	—	16-22
	1060	Itraconazole	<0.0004-16	0.001-0.03	0.0022-1	—	17, 19, 20, 22

(continued)

Table 1. (continued)

Fungal Pathogen	n	Agent	MIC Range	MIC_{50}	MIC_{90}	MFC_{90}	Reference Numbers
	2329	Voriconazole	<0.0004-16	0.001-0.5	0.0025-2	—	16-22
	2048	Posaconazole	≤0.008-16	0.03-0.06	0.06-0.5	—	16, 17, 21, 22
	1431	Anidulfungin	<0.008-4	0.015-0.031	0.06-2	—	17, 21, 22
	2053	Caspofungin	≤0.008-16	0.03-0.5	0.03-1	—	16, 17, 21, 22
	1963	Micafungin	≤0.008-1	0.015	0.03	—	16, 17, 21
Candida glabrata	1005	Isavuconazole	0.0011-8	0.0039-0.5	0.02-2	>16	16-22
	482	Amphotericin B	0.0063-12	0.05-1	0.1-1	—	17, 19, 20, 22
	382	Flucytosine	0.016 to ≥128	0.063	0.063	—	17, 19
	1020	Fluconazole	0.093 to ≥ 128	0.64-16	3.4-64	—	16-22
	482	Itraconazole	<0.0013 to >8	0.005-1	0.019-2	—	17, 19, 20, 22
	1020	Voriconazole	<0.0016-128	0.0076-0.5	0.043-2	—	16-22
	895	Posaconazole	0.03-16	0.25-1	0.5-2	—	16, 17, 21, 22
	668	Anidulafungin	<0.008-4	0.06-0.063	0.063-0.12	—	17, 21, 22
	903	Caspofungin	0.015-16	0.03-0.5	0.06-1	—	16, 17, 21, 22
	845	Micafungin	≤0.008-2	0.015	0.03	—	16, 17, 21
Candida krusei	159[b]	Isavuconazole	0.0032-4	0.0041-0.5	0.011-1	0.5-4	16-21
	90	Amphotericin B	0.1-2	0.1-1	0.2-2	—	17, 19, 20
	59	Flucytosine	8-32	16	16	—	17, 19
	145	Fluconazole	3.7 to ≥128	5.5-32	8.8-64	—	16-21
	90	Itraconazole	0.0025-4	0.0041-0.5	0.0079-0.5	—	17, 19, 20
	177	Voriconazole	0.012-4	0.016-0.5	0.03-1	—	16-21
	143	Posaconazole	0.12-2	0.25-0.5	0.5	—	16, 17, 21
	111	Anidulafungin	0.03-2	0.06	0.12	—	17, 21
	148	Caspofungin	0.03-8	0.12	0.25	—	16, 17, 21
	148	Micafungin	0.015-0.25	0.12	0.12	—	16, 17, 21
Candida lusitaniae	80	Isavuconazole	<0.0004-0.12	0.00059-0.03	0.0024-0.06	—	16, 20, 21
	19	Amphotericin B	0.05-0.1	0.013	0.025	—	20
	80	Fluconazole	≤0.06-2	0.076-0.5	0.15-1	—	16, 20, 21
	19	Itraconazole	<0.0004-0.0034	0.0006	0.0021	—	20
	61	Posaconazole	0.015-0.25	0.06	0.12	—	16, 21
	80	Voriconazole	<0.0004-0.03	≤0.008	0.0021-0.015	—	16, 20, 21
	28	Anidulafungin	0.03-2	—	—	—	21
	61	Caspofungin	0.015-0.5	0.25	0.5	—	16, 21
	61	Micafungin	0.015-1	0.25	0.25	—	16, 21
Candida parapsilosis	909[b]	Isavuconazole	<0.0004-16	0.0015-0.06	0.011-0.12	16	16-22
	395	Amphotericin B	0.05-2	0.1-1	0.2-1	—	17, 19, 20, 22
	307	Flucytosine	0.063 to >32	0.125 to ≤0.5	0.125 to ≤0.5	—	17, 19
	915	Fluconazole	0.077-128	0.23-1	0.61-2	—	16-18, 20-22
	395	Itraconazole	0.00042-1	0.0019-0.12	0.0059-0.25	—	17, 19, 20, 22
	928	Voriconazole	0.00054-1	0.0035-0.031	0.015-0.125	—	16-22
	806	Posaconazole	0.015-0.5	0.063-0.12	0.12-0.25	—	16, 17, 21, 22
	608	Anidulafungin	0.03-4	2	2-4	—	17, 21, 22
	805	Caspofungin	0.03-4	0.25-1	0.5-2	—	16, 17, 21, 22
	746	Micafungin	0.015-4	1	2	—	16, 17, 21
Candida tropicalis	494[b]	Isavuconazole	<0.0004-16	0.0046-0.06	0.008-0.25	>16	16-22
	271	Amphotericin B	0.025-2	0.05-1	0.2-1	—	17, 19, 20, 22
	178	Flucytosine	0.063 to ≥128	0.125 to ≤0.5	≤0.5 to 128	—	17, 19
	526	Fluconazole	0.04 to >64	0.2-1	0.3-2	—	16-22
	271	Itraconazole	<0.0004-8	0.004-0.063	0.0095-0.125	—	17, 19, 20, 22
	526	Voriconazole	<0.0004-2	0.011-0.063	0.06-0.125	—	16-22
	453	Posaconazole	≤0.008-8	0.03-0.06	0.12-0.25	—	16, 17, 21, 22
	348	Anidulafungin	≤0.008-4	0.015-0.063	0.03-0.125	—	17, 21, 22

(continued)

Table 1. (continued)

Fungal Pathogen	n	Agent	MIC Range	MIC_{50}	MIC_{90}	MFC_{90}	Reference Numbers
	458	Caspofungin	≤0.008-4	0.03-0.5	0.06-1	—	16, 17, 21, 22
	398	Micafungin	≤0.008-2	0.03	0.06	—	16, 17, 21
Cryptococcus spp	165	Isavuconazole	0.002-0.063	0.004	0.016	—	32
	165	Amphotericin B	0.016-1	0.25	0.25	—	32
	165	Flucytosine	0.063-64	4	8	—	32
	165	Fluconazole	0.25-64	2	4	—	32
	165	Itraconazole	0.016-1	0.031	0.25	—	32
	165	Voriconazole	0.016-0.25	0.031	0.125	—	32
	165	Posaconazole	0.002-0.125	0.004	0.016	—	32
Cryptococcus gattii	995	Isavuconazole	0.008-0.5	0.03-0.125	0.06-0.25	—	13, 30, 33, 38, 42, 95
	499	Amphotericin B	<0.016-1	0.25	0.25-0.5	—	33, 38, 42, 95
	492	Flucytosine	0.06 to >64	1-2	2-8	—	33, 38, 42
	582	Fluconazole	0.25-64	2-4	8	—	30, 33, 38, 42
	540	Itraconazole	<0.016-1	0.125-0.25	0.25-0.5	—	30, 33, 38
	492	Posaconazole	<0.015-0.5	0.03-0.125	0.125-0.25	—	33, 38, 42
	589	Voriconazole	<0.015-1	0.125	0.125-0.25	—	30, 33, 38, 42, 95
Cryptococcus neoformans	2395[c,d]	Isavuconazole	0.0009-0.5	0.0053-0.06	0.0086-0.125	—	13, 16, 20, 21, 37, 39, 40, 42, 95, 98
	972	Amphotericin B	0.0063-2	0.013-0.25	0.025-0.5	—	20, 37, 39, 40, 42, 95, 98
	886	Flucytosine	<0.063 to >64	4	8	—	39, 40, 42, 98
	1081	Fluconazole	0.125-64	1-4	2-8	—	16, 20, 21, 37, 39, 40, 42, 98
	891	Itraconazole	<0.0004-0.5	0.0033-0.125	0.005-0.25	—	16, 20, 39, 40, 98
	1059	Posaconazole	<0.015-1	0.03-0.12	0.06-0.25	—	16, 21, 37, 39, 40, 42, 98
	1087	Voriconazole	0.0021-1	0.0077-0.063	0.012-0.125	—	16, 20, 21, 37, 39, 40, 42, 95, 98
	46	Anidulafungin	8-32	—	—	—	21
	46	Caspofungin	8-32	—	—	—	21
	46	Micafungin	32	—	—	—	21
Mucorales							
Absidia spp	116	Isavuconazole	0.03 to >8	1-4	8 to >8	4 to >16	11, 18, 20, 46, 47
	21	Amphotericin B	0.025-1	0.5	1	—	20, 47
	22	Fluconazole	8 to >200	16	32	—	20, 47
	22	Itraconazole	0.1-2	1	2	—	20, 47
	36	Voriconazole	4 to >16	8 to >8	>8	>8	18, 20, 47
	85	Posaconazole	0.03-16	0.25-1	1-2	4	11, 46, 47
	59	Ravuconazole	0.03-8	0.5-4	8	—	46, 47
Apophysomyces spp	22	Isavuconazole	0.25-8	2	4	—	48, 49
	22	Amphotericin B	0.06-4	2	4	—	48, 49
	22	Fluconazole	4 to >64	>64	>64	—	48, 49
	22	Itraconazole	0.03-2	1	2	—	48, 49
	22	Voriconazole	2 to >16	>16	>16	—	48, 49
	22	Posaconazole	0.125-1	0.5	1	—	48, 49
	18	Caspofungin (MEC)	0.5 to >16	>16	>16	—	49
	18	Anidulafungin (MEC)	0.008 to >8	>8	>8	—	49
Cunninghamella spp	27	Isavuconazole	0.12 to >100	2-4	>8	16 to >16	11, 18, 20, 46
	2	Fluconazole	>100	—	—	—	20
	2	Itraconazole	0.2-0.78	—	—	—	20

(continued)

Table 1. (continued)

Fungal Pathogen	n	Agent	MIC Range	MIC_{50}	MIC_{90}	MFC_{90}	Reference Numbers
	9	Voriconazole	12.5 to >16	>8	>8	>8	11, 18, 20
	12	Posaconazole	0.12-1	1	1	8	11, 46
	4	Ravuconazole	0.12-1	—	—	—	46
Lichtheimia ramosa	3	Isavuconazole	2-8	—	—	—	48
	3	Amphotericin B	0.125-0.25	—	—	—	48
	3	Fluconazole	64	—	—	—	48
	3	Itraconazole	0.25-2	—	—	—	48
	3	Voriconazole	8-16	—	—	—	48
	3	Posaconazole	0.25-1	—	—	—	48
Mucor spp	146	Isavuconazole	<0.015 to >200	2 to >8	8 to >8	>8	11, 18, 20, 26, 46-48
	32	Amphotericin B	0.03-1	0.5	1	—	20, 47, 48
	33	Fluconazole	8 to >200	16	32	—	20, 47, 48
	33	Itraconazole	0.2 to >200	1	1	—	20, 47, 48
	63	Voriconazole	2 to >200	8 to >8	8 to >8	>8	11, 18, 20, 47, 48
	81	Posaconazole	0.015-32	0.5-1	1-2	>8	11, 46-48
	50	Ravuconazole	0.5 to >128	4	8	—	46, 47
Rhizomucor spp	41	Isavuconazole	0.015 to >8	2 to >8	>8	>8	11, 20, 46
	3	Amphotericin B	0.025-0.05	—	—	—	20
	3	Fluconazole	90 to >200	—	—	—	20
	3	Itraconazole	0.1-0.78	—	—	—	20
	12	Voriconazole	>8	>8	>8	>8	11, 20
	26	Posaconazole	0.03-4	0.25-1	0.5-4	>8	11, 46
	8	Ravuconazole	0.015-1	—	—	—	46
Rhizopus spp	258	Isavuconazole	0.12 to >8	1-8	2 to >8	>8	11, 18, 20, 26, 46-48, 50
	92	Amphotericin B	0.03-1	0.03-0.5	0.2-1	—	20, 47, 48, 50
	94	Itraconazole	0.06-100	0.5-5	2-16	—	20, 47, 48
	94	Fluconazole	4 to >200	8-64	16-64	—	20, 47, 48
	113	Voriconazole	1 to >16	2 to >8	8 to >8	>8	11, 18, 20, 47, 48
	206	Posaconazole	0.03-32	0.25-2	0.5-4	>8	11, 46-48, 50
	64	Ravuconazole	0.06-8	2	4-5	—	46, 47
Syncephalastrum spp	13	Isavuconazole	0.125-8	1	8	1-16	18, 48
	11	Amphotericin B	0.03-0.125	0.06	0.06	—	48
	11	Fluconazole	64	64	64	—	48
	11	Itraconazole	0.125-16	0.25	16	—	48
	13	Voriconazole	4 to >16	8	16	—	18, 48
	11	Posaconazole	0.06-1	0.5	1	—	48
Dimorphic fungi							
Blastomyces dermatitidis	9	Isavuconazole	<0.0004-4	<0.0004	0.0008	—	20, 47
	9	Amphotericin B	0.025-0.5	0.05-0.25	0.2	—	20, 47
	9	Itraconazole	<0.0004-4	<0.0004	0.0008	—	20, 47
	9	Fluconazole	0.06-32	0.11-8	—	—	20, 47
	9	Voriconazole	0.0016-2	0.0063-1	0.0063	—	20, 47
	6	Posaconazole	0.25-1	0.5	—	—	47
	6	Ravuconazole	0.125-4	1	—	—	47
Histoplasma capsulatum	33	Isavuconazole	0.0031-2	<0.0063-0.5	0.0063-2	—	20, 47, 54
	33	Amphotericin B	0.013-0.25	0.05-0.125	0.05-0.25	—	20, 47, 54
	31	Itraconazole	<0.0004-2	<0.0004-0.5	<0.0004-1	—	20, 47
	31	Fluconazole	0.5-32	0.7-4	1-16	—	20, 47

(continued)

Table 1. (continued)

Fungal Pathogen	n	Agent	MIC Range	MIC_{50}	MIC_{90}	MFC_{90}	Reference Numbers
	33	Voriconazole	0.0063-2	0.0063-0.25	0.025-1	—	20, 47, 54
	31	Posaconazole	0.03-2	0.25	2	—	47, 54
	28	Ravuconazole	0.125-2	0.5	1	—	47
	2	Caspofungin	0.25-1	—	—	—	54
Coccidioides posadasii	36	Isavuconazole	0.06-1	0.25	0.5	—	47, 54
	36	Amphotericin B	0.03-0.125	0.06	0.125	—	47, 54
	30	Itraconazole	0.03-0.5	0.125	0.5	—	47
	30	Fluconazole	2-64	8	32	—	47
	36	Voriconazole	0.06	0.125	0.5	—	47, 54
	36	Posaconazole	0.06-1	0.125	0.5	—	47, 54
	30	Ravuconazole	0.125-1	0.25	0.5	—	47
	6	Caspofungin	0.06-0.25	—	—	—	54
Filamentous fungi							
Fusarium spp	136	Isavuconazole	0.25 to >16	4-8	>8	>8	20, 26, 47, 52, 53
	126	Amphotericin B	0.125-8	2	2	—	20, 47, 52, 53
	120	Itraconazole	4 to >16	8	>16	—	20, 47, 53
	120	Fluconazole	32 to >64	>64	>64	—	20, 47, 53
	126	Voriconazole	1 to >16	8	8	—	20, 47, 52, 53
	110	Posaconazole	0.125 to >16	8	>8	—	47, 53
	30	Ravuconazole	2 to >8	8	>8	—	47
Scedosporium spp							
Scedosporium apiospermum	13	Isavuconazole	0.25 to >16	1	8	—	20, 21, 26, 53
	3	Amphotericin B	1.56 to >200	—	—	—	20
	3	Fluconazole	7.8-27	—	—	—	20
	3	Itraconazole	0.39 to >200	—	—	—	20
	3	Posaconazole	0.5-2	—	—	—	21
	6	Voriconazole	0.12-0.77	—	—	—	20, 21
	3	Anidulafungin[e]	1-4	—	—	—	21
	3	Caspofungin[e]	0.25-16	—	—	—	21
	3	Micafungin[e]	0.5-32	—	—	—	21
Scedosporium prolificans	46	Isavuconazole	1 to >200	1 to >16	>8	—	20, 26, 51, 52
	41	Amphotericin B	8 to >200	>16	>16	—	20, 51, 52
	3	Fluconazole	>200	—	—	—	20
	40	Itraconazole	>16 to >200	>16	>16	—	20
	41	Voriconazole	4 to >16	16	>16	—	20, 51, 52
	37	Posaconazole	>16 to >16	>16	>16	—	51
	37	Anidulafungin[e]	0.5 to >8	4	>8	—	51
	37	Caspofungin[e]	2 to >8	>8	>8	—	51
	37	Micafungin[e]	0.125-8	>8	>8	—	51
Scedosporium dehoogi	22	Isavuconazole	2 to >16	8	>16	—	51
	22	Amphotericin B	2 to >16	16	>16	—	51
	22	Itraconazole	0.5 to >16	>16	>16	—	51
	22	Voriconazole	0.5 to >16	1	8	—	51
	22	Posaconazole	0.5 to >16	1	>16	—	51
	22	Anidulafungin[e]	1 to >8	8	>8	—	51
	22	Caspofungin[e]	1 to >8	8	>8	—	51
	22	Micafungin[e]	0.125 to >8	0.5	>8	—	51

(continued)

Table 1. (continued)

Fungal Pathogen	n	Agent	MIC Range	MIC_{50}	MIC_{90}	MFC_{90}	Reference Numbers
Scedosporium aurantiacum	22	Isavuconazole	4-16	8	16	—	51
	22	Amphotericin B	16 to >16	>16	>16	—	51
	22	Itraconazole	1 to >16	>16	>16	—	51
	22	Voriconazole	0.5-1	0.5	1	—	51
	22	Posaconazole	1 to >16	1	>16	—	51
	22	Anidulafungin[e]	1 to >8	8	>8	—	51
	22	Caspofungin[e]	2 to >8	8	>8	—	51
	22	Micafungin[e]	1 to >8	8	>8	—	51

Abbreviations: AFLP, amplified fragment length polymorphism; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MEC, minimum effective concentration for 90% of isolates; MFC_{90}, minimum fungicidal concentration for 90% of isolates; MIC_{90}, minimum inhibitory concentration for 90% of isolates.
[a]Includes *Aspergillus lentulus* (n = 15), *Aspergillus nidulans* (n = 312), *Aspergillus oryzae* (n = 1), *Aspergillus sydowii* (n = 3), and *Aspergillus versicolor* (n = 75).
[b]Including susceptibility based on CLSI microdilution methodology in the table; the study also provided susceptibilities using EUCAST microdilution methodology.
[c]Study included MIC values determined for various amplified fragment length polymorphism (AFLP) genotypes; data shown for all genotypes combined (n = 300).
[d]A total of 870 isolates were AFLP1 genotype, 438 were not genotyped.
[e]For micafungin, the values shown are MEC_{50} and MEC_{90}; for caspofungin and anidulafungin, the MEC_{50} is shown; MEC (μg/mL): minimum effective concentration defined as the lowest concentration of drug that leads to the growth of small, rounded, compact hyphal forms rather than long, unbranched hyphal clusters; see in growth control.

Aspergillus spp[11,12,15,16,18,20,21,26-31]. Isavuconazole demonstrates fungicidal activity against most *Aspergillus* spp, including some isolates resistant to itraconazole, caspofungin, and amphotericin B, with minimum fungicidal concentration within 2 dilutions of the MIC.[11,12] The MIC_{90} values of *Aspergillus flavus, Aspergillus fumigatus*, and *Aspergillus terreus* (isavuconazole MIC_{90} values of 0.39-2 μg/mL, 1-4 μg/mL, and 0.39-4 μg/mL, respectively) appear comparable to those observed for itraconazole and voriconazole, whereas those for posaconazole are ~4-fold more active. However, MIC_{90} values for *Aspergillus niger* to isavuconazole ranged from 2 to 4 μg/mL, which is much higher than MIC_{90} values for posaconazole or voriconazole (0.5 and 1-2 μg/mL, respectively).[11,12,18,20,21,27]

Cryptococcus spp[13,20,30,32-42]. Amphotericin, flucytosine, and azole antifungals are commonly used in the management of cryptococcal infections. Based on in vitro susceptibility studies, isavuconazole appears to be an option for the treatment of cryptococcal infections, given its potent activity against *Cryptococcus neoformans* and the emerging pathogen *Cryptococcus gattii* (including isolates with reduced susceptibility to fluconazole), with MIC_{90} values of 0.008 to 0.25 μg/mL, similar to those observed with posaconazole and voriconazole. Isolates with poor susceptibility to fluconazole (MIC values of 16-64 μg/mL) had MIC values of 0.06 to 0.5 μg/mL for isavuconazole.[13,20,30,32-42]

Noncandidal, Noncryptococcal Yeasts

Trichosporon spp[20,21,43-45]. Isavuconazole demonstrates greater potency than many other antifungal agents against *Trichosporon* spp, with MIC_{90} values of 0.125 to 0.5 μg/mL; however, MIC_{90} values for voriconazole appear 1 to 2 dilutions lower than those of isavuconazole.[20,21,43-45]

Rhodotorula, Geotrichum,[43,45] *Saccharomyces,*[43,45] *and Pichia spp*[23,45]. Isavuconazole may provide a potential treatment option for fungal infections caused by several rare yeasts, including *Rhodotorula, Geotrichum, Saccharomyces*, and *Pichia* spp. Isavuconazole demonstrates in vitro activity similar to that of voriconazole and posaconazole, with MICs of 0.03 to 0.5 μg/mL for *Geotrichum capitatum*.[23,43,45] Amphotericin B, flucytosine, and fluconazole had MIC values that were several dilutions higher than isavuconazole and the other second-generation triazoles. The MIC_{90} values of isavuconazole for *Rhodotorula* spp and *Pichia* spp were the lowest of all agents tested at 0.03 to 2 μg/mL and 0.25 μg/mL, respectively.[23,43,45] Isavuconazole was also active against *Saccharomyces cerevisiae*, with an MIC_{90} of 0.25 to 0.5 μg/mL, which along with voriconazole (MIC_{90} of 0.125-0.25 μg/mL) had the most potent activity compared with fluconazole, posaconazole, amphotericin B, and flucytosine.[43,45]

Mucorales[11,18,20,26,46-50]

Amphotericin B and posaconazole are the only currently available antifungal agents active against the Mucorales, which include *Rhizomucor* spp, *Absidia* spp (now *Lichtheimia* spp), *Rhizopus* spp, *Mucor* spp, and *Cunninghamella* spp. Isavuconazole displays variable in vitro activity against the Mucorales, with wide MIC ranges

of 0.12 to >8 μg/mL for *Rhizopus* spp, 0.038 to >8 μg/mL for *Absidia* spp, <0.015 to >8 for *Mucor* spp, 0.015 to >8 μg/mL for *Rhizomucor* spp, and 0.12 to >8 μg/mL for *Cunninghamella* spp, which are 4- to 16-fold higher than those for posaconazole and amphotericin, but the lower end of the reported MIC ranges for these species are lower as compared with voriconazole.[11,18,20,26,46-50]

Filamentous[20,21,26,47,51-53] and Dimorphic Fungi[20,47,54]

Isavuconazole, similar to other azole antifungals, lacks activity against *Scedosporium prolificans*, with MIC_{90} values >8 μg/mL. Isavuconazole demonstrated activity against *Scedosporium apiospermum* with MIC values similar to those for voriconazole and posaconazole, although some isolates have shown MIC values >8 μg/mL.[20,21,26,47,51,52] Similarly, isavuconazole exhibits poor activity (MIC_{90} values >8 μg/mL) against the hyaline septate mold *Fusarium* spp, similar to those observed for voriconazole, posaconazole, and ravuconazole, but lower MIC values than those observed for fluconazole or itraconazole.[20,21,26,47,51-53]

In several small in vitro studies, isavuconazole demonstrated MIC_{90} values of 0.0063 to 2 μg/mL to *Histoplasma capsulatum*, similar to those of posaconazole, itraconazole, and voriconazole.[20,47,54] Isolates from patients who failed fluconazole therapy for the treatment of *H capsulatum* exhibited reduced susceptibility to fluconazole and voriconazole but no significant changes in isavuconazole susceptibility.[55]

Isavuconazole has also demonstrated potent in vitro activity against the dimorphic fungi *Blastomyces dermatitidis*, and *Coccidioides posadasii*, with MIC_{90} values similar to posaconazole, voriconazole, ravuconazole, and itraconazole but consistently higher than those of fluconazole.[47]

Isavuconazole demonstrates potent activity against all the dematiaceous molds evaluated, including *Bipolaris spicifera* (now *Curvularia spicifera*), *Curvularia lunata, Alternaria alternata*, and *Exophiala* spp, with MIC_{90} values similar to those of itraconazole, voriconazole, and posaconazole and consistently lower than those of fluconazole.[20,47,56]

Resistance to Isavuconazole

Resistance to azole antifungal agents among *Candida* spp can occur by several mechanisms, including reduction of intracellular drug concentrations via the activation of efflux pumps, reduced cell membrane permeability, modifications in target enzymes, and alterations in sterol synthesis.[57,58]

As noted previously, cross-resistance of isavuconazole with other azole antifungals has been observed. For example, isavuconazole displays MIC values >1 μg/mL against many fluconazole-resistant *Candida glabrata*, most likely because of the expression of CDR efflux pumps.[21,59]

Because isavuconazole is a substrate of CDR1 and CDR2, but not of the efflux pumps MDR1 and FLU1, which confer resistance to voriconazole or fluconazole, whether cross-resistance to isavuconazole is observed in fluconazole-resistant clinical isolates will likely depend on the resistance mechanism(s) in the isolate. Mutations in ERG11, resulting in reduced affinity of azoles to 14-α-demethylase, will likely result in elevated MIC values to isavuconazole, whereas expression of MDR1 will likely have a limited effect.[59]

In contrast, azole resistance among *Aspergillus* spp (specifically *Aspergillus fumigatus*) is predominantly mediated by specific point mutations in TR/L98H in the CYP51A gene promoter region, causing amino acid changes and tandem repeats.[60] In a recent study, 2 isolates of *Aspergillus fumigatus* that displayed pan-triazole resistance (with MICs to itraconazole, voriconazole, and posaconazole of >16, 2, and 2 μg/mL, respectively) also displayed elevated MICs (8 μg/mL) to isavuconazole and tandem repeat point mutations in TR/L98H.[61-64] Whether isavuconazole can serve as a substrate for the Cdr1Bp efflux pumps, as is observed in non-Cyp51A-mediated itraconazole resistance in *Aspergillus*, is unknown.[30,65]

Pharmacodynamics[66-71]

Isavuconazole demonstrates concentration-dependent activity against *Candida* spp and in vitro and in vivo post–antifungal effects (PAFE) in the neutropenic murine model of invasive candidiasis. Isavuconazole serum concentrations that were 2-fold the MIC were associated with a PAFE of 2 hours, whereas concentrations of 5- to 100-fold the MIC were associated with a PAFE of 5 hours.[71]

The pharmacokinetic/pharmacodynamic parameter that links drug exposure to drug effect is the ratio of the area under the concentration-time curve (AUC) to the MIC (AUC/MIC) for the treatment of infections caused by *Candida* spp and *Aspergillus* spp.[71] In a murine neutropenic model of disseminated candidiasis with *Candida albicans*, a >90% probability of survival was associated with AUC/MICs of 270 and 670 in temporarily and persistently neutropenic mice, respectively.[71]

Pharmacokinetics

The pharmacokinetics of isavuconazole have been assessed in healthy adult Caucasian and Chinese individuals, in adult patients with neutropenia, in immunocompromised adult patients with esophageal candidiasis, and in adult patients with liver disease, including cirrhosis.[6,71-76] Table 2 lists the pharmacokinetic parameters for the oral (hard gelatin capsules) and IV formulations of isavuconazole and Table 3 the effect of liver impairment on the pharmacokinetic parameters of isavuconazole.

Table 2. Mean Pharmacokinetic Parameters of Isavuconazole.[6,72,79]

Parameter	Results	Comments[a]
C_{max} (mg/L)	2.59/2.47	SD, 200 mg[b] po/IV[c]
	2.56/2.55	SS, 200 mg LD, then 100 mg daily po/IV
t_{max} (h)	1.8/1.0	SD, 200 mg po/IV
	3.5	SS, 200 mg LD, then 100 mg daily po
$t_{1/2}$ (h)	77.1/80.4	SD, 200 mg po/IV
	84.5/117	SS, 200 mg LD, then 100 mg daily po/IV
Cl_s/F (L/h)	2.59	SD, 200 mg po
Cl_s (L/h)	2.80	SD, 200 mg IV
Cl_{ss}/F (L/h)	2.51	SS, 200 mg LD, then 100 mg daily po
Cl_{ss} (L/h)	3.19	SS, 200 mg LD, then 100 mg daily IV
Vd_{ss}/F (L)	308	SS, 200 mg LD, then 100 mg po daily
Vd_{ss} (L)	542	SS, 200 mg LD, then 100 mg IV daily IV
$AUC_{0-\infty}$ (mg h/L)	78.5/73.2	SD, 200 mg po/IV
	255/236	SS, 200 mg LD, then 100 mg po/IV daily
Protein binding (%)	>99%	
Bioavailability	>95	

Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve from time zero to infinity; Cl/F, total body clearance following oral administration; Cl_s, total body clearance following IV administration; C_{max}, maximal concentration; IV, intravenous; $t_{1/2}$, elimination half-life; t_{max}, time to reach maximal concentration; SD, single dose; SS, steady state; Vd_{ss}, distribution volume at steady state.
[a]Healthy adult elderly and nonelderly volunteers.
[b]Equivalent to 361 mg of isavuconazonium.
[c]1 Hour infusion.

Table 3. Effect of Mild and Moderate Hepatic Disease on Oral and IV Isavuconazole Pharmacokinetics.[a,73]

	Oral Administration			IV Administration		
	Hepatic Function			Hepatic Function		
Mean Pharmacokinetic Parameters	Healthy	Mild	Moderate	Healthy	Mild	Moderate
C_{max} (µg/mL)	0.84	0.73	0.47	1.09	0.98	0.84
$AUC_{0-\infty}$ (µg·h/mL)	0.045	0.098	0.062	0.039	0.072	0.101
Cl/F or Cl_s (L/h)	2.38	1.26	1.82	2.73	1.93	1.43
Vd_{ss} (L)	475	485	598	422	492	471
$t_{1/2}$ (h)	148	292	240	123	224	302

Abbreviations: C_{max}, maximal concentration; $AUC_{0-\infty}$, area under the concentration-time curve from time zero to infinity; t_{max}, time to reach maximal concentration; Cl_s, total body clearance following IV administration; Cl/F, total body clearance following oral administration; Vd_{ss}, distribution volume at steady state; $t_{1/2}$, elimination half-life; IV, intravenous.
[a]Sample sizes: 16 healthy patients, 16 patients with mild hepatic impairment, and 16 patients with moderate hepatic impairment; study did not specify number of patients assigned to oral versus IV administration.

Human pharmacokinetics of isavuconazole have been assessed in single and multiple ascending dose studies in healthy adult males and in multiple ascending dose studies in adult male and female patients status postchemotherapy for acute myeloid leukemia.[6,72,75] The pharmacokinetic parameters are characterized by slow elimination (76-104 hours), low plasma clearance (approximately 10% of liver blood flow), extensive tissue distribution, volume of distribution (V_d) of 450 L, and high (>99%) linear protein binding, predominantly to serum albumin.[6] Population pharmacokinetic modeling studies suggest that Asian populations have a total clearance ~40% lower than that observed in predominantly Caucasian populations and that the peripheral volume of distribution increases with body mass index and is greater in patients as compared with healthy individuals.[77]

Following IV administration, isavuconazonium is rapidly ($t_{1/2}$ < 1 minute) and almost completely (>98%) cleaved

by plasma esterases to isavuconazole, the active moiety of the drug, and an inactive cleavage product (BAL8728).[7]

Following oral administration, isavuconazonium undergoes chemical hydrolysis in the gastrointestinal lumen to isavuconazole. Isavuconazole is well absorbed, with a time to maximal absorption (t_{max}) of 1.5 to 3 hours. Its high oral bioavailability allows one-to-one dosage conversions from the IV formulation.[6] Despite a delay in t_{max} of isavuconazole from 1.5 to 4 hours to 4 to 12 hours following administration of a high-fat meal, there is no clinically relevant food effect on the AUC, $t_{1/2}$, or plasma concentration at 24 hours.[78,79]

Metabolism and Elimination

Steady-state plasma concentrations of isavuconazole are well described by a linear 2-compartment model with first-order input and moderate intersubject variability.[6] The steady-state V_d is very large (304-494 L), without large variability between different dosages.[6] However, data describing the penetration of clinically relevant tissue sites in humans, including lung tissue or cerebrospinal fluid (CSF), are not available.

Single-dose ascending pharmacokinetic parameters of oral isavuconazole were assessed following administration of oral doses of 100, 200, and 400 mg and IV dosages of 50, 100, and 200 mg.[6] Following a single 1-hour infusion of isavuconazole, maximum plasma concentrations (C_{max}) were achieved within 0.75 to 1 hour after the start of infusion. The AUC of isavuconazole following oral and IV doses increased slightly more than proportionally to dose increase, indicating a moderate deviation from linear kinetics.

Multiple-dose pharmacokinetic parameters of oral and IV isavuconazole were assessed following administration of oral loading doses (LDs) of 100 or 200 mg, followed by maintenance doses (MDs) of 50 or 100 mg daily for 21 days, and following administration of IV LDs of 100 or 200 mg, followed by MDs of 50 or 100 mg daily for 14 days.[72] In contrast to the single-ascending dose study, the C_{max} and AUC increased proportionally to dose following oral and IV administration, indicating linear kinetics, and plasma drug accumulations after oral and IV administration were 3.8- and 5.2-fold, respectively. Steady-state plasma concentrations were not achieved by day 21 with this multiple-dose regimen; thus, based on the results of population pharmacokinetic modeling, subsequent clinical trials have utilized a multiple-dose loading regimen of 200 mg IV 3 times daily for 2 days, followed by IV or oral doses of 200 mg daily.[72,77,80,81]

Because <1% of an administered isavuconazole dose is eliminated via the kidney, it does not accumulate in patients with renal dysfunction, including those with end-stage renal disease, and the high protein binding (>99%) precludes removal by hemodialysis.[76] Urinary recovery of isavuconazole is negligible (<0.4% of the infused dose), with maximal urinary concentrations of 0.890 μg/mL following infusion of 200-mg dosages; most of the drug is eliminated via feces.[6] Therefore, similar to voriconazole, given minimal urinary concentrations of active drug, isavuconazole would not be an optimal agent for the management of candiduria.

Special Populations

Currently, no data are available assessing drug penetration of CSF or the pharmacokinetics of isavuconazole in pregnant, obese, or pediatric (age <18 years old) patients. Similar to other highly protein bound antifungal agents, including itraconazole, posaconazole, amphotericin B, and the echinocandins (but not fluconazole or voriconazole), the CSF penetration of isavuconazole is likely to be low, especially in the absence of inflammation or other disruptions of the blood brain barrier.[4,82] However, isavuconazole may achieve concentrations in the brain parenchyma sufficient to be clinically effective, given that it demonstrated success in animal models that included infected brain tissue.[82] Nursing mothers should not breast-feed children while taking isavuconazole because animal data showed levels up to 17 times the plasma levels in lactation milk. The clearance of isavuconazole is similar in patients and healthy individuals, and the C_{max} and AUC of isavuconazole appear to be similar in elderly (≥65years) and younger individuals (18-45 years) and in male and female patients.[83]

Following administration of single oral or IV doses equivalent to 100 mg of isavuconazole in patients with alcohol-related mild or moderate liver disease (average Child-Pugh score 5.4 [class A] or 7.4 [class B], respectively), no differences are observed in the conversion of prodrug to the active drug moiety. However, the systemic clearance of isavuconazole is significantly decreased, resulting in a roughly 2-fold increase in $t_{1/2}$ and AUC.[73] Because simulation models using these pharmacokinetic parameters predicted substantial accumulation of isavuconazole in patients with mild and moderate hepatic disease, the investigators suggested that following a normal LD, a 50% reduction of the MD in this population is necessary and that the use of isavuconazole in patients with severe hepatic disease should be avoided.[73,83]

Drug Interactions

Data regarding the drug-interaction profile of isavuconazole are currently limited to a few abstracts and FDA briefing documents. Similar to other azole antifungals, in vitro, isavuconazole is a substrate of cytochrome P450 (CYP) 3A4/5; an inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6, P-glycoprotein (P-gp), breast cancer

resistance protein (BRCP), and human organic cation transporter (OCT2)–mediated drug transporters; and a weak inducer of CYP3A4/5, CYP2B6, CYP2C8, and CYP2C9.[83] However, based on in vivo drug interaction studies, isavuconazole appears to be a mild to moderate inhibitor of CYP3A4, a mild inducer of CYP2B6, and a mild inhibitor of P-gp, BRCP, OCT1/OCT2, and human multidrug and toxin extrusion (MATE1); it also has mild indirect inhibitory effects on substrates of uridine diphosphate-glucuronosyltransferase such as mycophenolic acid. It does not inhibit or induce CYP1A2, CYP2C9, or CYP2C19; inhibit CYP2A6 or CYP2D6; or inhibit sensitive substrates of BRCP, human organic anion transporters (OAT1/OAT2), organic anion-transporting polypeptide (OATP)1B1/OATP1B3, or MATE2-K. The potential effects of herbal products, smoking, and alcohol use have not been evaluated.[76,83] Overall, isavuconazole appears to have a drug interaction profile similar to that of fluconazole or itraconazole, with fewer drug interactions than voriconazole.[84]

Coadministration of isavuconazole with ketoconazole, a potent inhibitor of CYP3A4, increases the exposure of isavuconazole by 5.2-fold.[20] Conversely, administration of isavuconazole with rifampicin, a potent inducer of CYP3A4, resulted in a 4-fold decrease in the C_{max} and a 40-fold decrease in the $AUC_{0-\infty}$ of isavuconazole.[83]

Coadministration with single doses of the CYP3A4 substrates tacrolimus and sirolimus increased the AUC of tacrolimus and sirolimus by 1.25- and 84-fold, respectively. In contrast, voriconazole typically increases the AUC of tacrolimus by 3- to 10-fold and sirolimus by 7- to 11-fold.[76,84,85] Isavuconazole, administered orally at lower doses than those proposed clinically, had no apparent effect on the pharmacokinetics of cyclosporine. Therapeutic drug monitoring (TDM) of cyclosporine, sirolimus, and tacrolimus levels is recommended during coadministration with isavuconazole.[83]

In the proposed labeling for isavuconazole, concomitant administration of isavuconazole with strong inducers (eg, rifampin) or strong inhibitors of CYP3A (eg, lopinavir/ritonavir) is contraindicated. Coadministration of isavuconazole with drugs that are P-gp substrates and have a narrow therapeutic window (eg, digoxin, colchicine, dabigatran) may require dose adjustment; monitoring of digoxin levels is recommended, as is monitoring for mycophenolic acid–related toxicity during coadministration with mycophenolate mofetil.[83]

When administered concurrently with isavuconazole, no dose adjustments are recommended for warfarin (or other CYP2C9 substrates), methadone, the OCT1/OCT2 substrate metformin, CYP1A2 or CYP2C8 substrates such as caffeine or repaglinide, omeprazole (or other CYP2C19 substrates), the BCRP substrate methotrexate, methadone (a CYP2B6/3A4 substrate), dextromethorphan (or other CYP2D6 substrates), midazolam (although a 2.05-fold increase in AUC occurs), prednisone, atorvastatin (a substrate of OATP1B1/1B3 and CYP3A4), or oral contraceptives comprising ethinyl estradiol and norethindrone.

Of note, although coadministration with voriconazole results in a 1.3-fold increased systemic exposure of the CYP2B6 substrate bupropion, systemic exposure of bupropion is reduced by 42% during coadministration with isavuconazole. Caution is advised if isavuconazole is coadministered with CYP2B6 substrates, especially with narrow therapeutic index drugs such as efavirenz and cyclophosphamide.[83]

Coadministration of esomeprazole (40 mg daily for 10 days) with isavuconazole (also dosed to steady state) suggests that administration of medications that alter the gastric pH (eg, proton-pump inhibitors, H2-receptor antagonists, and antacids) do not significantly affect the pharmacokinetics of isavuconazole.[83]

Animal Models of Infection

An in vivo efficacy analysis evaluating the use of isavuconazole, voriconazole, and fluconazole in neutropenic murine models found isavuconazole to be as effective as voriconazole and more effective than fluconazole at reducing the brain burden of *Candida tropicalis* and *Candida krusei*.[86] All 3 agents were equally effective in reducing kidney burden of *Candida tropicalis* and *Candida krusei*. Similarly, isavuconazole demonstrated in vivo efficacy in 4 murine models of mucormycosis and in murine and rabbit models of aspergillosis.[66,68,87,88]

Clinical Efficacy Trials and Case Reports in Humans

Phase III clinical trials evaluating the use of this agent for the treatment of systemic candidiasis, aspergillosis and renal impairment, and invasive fungal disease caused by rare molds, yeasts, or dimorphic fungi are currently under way, recently completed, or available only in abstract form or in FDA briefing documents. Several case reports have documented the successful use of isavuconazole for the treatment of disseminated mucormycosis and the rare fungal pathogen *Pseudozyma aphidis*.[89-91]

Oropharyngeal and Esophageal Candidiasis

A phase II double-blind, multicenter, randomized clinical trial evaluated 3 different dosing strategies (50 mg daily, 100 mg daily, and 400 mg weekly) of isavuconazole in comparison to fluconazole for treatment in 160 immunocompromised patients with *Candida* esophagitis. The doses evaluated were well tolerated and associated with sustained clinical cure rates of 90% to 95% at 14 days and 90% at 28 days after the end of therapy, similar to those for fluconazole.[92]

Candidemia

The ACTIVE study is a phase III, double-blind, randomized, active control, parallel assignment efficacy trial evaluating the safety and efficacy of IV and oral isavuconazole, compared with caspofungin followed by voriconazole, for the treatment of candidemia and other invasive *Candida* infections. This trial was registered with clinicaltrials.gov in 2006 and remains ongoing but is no longer recruiting participants. The primary outcome of this trial is overall response, defined as the resolution of signs and symptoms of infection and mycological eradication. Secondary outcomes include mycological response, time to first confirmed negative culture, and all-cause mortality.[93]

Aspergillosis and Infections Caused by Other Filamentous Fungi

The SECURE study is a phase III, double-blind, randomized, active control, parallel assignment multinational trial in 527 individuals with proven or probable invasive fungal disease caused by *Aspergillus* spp or other filamentous fungi evaluating the safety and efficacy of isavuconazole 200 mg IV 3 times daily for 2 days, followed by 200 mg daily (IV or oral) versus voriconazole 6 mg/kg IV twice daily on day 1, 4 mg/kg IV twice daily on day 2, then either 4 mg/kg IV twice daily or 200 mg oral twice daily for up to 84 days.[80,81] The primary outcome measure of the trial was day 42 all-cause mortality; secondary end points included overall treatment response (a composite of clinical, mycological, and radiological responses), survival time, mycological response, and overall outcome at different time points and in predefined subpopulations.[94] At this time, the results of this study, which are available only in abstract form and in FDA briefing documents, indicate that isavuconazole demonstrated noninferior efficacy compared with voriconazole for the primary end point. Of note, results as analyzed by the study sponsor differ slightly from that of the FDA analysis because of differences in the number of modified intention-to-treat patients defined as having *probable* aspergillosis. In the modified intention-to-treat population, all-cause mortality through days 42 and 84 were comparable for both agents: 28/143 (19.6%) and 43/143 (30.1%) for isavuconazole versus 30/129 (23.3%) and 48/129 (37.2%) for voriconazole, respectively, and overall response at the end of therapy was 50/143 (35.0%) for isavuconazole versus 47/129 (36.4%) for voriconazole. Isavuconazole was well tolerated, with fewer drug-related adverse effects than voriconazole.

In a subanalysis of patients enrolled in the SECURE study, outcomes of patients with active malignancies (newly diagnosed or relapse; UncCA) at baseline were compared with that for patients without baseline uncontrolled malignancies (including patients without malignancies). Outcomes for both voriconazole and isavuconazole were comparable, and patients with UncCA had a higher mortality rate than patients without UncCA.[80,81]

VITAL is a phase 3, open-label, multicenter trial conducted to evaluate efficacy and safety of isavuconazole in patients with emerging IFIs. Patients received isavuconazole 200 mg 3 times daily for 2 days followed by 200 mg daily (IV or oral). Safety, mortality, the incidence of proven and probable IFIs (based on EORTC/MSG criteria), and the overall response at end-of-treatment were determined by an independent data review committee.[95] Complete results of this study are not yet available.

In a subanalysis of patients in the SECURE and VITAL studies, isavuconazole appeared to be promising for the treatment of invasive mold infections caused by *Fusarium* and *Scedosporium* spp, which are typically associated with high morbidity and mortality, particularly in immunocompromised patients, and for which current treatment options are limited. In this analysis, 3/9 (33.3%) and 1/3 (33.3%) patients infected by *Fusarium* and *Scedosporium* spp, respectively, experienced overall complete response to isavuconazole, and 6/9 (66.6%) and 2/3 (66.6%), respectively, experienced failure (defined as partial response, stable disease, or progression of disease).[52]

The role of isavuconazole in the treatment of patients with proven or probable aspergillosis caused by *Aspergillus fumigatus* (who also have renal impairment) or with invasive fungal diseases caused by rare molds, yeasts, and dimorphic fungi is being evaluated in an ongoing phase III trial.[83,96] The study is designed as a nonrandomized, open-label, uncontrolled, single-group assignment safety/efficacy trial; isavuconazole is administered at the same dosages as in the SECURE and VITAL trials. The primary outcome is day 42 mortality, and secondary outcomes include clinical, mycological, and radiological response at day 42, day 84, at the end of therapy, and overall. Preliminary data presented to the FDA reported similar mortality rates for invasive mold infections in a matched case control analysis of patients treated with isavuconazole and patients enrolled in the Fungiscope registry who received amphotericin-based formulations.[76]

Safety

Overall, isavuconazole is well tolerated in humans and appears to be favorable when compared with the safety profile of voriconazole, with fewer skin, eye, and hepatobiliary adverse events (AEs). Animal data have shown no evidence of mutagenesis, allergic reactions, or phototoxicity, and dose escalation studies in healthy individuals and neutropenic patients have reported no major adverse effects. AEs appear to be mild and limited; the most commonly reported AEs following oral or IV administration of isavuconazole include gastrointestinal disorders (diarrhea, nausea, and

vomiting), rash, elevated liver chemistry tests, cough, conjunctivitis, and dizziness.[6,72,76]

Azole antifungals can cause QT prolongation and inhibit the metabolism of many QT prolonging drugs; however, to date, isavuconazole has not demonstrated QTc interval prolongation.[6,72] Isavuconazole was noted to cause dose- and concentration-related QTc interval shortening in 2 studies; in phase III clinical trial data, this toxicity occurred with an incidence of 0.4%. The clinical significance of isavuconazole-induced QTc shortening, which is hypothesized to be a result of a slight block of the calcium channel, is unknown at this time.[83] However, the proposed package insert suggests that isavuconazole be contraindicated in patients with familial short-QT syndrome and that caution be exercised during coadministration of isavuconazole with drugs known to decrease the QT interval.[76]

Dosage and Administration

Population pharmacokinetic modeling studies suggest that the proposed adult clinical dose of isavuconazole 200 mg IV or oral 3 times daily on days 1 and 2, followed by 200 mg IV or oral daily, would adequately treat isolates with MICs of 0.06 to 4 mg/L (CLSI methodology) or 2 to 4 mg/L (EUCAST methodology), depending on the pharmacodynamic target; these would predict successful outcomes for *Aspergillus* species, with MIC values as high as 2 or 4 μg/mL (CLSI and EUCAST methodologies, respectively), regardless of CYP51A mutations.[77] The IV formulation should be administered through an in-line filter (0.2-1.2 μm pore size) over 1 hour to reduce the risk for infusion-related reactions.[76]

Isavuconazole should not be utilized in patients <18 years old, nursing mothers, or patients with severe hepatic impairment. No dosage adjustments are necessary in patients with mild or moderate hepatic impairment, in elderly or renally impaired patients, or based on age, gender, weight, or race (Asian/non-Asian).[83]

Therapeutic Drug Monitoring

TDM is generally recommended for agents with a narrow therapeutic index, an established relationship between plasma drug concentrations and efficacy or toxicity, or variable or unpredictable pharmacokinetics.[97] Isavuconazole serum levels vary only moderately (CV < 20%); however, because the correlation between plasma levels and adverse effects and efficacy have not been fully assessed at this time, the utility of TDM remains to be determined.

Availability

In February 2010, Basilea entered into a license, codevelopment and copromotion agreement with Astellas Pharma Inc for the phase III clinical development of isavuconazole.[83] In May 2013, October 2013, and November 2014, US orphan drug designation was granted to isavuconazole for the treatment of invasive aspergillosis, zygomycosis (now referred to as mucormycosis), and invasive candidiasis, respectively.[83] Isavuconazole was approved by the FDA in March 2015, and will be marketed in the United States with the brand name Cresemba by Basilea's partner, Astellas. It is approved for patients 18 years of age and older for the treatment of invasive aspergillosis and invasive mucormycosis (also known as zygomycosis). It is currently under regulatory review by the European Medicines Agency for the treatment of invasive aspergillosis and mucormycosis in adults.[85] Isavuconazonium will be available as a sterile, lyophilized powder for IV infusion, containing 372.6 mg isavuconazonium, corresponding to 200 mg isavuconazole. The oral formulation is a hard capsule containing 186.3 mg isavuconazonium, corresponding to 100 mg isavuconazole.

Summary

Isavuconazole is a broad-spectrum triazole antifungal that offers several advantages over other azole antifungals, including high prodrug water solubility (obviating the need for cyclodextrin); high oral bioavailability (allowing one-to-one dosage conversions from the IV formulation); predictable, linear pharmacokinetics with no relevant food effect; and potentially fewer drug interactions than itraconazole or voriconazole. Isavuconazole displays an expanded spectrum of activity against many clinically important fungal pathogens, including *Candida* spp and many fluconazole-resistant strains, *Aspergillus* spp, and *Candida krusei, Cryptococcus* spp, and some species of *Scedosporium*, with variable activity against the Mucorales. Isavuconazole provides a clinically useful alternative to voriconazole for the treatment of invasive aspergillosis. It may also prove useful for the treatment of candidemia and invasive mold infections; however, these indications await the results of clinical trials.

Declaration of Conflicting Interests

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