

# Isavuconazole for the treatment of invasive aspergillosis and mucormycosis: current evidence, safety, efficacy, and clinical recommendations

Suganthini Krishnan  
Natesan<sup>1,2</sup>  
Pranatharthi H  
Chandrasekar<sup>1</sup>

<sup>1</sup>Division of Infectious Diseases, Department of Internal Medicine, Wayne State University, <sup>2</sup>John D Dingell VA Medical Center, Detroit, MI, USA

**Abstract:** The majority of invasive mold infections diagnosed in immunocompromised cancer patients include invasive aspergillosis (IA) and mucormycosis. Despite timely and effective therapy, mortality remains considerable. Antifungal agents currently available for the management of these serious infections include triazoles, polyenes, and echinocandins. Until recently, posaconazole has been the only triazole with a broad spectrum of anti-mold activity against both *Aspergillus* sp. and mucorales. Other clinically available triazoles voriconazole and itraconazole, with poor activity against mucorales, have significant drug interactions in addition to a side effect profile inherent for all triazoles. Polyenes including lipid formulations pose a problem with infusion-related side effects, electrolyte imbalance, and nephrotoxicity. Echinocandins are ineffective against mucorales and are approved as salvage therapy for refractory IA. Given that all available antifungal agents have limitations, there has been an unmet need for a broad-spectrum anti-mold agent with a favorable profile. Following phase III clinical trials that started in 2006, isavuconazole (ISZ) seems to fit this profile. It is the first novel triazole agent recently approved by the United States Food and Drug Administration (FDA) for the treatment of both IA and mucormycosis. This review provides a brief overview of the salient features of ISZ, its favorable profile with regard to spectrum of antifungal activity, pharmacokinetic and pharmacodynamic parameters, drug interactions and tolerability, clinical efficacy, and side effects.

**Keywords:** isavuconazole, aspergillosis, mucormycosis, efficacy, antifungal therapy, novel azole, tolerability, drug interactions

## Introduction

Invasive fungal infections (IFIs) continue to pose a therapeutic challenge in immunocompromised patients.<sup>1,2</sup> Despite timely and effective antifungal therapy, the mortality from IFI remains significant.<sup>3–10</sup> This is in part attributed to the potent immunosuppressive chemotherapeutic regimens and aggressive transplant protocols. Invasive aspergillosis (IA) and mucormycosis are the most frequently encountered mold infections in immunocompromised cancer patients and hematopoietic stem-cell transplant recipients.<sup>11,12</sup> Prophylactic protocols implemented in various institutions have altered the spectrum of invasive mold infections.<sup>13</sup> Antifungal combination therapies have been tried in refractory mold infections.<sup>14</sup> Also, there are reports of emerging azole resistance from several institutions around the world.<sup>15</sup> Antifungal classes currently available for the treatment of IFI include polyenes, azoles, and echinocandins.<sup>16,17</sup> Each class of antifungal agents has its limitations including side effects, limited spectrum of activity, drug interactions, and lack of oral formulations. One of the most recent additions to the antifungal armamentarium is isavuconazole (ISZ), a novel triazole agent that has shown good clinical efficacy

Correspondence: Suganthini Krishnan Natesan  
Division of Infectious Diseases, John D Dingell VA Medical Center, 4646 John R, Room C3917, Detroit, MI 48201, USA  
Tel +1 313 576 3057  
Fax +1 313 576 1242  
Email skrishn@med.wayne.edu

against IA and mucormycosis.<sup>18–20</sup> This article provides an overview of this new agent, data on its efficacy in vitro and in vivo, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and potential advantages over other agents.

ISZ is the active moiety (BAL4815) obtained when the water-soluble prodrug called isavuconazium (BAL8557), with a very short half-life of <1 min, is cleaved by plasma esterases (Figure 1).<sup>21,22</sup>

## Mechanism of action

ISZ, like other triazoles, acts by inhibition of the cytochrome P450-dependent 14- $\alpha$ -lanosterol demethylase of the fungal cell membrane. This leads to accumulation of toxic cell membrane sterols and inhibition of ergosterol production, an integral component of the fungal cell membrane. Inhibition of fungal growth and replication follows, leading to cell death.<sup>23</sup> ISZ has been introduced as a broad-spectrum triazole with several advantages when compared with the currently available antifungal agents. As outlined below, several in vitro, in vivo, and clinical trials have validated its potency, efficacy, and safety.<sup>24–32</sup>

## In vitro activity

The in vitro activity of ISZ against several *Aspergillus* sp. and the *Mucorales* has been tested extensively using the standardized CLSI methodology to evaluate MIC<sub>50</sub> (minimum inhibitory concentration to inhibit 50% growth), MIC<sub>90</sub> (minimum inhibitory concentration to inhibit 90% of growth), and MFC (minimum fungicidal concentration).<sup>33,34</sup> Antifungal activity has been demonstrated against various *Aspergillus* sp. including *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus terreus*. The MIC<sub>50</sub> range was 0.25–1  $\mu$ g/mL; MIC<sub>90</sub> range was 0.39–4  $\mu$ g/mL. The exception was *Aspergillus niger* that had a higher MIC<sub>50</sub>/MIC<sub>90</sub> range of 2–4  $\mu$ g/mL, higher than that reported for voriconazole (VCZ) and posaconazole (POS) (1–2 and 0.5  $\mu$ g/mL, respectively) (Table 1).<sup>35,36</sup>

Given the recent reports of emerging azole-resistant isolates of *Aspergillus* species, some azole-resistant isolates were

tested in vitro. Isolates that exhibited L98, G138, G434C, and Y431C mutations showed pan-azole resistance, including ISZ resistance. However, isolates with the G54 mutation had lower MICs to ISZ compared with POS. ISZ also showed promising antifungal activity against *Aspergillus* species that were resistant to caspofungin (CFG) or amphotericin B (AMB). Demonstration of this variable susceptibility pattern among azole-susceptible and azole-resistant isolates raises the question about the need for susceptibility testing.<sup>37,38</sup> Epidemiological cutoff values have been established for ISZ against *Aspergillus* species (reported as 1  $\mu$ g/mL for *A. fumigatus*, *A. flavus*, and *A. terreus*, 0.25  $\mu$ g for *Aspergillus nidulans*, and 4  $\mu$ g/mL for *A. niger*). These values help in detecting non-wild-type isolates with reduced susceptibility to ISZ during screening.<sup>38–41</sup>

The major pathogens in mucorales family include *Rhizopus*, *Rhizomucor*, *Mucor*, *Lichtheimia* (formerly *Absidia*), and *Cunninghamella*. Antifungal agents active against this group of organisms at present are polyenes and selected newer azoles (POS and ISZ).

The susceptibility pattern of these molds (MIC<sub>50</sub>/MIC<sub>90</sub>) to ISZ is highly variable, dependent on the species tested, and exhibits a wide range (0.015–>8  $\mu$ g/mL). On the basis of this observation, susceptibility testing becomes necessary in some clinical situations (Table 2).<sup>42–46</sup>

## Combination studies

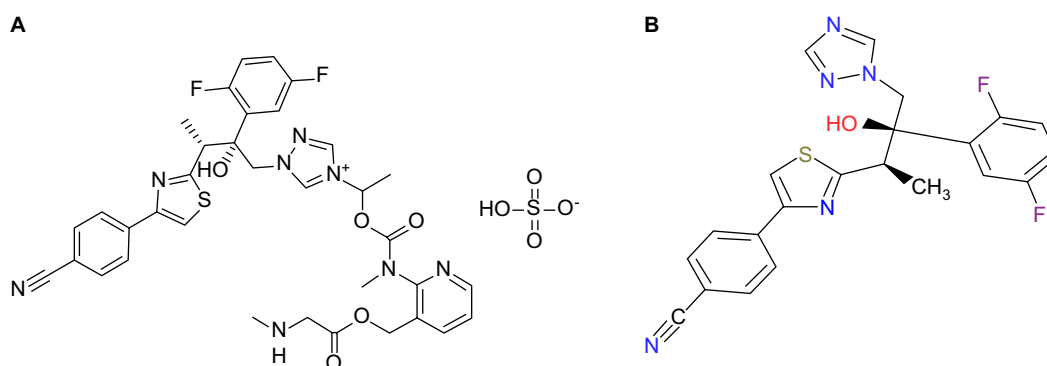
The combination of ISZ and micafungin (MFG) resulted in a synergistic interaction in *A. fumigatus*, *A. flavus*, *A. terreus*,

**Table 1** In vitro susceptibilities of *Aspergillus* sp. to ISZ

Organism	MIC <sub>50</sub> ( $\mu$ g/mL)	MIC <sub>90</sub> ( $\mu$ g/mL)
<i>Aspergillus fumigatus</i>	0.25–1	0.5–2
<i>Aspergillus flavus</i>	0.5–2	1–16
<i>Aspergillus terreus</i>	0.5–1	0.5–4
<i>Aspergillus niger</i>	0.5–2	2–4

**Notes:** Data compiled from 35–41,43–45.

**Abbreviations:** ISZ, isavuconazole; MIC<sub>50</sub>, minimum inhibitory concentration to inhibit 50% growth; MIC<sub>90</sub>, minimum inhibitory concentration to inhibit 90% of growth.



**Figure 1** Structure and chemistry of Isavuconazium (A) and Isavuconazole (B).

**Table 2** In vitro susceptibilities of mucorales to ISZ

Organism	MIC <sub>50</sub> (µg/mL)	MIC <sub>90</sub> (µg/mL)
<i>Lichtheimia</i> (Absidia)	0.5–4	4–8
<i>Rhizopus</i>	0.25–4	2–4
<i>Rhizomucor</i>	1–2	8–16
<i>Mucor</i>	2–4	8–16
<i>Cunninghamella</i>	1–2	8–16

**Notes:** Data compiled from.<sup>42,44–46</sup>

**Abbreviations:** ISZ, isavuconazole; MIC<sub>50</sub>, minimum inhibitory concentration to inhibit 50% growth; MIC<sub>90</sub>, minimum inhibitory concentration to inhibit 90% of growth.

and *Cunninghamella bertholletiae*, and indifferent interactions against *Mucor circinelloides*, *Rhizopus microsporus*, and *Rhizopus oryzae*. The ISZ-AMB combination resulted in antagonism in *A. fumigatus*, *A. flavus*, *Fusarium solani*, and *R. microsporus* but indifferent interaction against *Lichtheimia corymbifera*, *M. circinelloides*, and *R. oryzae*. The type of ISZ-AMB interaction against *A. terreus* and *C. bertholletiae* appeared to be concentration dependent. Interestingly, the ISZ-MFG combination was found to be concentration and organism dependent (i.e., for *C. bertholletiae* and *L. corymbifera* at ISZ concentrations near the MIC, the interactions were synergistic, and at low ISZ concentrations, the interactions were antagonistic).<sup>47,48</sup> Given the inherent limitations with in vitro combination studies, in vivo studies are needed before any recommendations are made for combination therapy.

### Efficacy in vivo (animal models)

Animal models using ISZ have focused on dose determination, data on PK and PD parameters, and efficacy studies in neutropenic murine models of mucormycosis and IA. Results from these studies have been favorable.<sup>49</sup> Tissue distribution in male rats was evaluated using radiolabeling technology, after a single intravenous infusion of 3 mg/kg of ISZ. Quantitative whole-body autoradiography was used for the specific detection of <sup>14</sup>C and <sup>3</sup>H radioactivity, and total radioactivity in blood and plasma was analyzed by liquid scintillation counting. The <sup>14</sup>C label was in the active drug moiety and the <sup>3</sup>H label was in the pro-moiety. Maximum <sup>14</sup>C radioactivity was detected in all tissues at 0.5 h postadministration. All tissues had good levels, except eye lens, with highest levels found in the adrenal cortex (6.92 µg-equiv/g) and liver (6.14 µg-equiv/g) with tissue/plasma concentration reported at ratios of 15.2 and 13.5, respectively. High levels of <sup>14</sup>C radioactivity (tissue/plasma ratios >5) were found in other tissues. Lung-to-brain plasma ratios at 0.5 h post-dose were 2.28 and 1.86, respectively. At 144 h, only adrenal medulla and liver contained quantifiable levels (>0.02 µg-equiv/g) of <sup>14</sup>C. <sup>3</sup>H radioactivity was widely distributed as well at 0.5 h and tissue levels declined rapidly, with all tissues containing

low to nondetectable <sup>3</sup>H radioactivity by 8 h, except intestinal contents and kidney. Excretion was almost complete within 144 h, with ~80% <sup>14</sup>C radioactivity recovered in bile/feces and 20% in urine. Results from these studies show that ISZ is widely distributed in tissue, including the eye and brain. Data appear promising for the treatment of ophthalmic and central nervous system invasive mold infections.<sup>50</sup>

Another in vivo study demonstrated the PD profile of ISZ using a neutropenic murine model of invasive pulmonary aspergillosis (IPA). Ten isolates of *A. fumigatus* isolates (4 *Cyp51* wild type and 6 *Cyp51* mutants; MIC of 0.125–8 mg/L) were used for infection. Mice were subsequently treated with 40–640 mg/kg/12 h oral prodrug (BAL8557) for 7 days and efficacy was determined by quantitative aspergillus PCR of lung homogenates. The infection model was uniformly lethal in untreated control mice. PD endpoints included static dose area under the curve (AUC)/MIC and 1 log<sub>10</sub> kill AUC/MIC. The results were similar with both *Cyp* wild type and mutant groups. A stasis endpoint was achieved for all isolates with an MIC of ≤1 mg/L and 1 log<sub>10</sub> kill in all isolates with an MIC of ≤0.5 mg/L. The static dose range was 65–617 mg/kg/12 h. The corresponding median free drug AUC/MIC was near 5. The 1 log<sub>10</sub> kill dose range was 147–455 mg/kg/12 h and corresponding median free drug AUC/MIC of 11.1. The results were similar to those reported for other triazoles.<sup>51</sup>

Given reports of azole resistance, the in vivo efficacy of 0.25, 1, 4, 16, 64, 128, 256, and 512 mg/kg body weight/day of the prodrug isavuconazonium sulfate (BAL8557) (ISZ-equivalent doses of 0.12, 0.48, 1.92, 7.68, 30.7, 61.4, 122.9, and 245.8 mg/kg/day, respectively) administered by oral gavage was studied in an immunocompetent murine model of IA against four clinical *A. fumigatus* isolates: a wild-type isolate and three azole-resistant isolates harboring substitutions in the *cyp51A* gene: G54W M220I, and TR<sub>34</sub>/L98H with EUCAST (European Committee on Antimicrobial Susceptibility Testing) reported ISZ MICs of 0.5, 4, and 8 mg/L, respectively. The maximum effect (100% survival) was reached at a prodrug isavuconazonium sulfate dose of 64 mg/kg for the wild-type isolate, 128 mg/kg for the G54W mutant, and 256 mg/kg two times per day (q12) for the M220I mutant. A maximum response was not achieved with the TR<sub>34</sub>/L98H isolates even with the highest dose of prodrug isavuconazonium sulfate (256 mg/kg q12). For a survival rate of 50%, the effective AUC<sub>0–24</sub>/MIC<sub>EUCAST</sub> ratio for ISZ total drug was 24.73 (95% confidence interval, 22.50–27.18). This study demonstrated that the efficacy of ISZ was dependent on both plasma concentration as well as the ISZ MIC of the fungal isolates. The quantitative relationship between exposure and effect (AUC<sub>0–24</sub>/MIC) can therefore be utilized to

maximize the efficacy of ISZ against azole-resistant strains of *Aspergillus* species.<sup>49</sup> Therapeutic drug monitoring for ISZ is not indicated at present. Further data are needed before making any final recommendation. Importantly, the above studies showed that ISZ is fungicidal as the observed MFC values were equivalent to the MIC values.

Next, the efficacy of the prodrug isavuconazonium sulfate was evaluated in a neutropenic mouse model of intratracheal infection caused by *Rhizopus delemar* 99–880 (a clinical isolate grown from brain tissue) with ISZ MIC<sub>100</sub> and MFC values of 0.25 µg/mL. Male ICR mice were rendered neutropenic by cyclophosphamide (200 mg/kg of body weight intraperitoneally [i.p.]) and cortisone acetate (500 mg/kg subcutaneously) on days –2 and 3 relative to infection. Mice were then infected intratracheally on day zero, with  $2.5 \times 10^5$  spores of *R. delemar* 99–880. The prodrug isavuconazonium sulfate at three different doses (80, 110, and 215 mg/kg) was given orally three times daily starting 8 h postinfection and continued through day 4. The higher dose of 215 mg/kg q8h of isavuconazonium sulfate demonstrated enhanced efficacy over that of placebo treatment of mice (70% survival in the isavuconazonium sulfate-treated mice versus 10% survival for placebo mice), after 21 days. As a high dose of ISZ (215 mg/kg q8h) demonstrated efficacy against *R. delemar* infection, the efficacy of this dose was compared with that of the standard therapy for mucormycosis (high dose of liposomal amphotericin B; LAmB). Eight hours postinfection, treatment with isavuconazonium sulfate (215 mg/kg q8h, given orally) or LAmB (15 mg/kg, given once daily through tail vein injection) started and continued through day 4. The primary endpoint for efficacy was the time to clinical disease based on clinical parameters in infected mice. ISZ showed similar efficacy as LAmB. The 21-day survival rates for ISZ, LAmB, and placebo-treated mice were 65%, 40%, and 15%, respectively. Treatment of the mice with the prodrug resulted in an approximately 1 log decrease in lung and brain fungal burdens compared with those of placebo-treated controls. This reduction in tissue fungal burden was comparable to that seen in the LAmB-treated group.<sup>52</sup>

## PK and PD

An important strategy utilized to optimize treatment outcomes of an antifungal agent is evaluation of its PD. The PD of ISZ was studied in a neutropenic murine model of IPA, using azole-susceptible and azole-resistant isolates of *A. fumigatus*. The PD target endpoints examined were static dose AUC/MIC ratio and the 1 log 10 killing AUC/MIC ratio. The static dose range was 65–617 mg/kg/12 h and a median free-drug AUC/MIC ratio near 5. The 1 log 10 killing dose range was 147–455 mg/kg/q12h and a median free-drug AUC/MIC of

11.1. Data were similar to that reported for other triazoles. ISZ has also demonstrated post-antifungal effect in vitro and in a neutropenic murine model of invasive candidiasis, with duration ranging from 2 to 5 h based on serum concentration achieved above MIC. A higher AUC/MIC ratio was associated with an increased survival rate in this model.<sup>53–55</sup> Human PK parameters have been assessed in healthy adult males using single and multiple ascending dose studies. These studies showed slow elimination (76–104 h), high protein binding to albumin (>99%), extensive volume of distribution of 450 L, time to maximum absorption of 1.5–3 h, and a high oral availability with no clinically relevant food effect on AUC or plasma concentration at 24 h. PK studies have also demonstrated ~40% lower clearance in Asian population compared to Caucasians, and a higher volume of distribution with higher body mass index in patients compared to healthy adults. The drug exhibits linear PK and is not removed by hemodialysis as 99% of drug is bound to protein and <1% is excreted in urine. Population PK studies were also performed in adults with mild and moderate hepatic impairment to evaluate clearance of ISZ in this setting. Less than twofold increase in ISZ trough levels was seen in subjects with mild to moderate hepatic impairment compared to healthy controls. Results were similar for both oral and intravenous routes tested.<sup>56,57</sup> Warn et al evaluated the plasma and renal concentrations of ISZ in a murine model of disseminated candidiasis and concluded that renal concentrations were higher than plasma levels, even after clearance of drug from plasma, the post-antifungal effect lasted ~5 to 8 h, and the AUC/MIC ratio associated with a 90% probability of survival in temporarily and persistently neutropenic mice were 270 and 670, respectively.<sup>58</sup> An open-label study evaluated ISZ as a prophylactic agent in neutropenic patients with acute myeloid leukemia with good results.<sup>59</sup> Multiple-dose PK tested in healthy subjects demonstrated that the maximum ISZ concentration in the plasma ( $C_{max}$ ) and AUC increased proportionally to the administered dose. At steady state, the volume of distribution was large and amounted 308–542 L. Measured  $C_{max}$  values were 2.56 and 2.55 µg/mL after oral and intravenous administration, respectively, which confirmed the bioequivalence of both oral and intravenous formulations of ISZ.<sup>60–65</sup> Evaluation of PK parameters from phase I and phase III studies from SECURE trial concluded that adequate ISZ levels were achieved in serum and the long elimination half-life of ISZ (terminal phase half-life of 25–31 h) supported once- or twice-daily dosing for clinical trials.<sup>66</sup> Dose adjustments are, therefore, not required when switching between oral and intravenous formulations, and absorption is not dependent on food or drugs that increase the gastric pH.<sup>67,68</sup> Concentration-dependent efficacy was tested in a

rabbit model of IPA. There was a dose-dependent reduction in fungal burden as indicated by colony counts in the lung and a decline in beta-D glucan and galactomannan levels in the bronchoalveolar fluid.<sup>69</sup> Another study that analyzed results from phase III SECURE trial found that both length of stay in the hospital and utilization of resources were better with ISZ (9 days) compared with VCZ (19 days), particularly in patients with moderate to severe renal insufficiency.<sup>70</sup> However, the study population was small and the results were not statistically significant. Therefore, more clinical data are needed before making any conclusions from this study.

## Drug interactions

ISZ has fewer drug interactions *in vivo*, compared with VCZ and POS. ISZ is a mild to moderate inhibitor of CYP3A4 and a mild inducer of CYP2B6 (Table 3). It differs from other azoles in that it has negligible effect on CYP1A2, CYP2C9, CYP2C19, CYP2A6, or CYP2D6. Dosage adjustment is not needed for warfarin therapy.<sup>71</sup> Concomitant use of strong inducers (eg, rifampin) or strong inhibitors (eg, Ritonavir) of CYP3A is contraindicated, along with ISZ.<sup>72</sup> Coadministration of tacrolimus or sirolimus increases the AUC 1.25- and 84-fold, respectively.<sup>73</sup> Thus, therapeutic drug monitoring of such drugs is indicated with concomitant use of ISZ. Drugs that are *P*-glycoprotein substrates (eg, digoxin, colchicine, mycophenolate) may need dosage adjustment and close monitoring of serum levels to avoid toxicities.<sup>74-77</sup>

## Clinical efficacy trials

ISZ was studied in three phase III trials, one for candidiasis (ACTIVE), one for aspergillosis (SECURE), and one for mucormycosis (VITAL).

## ISZ for IA (SECURE trial)

ISZ received FDA approval based on the results from the SECURE study. This was a global, multicenter, double-blinded,

phase III, noninferiority trial that spanned a 7-year period from March 2006 through March 2013. A total of 516 adult patients with proven, probable, or possible invasive mold infections, as defined by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria, were randomized to a 1:1 ratio, and received either isavuconazonium sulfate 372 mg (prodrug; equivalent to 200 mg ISZ; intravenously three times a day for first 2 days, then either intravenously or orally once daily) or VCZ at a dose of 6 mg/kg intravenously twice daily on day 1, 4 mg/kg intravenously twice daily on day 2, and then intravenously 4 mg/kg twice daily or orally 200 mg twice daily from day 3 onward. The primary endpoint was all-cause mortality at day 42, in patients who received at least one dose of the study drug (ITT, intention-to-treat population), using a noninferiority margin of 10%. All-cause mortality at day 42 for the ITT population was 19% with ISZ (48 patients) and 20% with VCZ (52 patients), indicating noninferiority of ISZ compared to VCZ. Gastrointestinal complaints were the most common adverse effects reported and were similar in both treatment groups (96%–98%). Patients in ISZ arm had a lower frequency of hepatobiliary disorders (9% vs 16%;  $p=0.016$ ), eye disorders (15% vs 27%;  $p=0.002$ ), and cutaneous disorders (33% vs 42%;  $p=0.037$ ). Overall drug-related adverse events were reported in 42% of patients receiving ISZ and in 60% of patients receiving VCZ ( $p<0.001$ ). As this trial included patients who had mold infections other than aspergillosis, a subset analysis was performed to evaluate the efficacy of ISZ in patients with IA. Within this subset of 231 patients who had IA, 16% had proven aspergillosis and 84% had probable aspergillosis. Hematological malignancy was the most common underlying condition documented in 84% of patients; 65% were neutropenic and 20% had received a hematopoietic stem-cell transplant. For the 231 patients who had proven or probable IA, the all-cause mortality at 42 days was 18.7% in the ISZ arm and 22.2% in the VCZ arm. Again the results were similar in the two arms. Treatment success at

**Table 3** Drug interactions with ISZ

Drugs that increase serum ISZ levels	Drugs that decrease serum ISZ levels	Serum drug levels increased by ISZ	Serum drug levels decreased by ISZ
Ritonavir	Rifampin	Sirolimus	Bupropion
Lopinavir/Ritonavir	Rifabutin	Tacrolimus	Lopinavir/ritonavir
Effavirenz	Phenytoin	Cyclosporine	
Ketoconazole (contraindicated)	Carbamazepine	Mycophenolate mofetil	
	St John's Wort	Digoxin	
	Long-acting barbiturates	Colchicine	
		Dabigatran	
		Atorvastatin (mild)	
		Midazolam (mild)	

**Note:** Data from.<sup>71-78,87</sup>

**Abbreviation:** ISZ, isavuconazole.

the end of treatment (35% vs 38.9%) was comparable between the ISZ and VCZ arms. The trial concluded that ISZ was noninferior to VCZ for the treatment of invasive mold infections including IA, had a better tolerability and safety profile compared with VCZ, and the data support the use of ISZ as primary therapy for IA.<sup>88</sup>

### ISZ for mucormycosis (VITAL trial)

Given the infrequent occurrence of invasive mucormycosis and other rare molds, and the high mortality associated with these infections, this study was difficult to perform. As expected, enrollment was modest in this nonrandomized clinical trial. This was a noncomparator, single-arm, open-label, matched, case-control trial that evaluated the efficacy of ISZ, and the results were compared with a database of similarly infected patients treated with a polyene. This study allowed both primary treatment of invasive mold infections and salvage treatment of patients who were intolerant of or failing prior antifungal therapy. The study recruited adult patients from 34 centers around the world, from April 2008 to April 2013. Patients were treated with ISZ 200 mg (as its intravenous or oral water-soluble prodrug, isavuconazonium sulfate) three times daily for six doses, followed by 200 mg/day until invasive fungal disease resolution, failure, or for 180 days or more. ISZ was given as primary therapy, or in patients intolerant of prior therapy, it was administered as salvage therapy. A total of 149 patients were enrolled in the study, of which 37 patients had proven (86%) or probable (14%) invasive mucormycosis. Out of these 37 patients, 21 patients had not received prior antifungal therapy, 11 patients had refractory disease, and 5 were intolerant to prior antifungal therapy. The underlying conditions seen in these 37 patients were hematological malignancy (59%), allogenic stem-cell transplant (35%), and neutropenia (27%); only 4/37 patients had diabetes as a major risk factor; 22/37 patients presented with pneumonia (59%), and half of the patients with pulmonary involvement also had sinus, ocular, or central nervous system infection. The median duration of treatment with ISZ was 84 days (range of 2–882 days).

Cases of mucormycosis treated with ISZ as primary treatment were matched with controls from the Fungiscope Registry, recruited from 17 centers worldwide. Controls received AMB-based treatment. The primary endpoint was all-cause mortality at day 42, and overall response (treatment success or failure) at day 42, as determined by an independent data review committee based on prespecified criteria. The all-cause mortality at day 42 was 38%. Mortality was higher among patients who had refractory disease or were intolerant to prior therapy (43.7%), compared with those who were treated for primary mucormycosis (33.3%). The overall response rate at

day 42 was 31.4%. A matched case-control analysis was performed comparing the 21 patients who had primary treatment with ISZ with the cases of 33 patients who were treated with AMB and whose data had been entered into the global Fungiscope Registry, an ongoing observational database. Matching was done by severity of infection, hematologic malignancy, and whether surgical debridement was performed. In this analysis, ISZ-treated and AMB-treated patients had similar mortality (33.3% vs 41.3%, respectively). Assessment of these 37 patients on day 42 showed partial response in 4 (11%), stable disease in 16 (43%), disease progression in 1 (3%), missing assessments in 3 (8%), and 13 patients had died (35%). The all-cause crude mortality at day 42 was 7 out of 21 (33%) in the ISZ-treated patients, compared to 13 of 33 (39%) AMB-treated, matched controls. The study concluded that the clinical efficacy and tolerability of ISZ were similar to that of AMB against mucormycosis. The US FDA approved use of ISZ for invasive mucormycosis based on the above data.<sup>89</sup>

### ISZ for the treatment of candidemia and invasive candidiasis (ACTIVE trial)

This was a phase III, randomized, double-blind multinational clinical trial that evaluated the safety and efficacy of ISZ compared with CFG followed by oral VCZ. Patients with proven candidemia or invasive candidiasis were randomized (1:1) to ISZ (200 mg IV TID for 2 days, followed by 200 mg IV QD) or CFG (70 mg IV QD on day 1, followed by 50 mg IV QD) for a maximum of 56 days. A total of 450 patients were randomized; 400 patients comprised the modified ITT population. After 10 days of treatment, patients were switched to oral ISZ (ISZ arm) or VCZ (CFG arm). Primary efficacy endpoint was successful overall response (based on successful clinical and mycological responses as evaluated by an independent Data-Review Committee) at the end of intravenous therapy in patients with proven infection who received  $\geq 1$  dose of study drug (modified intent-to-treat population). The prespecified noninferiority margin was set at 15%. The secondary outcome was measured by an assessment of overall response at the end of treatment + 2 weeks. All-cause mortality at Days 14 and 56 and safety were also assessed. The primary endpoint of successful overall response at the end of intravenous therapy was 60.3% in the ISZ arm and 71.1% in the CFG arm. The results did not meet the noninferiority margin and hence did not meet the primary endpoint. The key secondary endpoint, overall response at the end of intravenous therapy + 2 weeks (54.8% for ISZ vs 57.2% for CFG), was similar in both arms. The all-cause mortality was also similar in both arms (14.6% ISZ vs 12.4% CFG). Both drugs were safe and well tolerated. On the basis of the findings mentioned above, ISZ

is not currently approved for the treatment of candidemia or invasive candidiasis.<sup>90</sup>

## Endemic fungi (VITAL study)

ISZ demonstrated good clinical activity against cryptococcosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, and blastomycosis and serves as a valuable alternative to currently available antifungal agents.<sup>91</sup>

## Safety data

Preclinical *in vivo* assays for evaluation of safety and mutagenicity were performed in rat and rabbit models. ISZ at systemic exposures below the therapeutic level was associated with a dose-dependent increase in skeletal abnormalities (rudimentary supernumerary ribs, zygomatic arch fusion, etc. in offspring). Administration of isavuconazonium sulfate to rats at a dose of 90 mg/kg/day (2.3-fold the human maintenance dose) during pregnancy through the weaning period showed an increased perinatal mortality of the pups. Studies using <sup>14</sup>C-labeled isavuconazonium sulfate to lactating rats demonstrated excretion of radiolabeled drug in the milk. ISZ did not affect the fertility of male or female rats treated with oral doses up to 90 mg/kg/day (2.3-fold the clinical maintenance dose based on mg/m<sup>2</sup>/

day comparisons). It was not shown to possess mutagenic or genotoxic properties, although specific carcinogenicity studies have not been performed. ISZ had some nonspecific inhibition of the hERG potassium channel and the L-type calcium channel. The *in vivo* 39-week repeated-dose toxicology studies in monkeys did not show QTc prolongation (unlike other triazoles) at doses up to 40 mg/kg/day. These preclinical *in vivo* studies did not indicate any major side effects with ISZ, other than caution in pregnancy. There are reports of QTc shortening with ISZ. Although the clinical significance of ISZ-induced QTc shortening is unknown, it would be reasonable to avoid ISZ in patients with familial short QT syndrome. Also, caution is warranted during the coadministration of ISZ with drugs known to shorten the QT interval (eg, lamotrigine, primidone, rufinamide).<sup>87</sup>

## Conclusion

Several *in vitro/in vivo* evaluations, safety/tolerability data, and results from phase III clinical trials have shown ISZ to have favorable PK and pharmacodynamic profile, and good clinical efficacy with few side effects or drug interactions as compared with available azoles and other antifungal agents (Table 4). The drug has been approved by the US FDA for the

**Table 4** Advantages of ISZ over other available triazole agents

Characteristic	ISZ <sup>86, 87</sup>	POS <sup>78, 79</sup>	VCZ <sup>80-84</sup>	Itraconazole <sup>85, 86</sup>
Anti-aspergillus and mucorales activity	Aspergillus + mucorales	Aspergillus + mucorales	Aspergillus	Aspergillus
Formulation	Oral/IV	Oral/IV	Oral/IV	Oral/IV
Oral bioavailability	Equivalent to intravenous	Depends on dosing frequency and food (range of 8%–47%)	90%–95%	30% tablet 50% solution
Food requirement for absorption	Not required	Increased absorption (with a fatty meal)	Decreased absorption (with a fatty meal)	Increased absorption with acidity
Kinetics	Linear and predictable	Nonlinear	Nonlinear	Nonlinear
Interpatient variability	Minimal	Significant	Significant	Significant
Half-life ( $t_{1/2}$ )	56–104 h	24–30 h	16–35 h	24–30 h
Cyclodextrin (for solubility)	Not required	Not required	Required	Not required
Cyp450 effects (resulting in multiple drug interactions)	Minimal (Cyp3A4)	Moderate (Cyp3A4, Cyp2C9, Cyp2C19)	High (Cyp3A4, Cyp2C8, Cyp2C9, Cyp2C19, Cyp2D)	High (Cyp3A4, Cyp2C9, Cyp2C19)
Food intake	Not required	Better absorption	Better absorption	Better absorption
Antacids/proton pump inhibitors	No change	Decreased level	Decreased	Decreased
Renal toxicity	None	None	Reported with intravenous formulation	None
Phototoxicity	None	None	Reported	Reported
Skin cancer	None	None	Reported	None
Neurological effects	Minimal	Sensorimotor, mono- and polyneuropathy	Sensorimotor, mono- and polyneuropathy	Sensorimotor, mono- and polyneuropathy
Visual toxicity	None	Hallucinations	Hallucinations	Hallucinations
QTc interval	Shortening (significance unknown)	Prolongation	Prolongation	Prolongation
Hepatobiliary	No data in patients with severe liver impairment	Reported	Reported	Reported
With warfarin	No interaction	Prolonged PT/INR	Prolonged PT/INR	Prolonged PT/INR

**Abbreviations:** ISZ, isavuconazole; POS, posaconazole; VCZ, voriconazole; PT, prothrombin time; INR, international normalized ratio.

management of both IA and mucormycosis. Data on primary therapy for mucormycosis are based on limited data. The drug is not approved for the treatment of candidemia or invasive candidiasis. The availability of oral and parenteral formulations that are bioequivalent is an added benefit. Clinical case reports postapproval are scarce at this time.<sup>92-94</sup> In addition, given the emergence of azole-resistant strains of aspergillus with differential susceptibility pattern, susceptibility testing of mold isolates may be required in some clinical settings. Likewise, although not required now, therapeutic drug monitoring may be indicated in selected circumstances. With a broad spectrum of anti-mold activity, excellent tolerability, safety, and availability in oral and intravenous formulations, ISZ is likely to be used inappropriately in empiric and prophylactic settings. Although the drug appears promising, caution is warranted before implementing widespread use, until more data become available.

## Disclosure

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