

# Newer Systemic Antifungal Agents

## Pharmacokinetics, Safety and Efficacy

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### Abstract

The past few years have seen the advent of several new antifungal agents, including those of a new class and a new generation of an existing class. Caspofungin, the first available echinocandin, has greatly expanded the antifungal armamentarium by providing a cell wall-active agent with candidacidal activity as well as demonstrated clinical efficacy in the therapy of aspergillosis refractory to available therapy. In addition, in clinical trials, caspofungin had comparable efficacy to amphotericin B for candidaemia and invasive *Candida* infections. Caspofungin and two more recently introduced echinocandins, micafungin and anidulafungin, are available as intravenous formulations only and characterised by potent anti-candidal activity, as well as few adverse events and drug interactions.

Voriconazole, the first available second-generation triazole, available in both intravenous and oral formulations, has added a new and improved therapeutic option for primary therapy of invasive aspergillosis and salvage therapy for yeasts and other moulds. In a randomised trial, voriconazole demonstrated superior efficacy and a survival benefit compared with amphotericin B followed by other licensed antifungal therapy. This and data from a noncomparative study led to voriconazole becoming a new standard of therapy for invasive aspergillosis. Voriconazole has several important safety issues, including visual adverse events, hepatic enzyme elevation and skin reactions, as well as a number of drug interactions. Posaconazole, only available orally and requiring dose administration four times daily, shows encouraging efficacy in difficult to treat infections due to zygomycetes. Ravuconazole, available in both intravenous and oral formulations, has broad-spectrum *in vitro* potency and *in vivo* efficacy against a wide range of fungal pathogens. Clinical studies are underway.

Despite the advances offered with each of these drugs, the morbidity and mortality associated with invasive fungal infections remains unacceptable, especially for the most at-risk patients. For individuals with severe immunosuppression as a result of chemotherapy, graft-versus-host disease and its therapy, or transplantation, new drugs and strategies are greatly needed.

Both the frequency and severity of invasive fungal infections in immunocompromised patients has increased steadily over the past two decades. Mortality due to invasive aspergillosis approaches

80–100% in high-risk patients, including those with underlying haematological malignancy, bone marrow or solid organ transplantation.<sup>[1-4]</sup> Apart from organ transplant recipients, individuals with AIDS

and patients hospitalised with severe illnesses, major increases in invasive fungal infections have been observed in patients with haematological malignancies who receive induction or consolidation chemotherapy and those who undergo bone marrow transplantation.<sup>[5-8]</sup>

This review focuses on newer antifungal agents, specifically the second-generation triazoles, voriconazole, posaconazole and ravuconazole, and the echinocandins, caspofungin, micafungin and anidulafungin (table I). The objective of the article is to update the previous review published in 2001,<sup>[9]</sup> focusing on the most recent additions to the antifungal armamentarium. Data regarding overall profile, *in vitro* and *in vivo* activity, pharmacokinetics and tissue distribution, as well as published clinical efficacy and safety data, are presented for each of these newer agents.

## 1. Cell Wall Synthesis Inhibitors

Developers of antifungal agents followed the lead of their antibacterial drug development colleagues in seeking drugs active against components of the fungal cell wall. Disruption of the fungal cell wall leads to osmotic stress, lysis and fungal cell death.<sup>[10]</sup> For most fungi, key cell wall elements include chitin,  $\beta$ - or  $\alpha$ -linked glucans and various mannoproteins. As these are unique to fungi and not found in human cells, agents active at these sites are particularly attractive targets and pose a low risk of mechanistic toxicity.

Cell wall-active agents include echinocandin lipopeptides and the nucleoside-peptide antibiotic nikkomycin Z.<sup>[11]</sup>

### 1.1 Echinocandin Lipopeptides

Echinocandins are natural cyclic hexapeptide antifungal compounds that noncompetitively inhibit 1,3  $\beta$ -D-glucan synthase, an enzyme complex that is unique to a number of fungi, which forms glucan polymers in the fungal cell wall.<sup>[12]</sup> Echinocandins are active against *Candida* spp. and *Pneumocystis jiroveci* (formerly known as *P. carinii*). Specific modifications to the N-acyl aliphatic or aryl side chains expand the antifungal spectrum to include *Aspergillus* spp.<sup>[12,13]</sup>

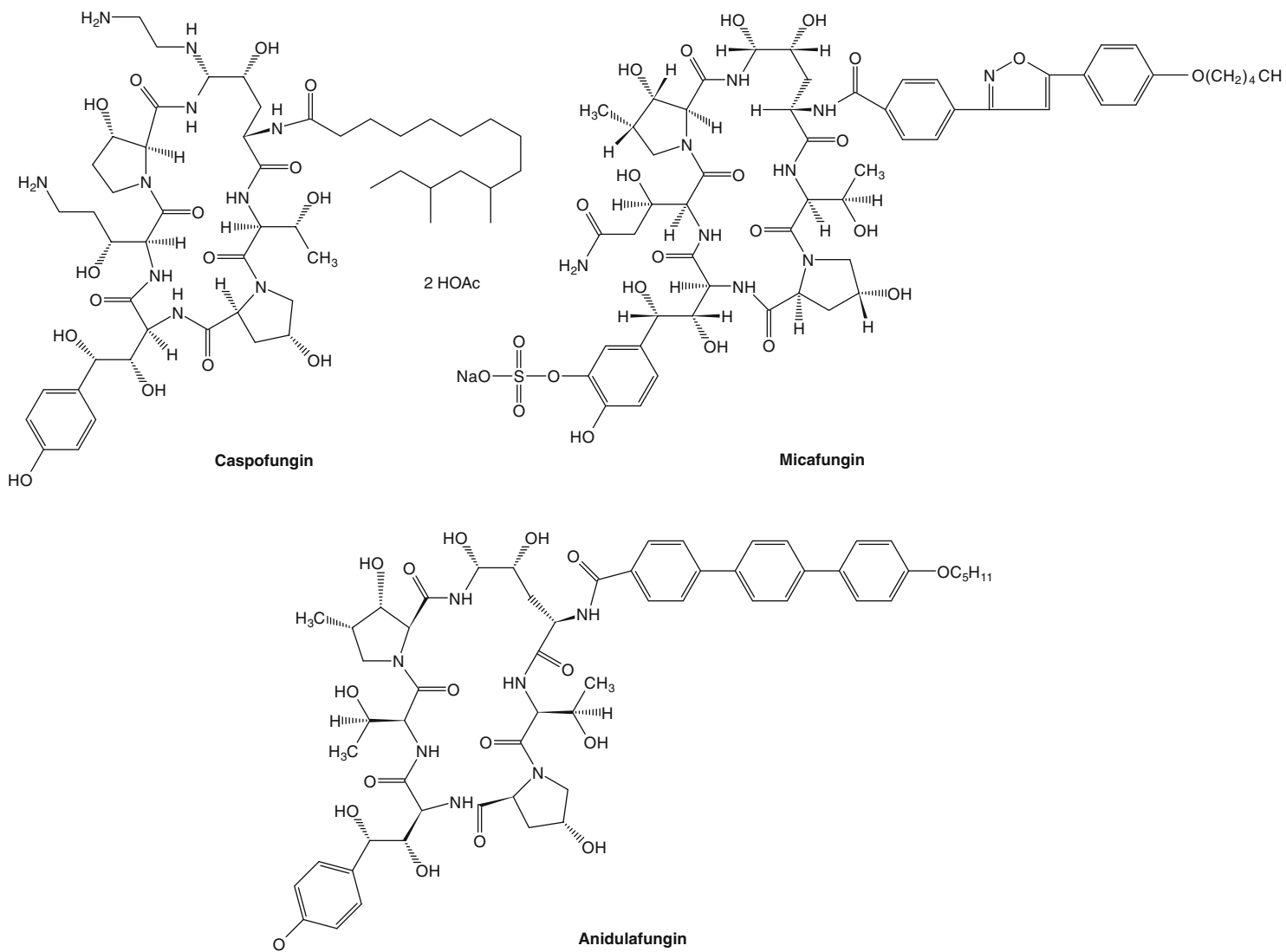
Caspofungin (formerly L-743872, MK-0991) is the only US FDA-approved echinocandin, while micafungin (FK-463) and anidulafungin (LY 303366, VER-002) are under review. All three echinocandins have poor bioavailability and are currently available only in intravenous formulation (figure 1). Thus far, all three have been associated with few drug interactions and good to excellent tolerability in clinical trials. Caspofungin is currently approved by the US FDA for use in treatment of candidaemia and salvage therapy of invasive aspergillosis.

#### 1.1.1 Caspofungin

The first approved echinocandin, caspofungin, is a semisynthetic derivative of pneumocandin B0, a

**Table I.** Systemic antifungal agents

Class/compound	Mechanism of action
<b>Antifungal compounds targeting fungal cell membrane</b>	
<i>Polyene antifungals</i>	
Amphotericin B Lipid formulations of amphotericin B	Interaction with ergosterol, formation of aqueous channels, increased membrane permeability to univalent and divalent cations, cell death
<i>Antifungal triazoles</i>	
Fluconazole Itraconazole Voriconazole Posaconazole Ravuconazole	Interaction with cytochrome P450; inhibition of C-14 demethylation of lanosterol, causing ergosterol depletion and accumulation of aberrant and toxic sterols in the cell membrane
<b>Antifungal compounds targeting fungal cell wall</b>	
<i>Echinocandins</i>	
Caspofungin Micafungin Anidulafungin	Inhibition of fungal $\beta$ -(1,3) glucan synthase complex, leading to depletion of cell-wall glucan and osmotic instability



**Fig. 1.** Chemical structures of the echinocandins caspofungin, micafungin and anidulafungin.

fermentation product of *Glarea lozoyensis*. Caspofungin is a water-soluble amphipathic lipopeptide that is available in an intravenous formulation only. Deresinski and Stevens<sup>[10]</sup> have recently published an extensive review of caspofungin.

#### *In Vitro* Activity

Caspofungin is fungicidal *in vitro* against *Candida* spp.,<sup>[14]</sup> including azole-resistant *Candida*,<sup>[15]</sup> and has potent activity *in vitro* against *Aspergillus* spp. and some dimorphic moulds, such as *Histoplasma capsulatum*, *Coccidioides immitis* and *Blastomyces dermatitidis*. *Cryptococcus neoformans* is relatively resistant to caspofungin, as are several yeasts including *Trichosporon* spp. and *Rhodotorula* spp.<sup>[16,17]</sup>

Activity *in vitro* is somewhat less against *C. parapsilosis*, *C. lusitanae* and *C. guilliermondii* than against other *Candida* spp.<sup>[16,18]</sup> *In vitro* studies have demonstrated no cross-resistance to azoles.<sup>[15]</sup>

Caspofungin has demonstrated activity against *Aspergillus* spp. In multiple studies, caspofungin has proven additivity or synergy with other azoles and amphotericin B, as well as calcineurin inhibitors, versus *Aspergillus* spp.<sup>[14,19-23]</sup> Caspofungin has limited *in vitro* activity against other moulds, including *Fusarium* spp., *Scedosporium* spp., zygomycetes, *Pseudallescheria boydii* or dematiaceous moulds.<sup>[16,24-26]</sup>

#### *In Vivo* Activity

Caspofungin has been extensively studied in animal models of invasive fungal infection, including in severely immunocompromised animals. In studies of invasive *Candida* infection in mice, including those due to fluconazole-resistant organisms (*C. krusei*, *C. glabrata*, etc.), caspofungin effectively prolonged survival, decreased fungal burden in target organs and sterilised kidneys in significant numbers of animals, even in the presence of neutropenia.<sup>[27-31]</sup> In a murine model of cryptococcosis, caspofungin was ineffective.<sup>[14,27]</sup>

Caspofungin demonstrated a survival advantage and reduction in organism-mediated pulmonary injury in a neutropenic rabbit model of invasive aspergillosis.<sup>[32]</sup> While caspofungin therapy was associated with concentration- and dose-dependent hyphal damage, rabbits treated with caspofungin had a paradoxical trend toward increased fungal burden

following therapy and increased galactomannan antigenaemia with therapy.<sup>[32]</sup> Fragmentation of hyphal elements, particularly at branch points, damages mycelium and leads to an increase in the number of viable mycelial units. These mycelia are damaged when examined via electron microscopy and exhibit reduced propensity for angioinvasion *in vitro* and *in vivo*. This allows for improved survival and ultimately eradication. Quantitative polymerase chain reaction analyses demonstrate a reduction in overall viable fungal burden.<sup>[33]</sup>

In a model of invasive aspergillosis in immunosuppressed guinea pigs, caspofungin in combination with voriconazole was associated with a mortality benefit similar to that of voriconazole alone, but the combination resulted in a reduced total number of positive cultures from any organ tested, including the important sites of brain, lung, liver and kidney.<sup>[34]</sup> This study and subsequent *in vivo* studies provide a rationale for testing the hypothesis of combination therapy for invasive aspergillosis in clinical trials.<sup>[35]</sup>

Caspofungin was studied alone and in combination with amphotericin in a murine model of coccidioidomycosis.<sup>[36]</sup> In the initial study, caspofungin, amphotericin B and liposomal amphotericin B were all associated with longer survival and decreased residual fungal burden. In the combination study, all treatments significantly prolonged survival and effectively decreased residual fungal burden in spleen and liver. Importantly, the combination of caspofungin and liposomal amphotericin B was associated with 100% sterilisation of the spleen and liver.<sup>[36]</sup>

#### Pharmacokinetics and Tissue Distribution

Like other echinocandins, caspofungin has low oral bioavailability and, thus, is available only in the intravenous formulation. The drug is highly protein bound (>95%) with extensive distribution into animal tissues, including brain (although concentrations are lower in brain and cerebrospinal fluid [CSF] of animals with uninflamed meninges).<sup>[17,37,38]</sup> Caspofungin is thought to undergo hepatic metabolism via spontaneous peptide hydrolysis and *N*-acetylation. The major degradation product has no antifungal activity and, thus, is not believed to contribute to clinical efficacy.<sup>[39,40]</sup> The drug is

not removed with haemodialysis and no dose adjustments are recommended for renal insufficiency or failure requiring haemodialysis.<sup>[39,40]</sup> Phase I studies demonstrated that plasma caspofungin concentrations increase with moderate hepatic insufficiency (Child-Pugh score 7–9). Consequently, the US FDA-approved US Package Insert (USPI) recommends using the standard loading dose (70mg) followed by a reduced daily dose of 35mg in patients with moderate hepatic impairment. Radiolabel studies demonstrated that 41% of the dose of caspofungin is excreted in the urine and 35% in faeces.<sup>[41]</sup>

Pharmacokinetics of caspofungin are linear with an elimination half-life ( $t_{1/2\beta}$ ) between 10 and 15 hours, allowing for once daily dose administration.<sup>[37,42]</sup> A 70mg loading dose leads to mean steady-state concentrations above 1 µg/mL at day 1; similar to those at day 14 when 50 mg/day is given without a loading dose.<sup>[10,42]</sup> This, along with the serious nature of the infections caspofungin is used to treat, led to the recommendation for a standard loading dose of 70mg. The plasma pharmacokinetics of caspofungin in children are different from those of adults. In order to achieve comparable drug exposure, 50 mg/m<sup>2</sup>/day is recommended for paediatric patients who are greater than 2 years of age.<sup>[43]</sup>

Caspofungin was studied with several drugs in phase I drug interaction studies. Despite the fact that caspofungin does not appear to inhibit P-glycoprotein or hepatic cytochrome P450 (CYP) enzymes *in vitro*, several significant interactions were observed in these studies. Cyclosporin (cyclosporine) increased the area under the plasma concentration-time curve (AUC<sub>24</sub>) of caspofungin by 35%.<sup>[39,40]</sup> In one study, several healthy volunteers who received caspofungin in combination with cyclosporin developed transient increases in alanine aminotransferase. Thus, the USPI warns against using caspofungin with cyclosporin unless the benefits outweigh the risks.<sup>[40]</sup> No significant interactions between caspofungin and amphotericin B, itraconazole, 2-hydroxy-itraconazole or mycophenolate were observed in phase I studies.<sup>[39]</sup>

Reductions in serum caspofungin concentrations (AUC) were seen in the presence of efavirenz, nevirapine, rifampin, dexamethasone, phenytoin or car-

bamazepine. Patients who require caspofungin along with these medications should receive caspofungin 70 mg/day.<sup>[39,40]</sup> Nelfinavir demonstrated no significant effect on the plasma pharmacokinetics of caspofungin and no dose adjustment is recommended.<sup>[44]</sup> In the same study, rifampin both inhibited and induced caspofungin disposition, resulting in decreased serum concentration 24-hours post-dose (C<sub>24h</sub>), i.e. decreased exposure to caspofungin, at steady state. Thus, consideration of increasing the caspofungin dose to 70 mg/day should be given when concomitant administration of rifampin is necessary.<sup>[44]</sup>

#### Clinical Efficacy

Caspofungin was approved for marketing in the US based on the demonstration of efficacy in the treatment of 56 patients with invasive aspergillosis refractory to standard therapy. In these well documented cases, caspofungin therapy was associated with success (complete or partial responses) in 41% of the patients.<sup>[39]</sup> A recent update of this study reported on a total of 90 patients and, again, success was seen in 45% of patients.<sup>[45]</sup> This is the same success rate demonstrated for several of the lipid formulations of amphotericin B in the salvage setting.

Caspofungin has been studied extensively in candidal infections. Caspofungin has demonstrated efficacy compared with amphotericin B deoxycholate for endoscopically proven oesophageal candidiasis<sup>[46]</sup> and successful treatment of refractory candidal infections, including a case of hepatosplenic candidiasis refractory to amphotericin B deoxycholate.<sup>[47]</sup> Most recently, results of an international randomised, double-blind study of caspofungin versus amphotericin B deoxycholate for treatment of invasive candidiasis supported the licensure of caspofungin for therapy of candidaemia and intra-abdominal infections, abscesses, peritonitis and pleural space infections due to *Candida* spp.<sup>[48]</sup> Of note, this trial included non-albicans *Candida* isolates from over 50% of the caspofungin patients, the vast majority of whom had successful outcomes. A noteworthy exception was the *C. parapsilosis* group. Approximately 20% of patients in each treatment arm had *C. parapsilosis* isolated at baseline. Five caspofungin-treated patients had persistently posi-

tive blood cultures for *C. parapsilosis* compared with no amphotericin B recipients. An accompanying editorial noted the relationship to the higher minimum inhibitory concentrations (MICs) for *C. parapsilosis* and the need for close monitoring for persistent fungaemia.<sup>[13]</sup>

Caspofungin was comparable with liposomal amphotericin B in the, to date, largest international, double-blind, multicentre study of empirical antifungal therapy for patients with persistent fever and neutropenia. Of note, patients who received caspofungin had greater survival (93% vs 89%), improved response to therapy of baseline invasive fungal infections (52% vs 26%), less nephrotoxicity (3% vs 12%), less infusion-related toxicity (35% vs 52%) and fewer drug-related adverse events (54% vs 69%).<sup>[49]</sup>

#### Clinical Safety

Caspofungin is generally well tolerated with few reported adverse events and an overall profile comparable with fluconazole and appreciably more favourable than amphotericin B deoxycholate.<sup>[48]</sup> Symptoms due to histamine release, possibly related to the fact that caspofungin is a basic polypeptide, were seen in approximately 2% of patients in the clinical trials. In the pivotal candidaemia trial, <3% of patients reported fever, flushing, nausea, headache, vomiting and infusion-related reactions.<sup>[48]</sup>

Abnormalities in serum transaminase levels were seen at frequencies similar to those reported for patients receiving fluconazole and more frequently in patients receiving high doses of caspofungin and ciclosporin.<sup>[40]</sup>

#### 1.1.2 Micafungin

Micafungin is a water-soluble lipopeptide echinocandin derived from chemical modification of the environmental mould *Coleophoma empedri*. Like the other echinocandins in development, micafungin is available in intravenous formulation only.<sup>[37,50]</sup>

#### *In Vitro* Activity

Micafungin demonstrates fungicidal activity against *Candida* spp., including isolates from severely ill immunocompromised patients and those resistant to fluconazole and itraconazole, and potency against clinical isolates of *Aspergillus* spp.<sup>[51-55]</sup> Micafungin has little *in vitro* activity against *C. neoformans*, *Fusarium solani*, *P. boydii*,

*Trichosporon* spp., or zygomycetes.<sup>[53,55]</sup> *In vitro* testing was also conducted on dimorphic fungi, with focus on its differential effects on yeast-like and mycelial forms, and micafungin was shown to have potent activity against the mycelial form of *H. capsulatum*, *B. dermatitidis*, and *C. immitis*, but no activity against the yeast forms.<sup>[56]</sup>

*In vitro* combination studies of micafungin with other echinocandins, azoles and nikkomycin Z demonstrate additive effects of micafungin and voriconazole/caspofungin versus *Aspergillus* spp.,<sup>[57]</sup> *in vitro* additivity or indifference when combined with voriconazole versus filamentous fungi,<sup>[58]</sup> and *in vitro* synergy when micafungin is combined with nikkomycin Z against *Aspergillus fumigatus*.<sup>[59]</sup>

#### *In Vivo* Activity

Micafungin has been extensively studied in animal models of invasive fungal infection, including severely immunocompromised animals. Activity has been demonstrated in models of disseminated azole-resistant *C. albicans* in mice, pulmonary aspergillosis in neutropenic rabbits and temporarily neutropenic mice, as well as prophylaxis against *P. jiroveci* infection in mice.<sup>[60-64]</sup> In a comparative study of *in vivo* efficacy and plasma pharmacokinetics of micafungin against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits, *in vivo* efficacy was seen in both infections. However, concentration- and dose-dependent clearance of *C. albicans* was seen while no significant microbiological clearance of *A. fumigatus* from lung tissue was observed in this model of invasive infection. Despite the lack of clearance of *A. fumigatus* from tissue, the rabbits with aspergillosis had improved survival and a reduction in pulmonary infarction when treated with micafungin.<sup>[63]</sup> This disparity between persistence of residual fungal burden in neutropenic hosts and improvement in survival is a general class effect of echinocandins where the hyphal structure is disrupted, growing cells are killed, but viable fungal elements may persist.<sup>[32,63,65]</sup>

The combination of micafungin and ravuconazole in a persistently neutropenic rabbit model of invasive aspergillosis demonstrated synergistic or additive activity of the combination versus single agents by a range of study parameters: survival,

residual fungal burden, pulmonary injury indices and galactomannan antigenaemia.<sup>[35]</sup> A study of micafungin combined with itraconazole, amphotericin B or nikkomycin Z in a murine model of aspergillosis demonstrated the efficacy of combination therapy, but no clear benefit versus therapy with amphotericin B or itraconazole alone.<sup>[66]</sup>

#### Pharmacokinetics and Tissue Distribution

Like caspofungin, micafungin has poor oral bioavailability and is only available in an intravenous formulation. The volume of distribution is small at 0.2–0.27 L/kg in adults and micafungin is highly protein bound (>99%).<sup>[67,68]</sup> Pharmacokinetics are linear and  $t_{1/2\beta}$  ranges from 3 to 6 hours in animals and 10 to 15 hours in humans.<sup>[68,69]</sup> Micafungin is metabolised by the liver, possibly by *O*-methyltransferase, with a small amount excreted renally.<sup>[68]</sup> A phase I study demonstrated that no dosage adjustment is needed in patients with severe renal failure.<sup>[70]</sup>

#### Clinical Efficacy

Micafungin has been studied in two open-label, dose-ranging studies of endoscopically proven oesophageal candidiasis in HIV patients in South Africa and South America at dosages of 12.5–100 mg/day. In these studies, a dose response was seen, with clinical success documented in 92% or more of the subjects treated with 50mg or higher (endoscopic documentation of resolution at 75 or 100 mg/day; safety okay up to 21 days at 100 mg/day).<sup>[71,72]</sup> Another international, double-blind, comparative study of several different dosages of micafungin (50, 100, 150 mg/day) versus fluconazole 200 mg/day in the treatment of HIV-positive patients with oesophageal candidiasis showed similar endoscopic cure rates (endoscopy grade 0) and safety profiles for micafungin at doses of 100 and 150 mg/day and fluconazole.<sup>[73]</sup>

In open-label studies of patients with deep fungal infections (candidiasis or aspergillosis) in Japan, 92% had clinical success following a mean of 22 days of therapy with varying dosages of micafungin.<sup>[74]</sup> A single-centre US study of micafungin at dosages of 50–150 mg/day with or without other antifungal therapy, in the treatment of 14 oncology patients with candidaemia demonstrated success in 11 of 12 patients (92%).<sup>[75]</sup>

The results of the first randomised, double-blind trial of micafungin were presented at the Inter-science Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in San Diego, CA, USA, in September 2002.<sup>[76]</sup> In a large, international, collaborative study of micafungin 50 mg/day versus fluconazole 400 mg/day as prophylaxis for invasive fungal infections in patients undergoing haematopoietic stem cell transplantation, success, defined as the absence of fungal infection for 4 weeks following study therapy, was seen in 80% of micafungin-compared with 73.5% of fluconazole-treated patients. This difference was significant in favour of micafungin. Micafungin recipients required less empirical therapy and, importantly, developed fewer infections due to *Aspergillus* spp. during neutropenia (one vs seven patients,  $p = 0.07$  in favour of micafungin). The median duration of therapy in this study was 18 days in both arms and the overall safety profile was comparable between these agents, with increased bilirubin, nausea and diarrhoea as the three most commonly reported drug-related adverse events in both arms.

Micafungin has been studied in children in a dose-ranging study of empirical therapy of persistently febrile children aged 2–17 years.<sup>[69]</sup> In this study, micafungin was well tolerated to dosages of 3.0 mg/kg/day. The plasma pharmacokinetic profile of micafungin in children is similar to that in adults.

To date, micafungin has been studied over a range of dosages and demonstrated efficacy as prophylaxis at 50 mg/day, while higher doses of 100–150 mg/day seem necessary to treat oesophageal candidiasis, apparently related to the need to penetrate the oesophageal lumen. Further dose-ranging studies are needed in order to define the optimal dosage of micafungin.

#### Clinical Safety

Micafungin has a similar safety profile to that of caspofungin. In several studies, the most commonly reported adverse events included nausea, vomiting, increased bilirubin levels and increases in liver function tests.<sup>[69,71,74-76]</sup> Histamine-related reactions, reported with caspofungin, have not been frequent in these initial studies of micafungin. In addition, the adverse interaction between caspofungin and ciclosporin was not observed for micafungin.<sup>[76]</sup>

### 1.1.3 Anidulafungin

Anidulafungin is the third echinocandin in development currently under regulatory review. Like caspofungin and micafungin, anidulafungin is available in the parenteral formulation only.

#### *In Vitro* Activity

Anidulafungin has broad-spectrum antifungal activity with demonstrated *in vitro* potency against yeasts, including fluconazole-resistant *Candida* isolates, dimorphic fungi and moulds including *Aspergillus* spp.<sup>[16,26,77-80]</sup> Of note, anidulafungin is not active against *C. neoformans*, a fungus that has a different composition of glucan polymer with predominant  $\beta$  1,6-linkage, or against *B. dermatitidis* because of greater cellular reliance upon  $\alpha$ -1,3 D glucan instead of  $\beta$  linkage.<sup>[81]</sup>

*In vitro* synergy testing with voriconazole and itraconazole demonstrated synergy with anidulafungin against *Aspergillus* spp. and indifference against *Fusarium* spp.<sup>[82]</sup>

#### *In Vivo* Activity

Anidulafungin has been studied in a number of animal studies, including models of invasive candidiasis and aspergillosis. In a comparative *in vivo* and pharmacokinetic study with amphotericin B deoxycholate in a model of fluconazole-resistant oropharyngeal and oesophageal candidiasis in immunocompromised rabbits, anidulafungin demonstrated dose- and concentration-dependent fungicidal activity in the tongue, oropharynx, oesophagus, stomach and duodenum.<sup>[83]</sup> Anidulafungin was superior to amphotericin B and fluconazole in clearing *C. albicans* from all tissues studied and was well tolerated with no observed elevations in liver function tests, electrolytes or renal parameters. In this study, anidulafungin demonstrated a linear and dose-proportional plasma and tissue pharmacokinetic profile.<sup>[83]</sup> An earlier *in vivo* and pharmacokinetic study compared anidulafungin with amphotericin B deoxycholate in a persistently neutropenic rabbit model of disseminated invasive candidiasis. In this setting, anidulafungin was as effective as amphotericin and fluconazole in the treatment of disseminated invasive candidiasis. It also demonstrated dose-dependent clearance of *C. albicans* from tissues, including brain, and linear plasma pharmacokinetics.<sup>[84]</sup>

In neutropenic immunocompromised rabbits, anidulafungin therapy led to improved survival and decreased lung injury when used as prophylaxis or therapy for invasive pulmonary aspergillosis.<sup>[65]</sup> Anidulafungin reduced the residual fungal burden and prolonged survival against both amphotericin B-susceptible and -resistant invasive *A. fumigatus* infection in a neutropenic mouse model.<sup>[85]</sup> In a comparative study with ravuconazole in immunosuppressed rabbits, anidulafungin therapy was associated with improved survival and decreased aspergillus antigenaemia, but did not eliminate organisms from tissue.<sup>[86]</sup>

In all of these animal models of invasive fungal infection, the elimination of hyphae is influenced by the number of neutrophils, monocytes and macrophages. The more profoundly compromised the host animal, the greater the residual fungal burden.

#### Pharmacokinetics and Tissue Distribution

Like caspofungin and micafungin, anidulafungin has poor oral bioavailability and is only available in an intravenous formulation. In studies in rabbits, anidulafungin demonstrated linear pharmacokinetics, peak plasma concentrations greater than the MIC values reported for most susceptible fungal pathogens and a large volume of distribution suggesting extensive distribution into tissues. These studies documented tissue concentrations in lung, liver, spleen, kidney and brain.<sup>[87]</sup>

In human volunteers, anidulafungin exhibits linear pharmacokinetics after single oral doses of 100–1000mg. Peak plasma concentrations in that study occurred 6–7 hour after ingestion and the  $t_{1/2\beta}$  was approximately 30 hours. The drug was well tolerated at doses of up to 700mg, with adverse gastrointestinal effects defining the maximum tolerated dose.<sup>[88]</sup> With the long plasma half-life, once-daily dose administration is anticipated.

A population pharmacokinetic analysis of anidulafungin in patients with candidiasis or aspergillosis demonstrated predictable plasma pharmacokinetics with low between-subject variability. The results suggest that no dosage adjustment of anidulafungin is required on the basis of age, weight, gender, ethnicity, HIV infection, fungal disease status or the use of concomitant medications.<sup>[89]</sup>



### Clinical Efficacy

Anidulafungin demonstrated equivalent efficacy to fluconazole in endoscopically and mycologically proven oesophageal candidiasis in a randomised, double-blind, international multicentre study with success documented in 242 of 249 evaluable anidulafungin patients (97.2%) and 252 of 255 fluconazole patients (98.8%), although more fluconazole patients had sustained responses. Treatment-related adverse events were reported in 10% of anidulafungin patients and 13% of fluconazole patients.<sup>[90]</sup>

In a noncomparative dose-ranging study of anidulafungin 100mg loading dose followed by 50 mg/day, 150mg loading dose followed by 75 mg/day, and 200mg loading dose followed by 100 mg/day for candidaemia, successful global response was seen in 83–92% of patients at end of therapy, 72–86% of patients at test-of-cure (2 weeks after end of therapy) and reported adverse events were similar to those seen in the general population.<sup>[91]</sup> A phase III study of anidulafungin in the treatment of candidaemia is ongoing.

## 2. Antifungals Targeting Cell Membrane

### 2.1 Triazole Antifungals

The azole antifungal agents in clinical use for systemic treatment contain either two or three nitrogen atoms in the azole ring and, thereby, are classified as imidazoles (ketoconazole and miconazole) or triazoles (itraconazole and fluconazole), respectively. Azole antifungal agents inhibit the synthesis of ergosterol, the major sterol component in the fungal plasma membrane, by interfering with the CYP-dependent enzyme lanosterol demethylase.

### 2.2 Newer Azole Antifungals

The newer azoles were developed to expand the spectrum activity of existing azoles, namely fluconazole or itraconazole, and provide fungicidal activity versus mould, as well as to improve on some of the limitations of these drugs, namely gastrointestinal toxicity and variable absorption for itraconazole (figure 2).

Voriconazole is the only US FDA-approved second-generation triazole, while posaconazole (SCH 56592) and ravuconazole are advancing in

clinical trials. Case reports and small uncontrolled studies have been published for posaconazole, but as yet no clinical data are available for ravuconazole. Like the earlier azoles, these newer agents act via inhibition of fungal CYP-dependent lanosterol 14- $\alpha$ -demethylase.<sup>[9,37]</sup>

Voriconazole and ravuconazole are structurally related to fluconazole, while posaconazole is similar in structure to itraconazole (figure 2). All three drugs are available orally, and voriconazole and ravuconazole have intravenous formulations or prodrugs. Like the earlier azoles, these three drugs have been associated with varying degrees of drug interactions and hepatotoxicity.

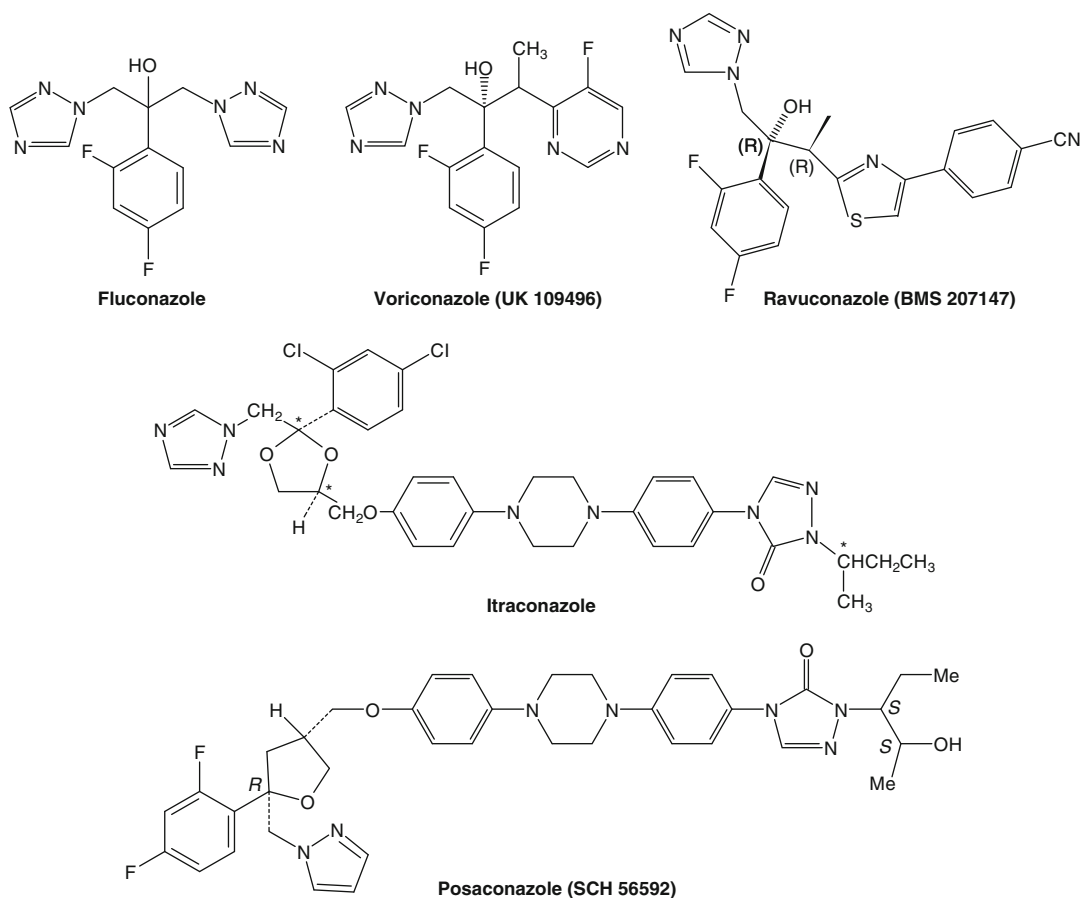
#### 2.2.1 Voriconazole

Voriconazole was developed from fluconazole by substituting a fluoropyrimidine ring for one of the azole groups to enhance the spectrum, and adding an  $\alpha$ -methyl group to provide fungicidal activity against *Aspergillus* spp. and other moulds.<sup>[92]</sup> Voriconazole was studied in humans for 10 years between the first human study in 1991 and its US FDA approval in December 2001. A broad-spectrum azole, voriconazole was studied in >1000 patients with infections due to *Aspergillus* spp., *Candida* spp., as well as a number of less common yeasts and moulds.<sup>[92]</sup>

#### *In Vitro* Activity

Voriconazole has broad *in vitro* antifungal activity against yeasts and moulds, with demonstrated activity against the most frequently isolated opportunistic pathogens, common dermatophytes and the fungi that cause endemic mycoses.<sup>[92-96]</sup> Of note, voriconazole has no activity against the agents of zygomycosis.<sup>[97-99]</sup>

Voriconazole shows fungicidal activity *in vitro* against multiple *Aspergillus* spp., including *A. terreus* which is inherently resistant to amphotericin B.<sup>[98,100-106]</sup> In a comparative study with amphotericin B, voriconazole demonstrated better fungicidal activity against *A. fumigatus* hyphae.<sup>[107]</sup> There are several definitions of *in vitro* fungicidal activity and its significance is not clear. Against *Candida* spp., voriconazole is 60- to 100-fold more potent than fluconazole and has activity against non-albicans *Candida* spp., including *C. krusei* that are inherently resistant to fluconazole.<sup>[98,108-111]</sup>



**Fig. 2.** Chemical structures of itraconazole and fluconazole, and the newazole antifungals, voriconazole, ravuconazole and posaconazole. \* indicates a symmetric carbon atom.

*In vitro* studies also demonstrate the activity of voriconazole against the fungi that cause endemic mycoses (*C. immitis*, *H. capsulatum*, *B. dermatitidis*, *Paracoccidioides brasiliensis*).<sup>[112]</sup> Voriconazole is also active against the less common but increasingly important emerging fungal pathogens including *Scedosporium apiospermum*, *S. prolificans*, *P. boydii* (asexual form of *S. apiospermum*), *Trichosporon* spp., *Acremonium kilensii* and *Fusarium* spp.<sup>[98,113-117]</sup>

#### *In Vivo* Activity

Voriconazole has demonstrated efficacy in animal models of pulmonary, disseminated and intravascular (including endocarditis) fungal infection. The guinea pig is the animal best suited for *in vivo* pharmacokinetic studies of voriconazole as the

plasma pharmacokinetics in guinea pigs are closest to those in humans. In an early study of voriconazole versus itraconazole in endocarditis, voriconazole was superior to itraconazole in both the prevention and treatment of left-sided *A. fumigatus* endocarditis.<sup>[118]</sup> More recently, Kirkpatrick et al.<sup>[119]</sup> performed studies in immunosuppressed guinea pigs with lethal invasive aspergillosis where voriconazole was associated with improved survival and significant reduction in tissue burden of *A. fumigatus*. In a study of disseminated *C. krusei* infection in neutropenic guinea pigs, voriconazole was associated with significantly greater clearance of yeast from the important target organs of brain, liver and kidney.<sup>[120]</sup>

### Pharmacokinetics and Tissue Distribution

Oral voriconazole is rapidly absorbed with maximum plasma concentrations ( $C_{\max}$ ) achieved 1–2 hours after dose administration in the fasted state. The oral bioavailability is 96%, thus allowing switching between intravenous and oral formulations. Administration with high-fat meals resulted in reduced plasma concentrations, so oral dose administration is recommended either 1 hour before or 1 hour after meals.<sup>[92]</sup>

The volume of distribution of voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues.<sup>[92]</sup> Plasma protein binding is moderate at 58%.<sup>[92]</sup> Voriconazole has been detected in brain, liver, kidney, heart, lung and spleen of autopsy specimens as well as the CSF of patients in concentrations approximately 50% that observed in plasma but still at multiples of trough concentrations.<sup>[37,92]</sup> In a comparative study in uninfected rabbits, voriconazole demonstrated prominent distribution into pulmonary epithelial lining fluid, whereas liposomal amphotericin B demonstrated an even distribution of amphotericin B into lung tissue, epithelial lining fluid and pulmonary alveolar macrophages.<sup>[121]</sup>

Metabolism is hepatic, primarily via N-oxidation. The major metabolite, the N-oxide, has no antifungal effect and is not believed to contribute to efficacy. Voriconazole is metabolised via several hepatic CYP isoenzymes, including CYP2C19, CYP2C9 and CYP3A4.<sup>[92]</sup>

As voriconazole has limited aqueous solubility, the intravenous formulation was prepared using a solubilising excipient, sulfobutylether- $\beta$ -cyclodextrin (SBECD). Because of potential concerns of nephrotoxicity and accumulation in plasma, the par-enteral solution of SBECD is not recommended in patients with a glomerular filtration rate <50 mL/min.<sup>[92]</sup>

Voriconazole pharmacokinetics are nonlinear in adults with a greater than proportional increase in plasma concentration with dose escalation.<sup>[122]</sup> Plasma steady state is achieved at approximately day 6 of therapy, but plasma concentrations close to steady state are attained within 24 hours when a loading dose regimen of 6 mg/kg intravenously or 400mg orally every 12 hours for two doses is used.

In children, voriconazole pharmacokinetics appear to be linear to doses of 4 mg/kg every 12 hours.<sup>[123]</sup>

Variability between individuals in plasma voriconazole concentration is high, while within individuals variation is low. Several factors are likely to contribute to this variability.<sup>[92]</sup>

CYP2C19 plays a major role in voriconazole metabolism and demonstrates genetic polymorphism with individuals of oriental descent having a greater likelihood of being poor metabolisers.<sup>[92]</sup>

As voriconazole is a substrate for CYP2C19, 2C9 and 3A4, multiple drug interactions are likely. Table II and table III outline the key data and recommendations regarding voriconazole drug interactions.

The recommended dose administration regimen for voriconazole is a standard loading dose of 6 mg/kg intravenously every 12 hours for two doses followed by 4 mg/kg intravenously every 12 hours for the treatment of invasive aspergillosis or other invasive mould infections with the option to step down to oral therapy at 400mg twice daily. This regimen is based on the pivotal clinical study in invasive aspergillosis where oral step-down therapy was allowed after a minimum of 7 days of intravenous therapy.<sup>[125]</sup> In Europe, voriconazole is also indicated for the treatment of refractory candidal infections, including *C. krusei*.

Dose adjustment is needed for patients with chronic hepatic impairment. A phase I study in patients with Child-Pugh A and B cirrhosis led to the recommendation to give the standard loading doses followed by half the daily maintenance dose in these patients. Patients with severe hepatic cirrhosis have not been studied. Importantly, this recommendation does not apply to patients with acute hepatic injury. Patients with acute injury as a result of graft-versus-host disease, veno-occlusive disease and haemodynamic hepatic injury were included in the pivotal and compassionate/emergency use voriconazole studies.<sup>[92]</sup> On the basis of these data, standard dose administration is recommended for these individuals.

No adjustment of oral voriconazole is needed in individuals with renal dysfunction as voriconazole is metabolised by the liver. The intravenous formulation is solubilised in SBECD that is renally excreted and accumulates in individuals with moderate renal impairment, as defined by a creatinine clear-

**Table II.** Effect of voriconazole on the pharmacokinetics of other drugs<sup>[61,124]</sup>

Drug/drug class	Mechanism of interaction by voriconazole	Drug plasma exposure ( $C_{max}$ and $AUC_T$ )	Recommendation/comments
Sirolimus	CYP3A4 inhibition	Significantly increased	Contraindicated
Rifabutin	CYP3A4 inhibition	Significantly increased	Contraindicated
Terfenadine, astemizole, cisapride, pimozone, quinidine, dofetilide	CYP3A4 inhibition	Likely to be increased (based on available data; not studied)	Contraindicated due to potential for QT prolongation and rare torsade de pointes
Ergot alkaloids	CYP inhibition	Likely to be increased (based on available data; not studied)	Contraindicated
Ciclosporin (cyclosporine)	CYP3A4 inhibition	$AUC_T$ significantly increased, no effect on $C_{max}$	When starting therapy with voriconazole, reduce ciclosporin to one half dose with frequent monitoring of ciclosporin concentrations. When voriconazole discontinued, ciclosporin concentrations must be frequently monitored and the dose increased as necessary
Tacrolimus	CYP3A4 inhibition	Significantly increased	When starting therapy with voriconazole, reduce tacrolimus to one-third of dose with frequent monitoring of tacrolimus concentrations. When voriconazole discontinued, tacrolimus concentrations must be frequently monitored and the dose increased as necessary
Phenytoin	CYP2C9 inhibition	Significantly increased	Frequent monitoring of phenytoin plasma concentrations and frequent monitoring of adverse events related to phenytoin
Warfarin	CYP2C9 inhibition	Prothrombin time significantly increased	Monitor prothrombin time/INR and adjust warfarin dose as needed
Omeprazole	CYP2C19/3A4 inhibition	Significantly increased	When initiating voriconazole therapy in patients receiving omeprazole >40mg, reduce the omeprazole dose by one-half. This effect may be similar for other proton pump inhibitors that are CYP2C19 substrates
HIV protease inhibitors	CYP3A4 inhibition	No significant effect on indinavir exposure; <i>in vitro</i> studies show potential for voriconazole to inhibit metabolism (increased plasma exposure)	No dosage adjustment required for indinavir; frequent monitoring for adverse events/toxicity related to other HIV protease inhibitors
NNRTIs	CYP3A4 inhibition	<i>In vitro</i> studies show potential for voriconazole to inhibit metabolism (increased plasma exposure)	Frequent monitoring for adverse events and toxicity related to NNRTIs
Benzodiazepines	CYP3A4 inhibition	<i>In vitro</i> studies show potential for voriconazole to inhibit metabolism (increased plasma exposure)	Frequent monitoring for adverse events and toxicity (i.e. prolonged sedation) related to benzodiazepines metabolised by CYP3A4; dose adjustment of benzodiazepine may be needed
HMG-CoA reductase inhibitors (statins)	CYP3A4 inhibition	<i>In vitro</i> studies show potential for voriconazole to inhibit metabolism (increased plasma exposure)	Frequent monitoring for adverse events and toxicity related to statins. Increased statin concentrations in plasma have been associated with rhabdomyolysis. Adjustment of the statin dosage may be needed

Continued next page

Table II. Contd

Drug/drug class	Mechanism of interaction by voriconazole	Drug plasma exposure ( $C_{max}$ and $AUC_T$ )	Recommendation/comments
Dihydropyridine calcium channel antagonists	CYP3A4 inhibition	<i>In vitro</i> studies show potential for voriconazole to inhibit metabolism (increased plasma exposure)	Frequent monitoring for adverse events and toxicity related to calcium channel antagonists. Adjustment of calcium channel antagonist dosage may be needed
Sulphonylurea oral hypoglycaemics	CYP2C9 inhibition	Plasma exposure likely increased (based on available data, not studied)	Frequent monitoring of blood glucose and for signs and symptoms of hypoglycaemia. Adjustment of oral hypoglycaemic drug dosage may be needed
Vinca alkaloids	CYP3A4 inhibition	Plasma exposure likely increased (based on available data, not studied)	Frequent monitoring for adverse events and toxicity (i.e. neurotoxicity) related to vinca alkaloids. Adjustment of vinca alkaloid dosage may be needed

**AUC<sub>T</sub>** = area under the concentration-time curve over the dose administration interval; **C<sub>max</sub>** = maximum concentration; **CYP** = cytochrome P450; **INR** = international normalised ratio; **NNRTI** = non-nucleoside reverse transcriptase inhibitor.

ance of <50 mL/min. In a study of parenteral voriconazole in patients with moderate renal dysfunction (creatinine clearance of 30–50 mL/min), the  $AUC_T$  (area under the concentration-time curve over the dose administration interval, here 12 hours) and  $C_{max}$  of SBECD increased by 4-fold and 50%, respectively, compared with controls.<sup>[126]</sup> Thus, oral voriconazole is recommended preferentially in individuals with renal impairment unless the benefits of therapy outweigh the potential risks.<sup>[92,126]</sup>

#### Clinical Efficacy

Voriconazole has been studied in the treatment of a number of invasive fungal infections with efficacy documented in case reports and clinical trials of invasive yeast and mould infections including aspergillosis,<sup>[124,125,127,128]</sup> candidiasis,<sup>[124,129,130]</sup> scedosporiosis and pseudallescheriasis,<sup>[124,131-136]</sup> paecilomycosis,<sup>[137]</sup> fusariosis,<sup>[124,138,139]</sup> coccidioidomycosis,<sup>[140]</sup> cryptococcosis<sup>[124]</sup> and other endemic mycoses.<sup>[124]</sup> Voriconazole has also been studied in invasive fungal infections in children.<sup>[123]</sup>

In a double-blind, double-dummy, international comparative study of voriconazole versus fluconazole for the treatment of endoscopically proven oesophageal candidiasis in AIDS patients, voriconazole was as effective as fluconazole, although voriconazole patients experienced more liver-related adverse events.<sup>[129]</sup> Ostrosky-Zeichner et al.<sup>[130]</sup> reported on 52 patients who received voriconazole as salvage therapy for invasive candidiasis, most of whom had documented progression of disease, had previously received multiple antifungal agents

(mean of two; 83% had received previous azole therapy). In this population, voriconazole was associated with a 56% complete or partial success rate following a mean duration of therapy of 60 days.<sup>[130]</sup> A randomised comparative study of voriconazole versus amphotericin B deoxycholate followed by fluconazole for treatment of candidaemia in non-neutropenic patients has completed and data are expected in 2004. Results of voriconazole therapy in a series of 11 HIV-infected patients from Thailand with *P. marneffe*i infection demonstrated success in eight of nine evaluable patients and no discontinuations as a result of adverse events.<sup>[141]</sup>

Voriconazole has demonstrated efficacy in clinical trials of invasive aspergillosis.<sup>[124,125,128]</sup> In a prospective, international, randomised open-label trial of voriconazole versus amphotericin B deoxycholate followed by other licensed antifungal therapy, patients treated with voriconazole experienced superior success rates and a 22% relative survival benefit.<sup>[125]</sup> In this study, voriconazole was well tolerated with significantly fewer severe drug-related adverse events. Lewis and colleagues<sup>[142]</sup> recently presented data on the pharmacoeconomic impact of this treatment strategy. The cost of other licensed antifungal therapies accounted for 96% of the total drug costs and was higher in the amphotericin B-treated patients (\$US794 328 vs \$US202 176 for voriconazole patients). They found a total drug cost per treatment success of \$US19 409 for amphotericin B compared with \$US10 262 for voriconazole (2003 values).<sup>[142]</sup>

**Table III.** Effect of other drugs on voriconazole pharmacokinetics<sup>[61,124]</sup>

Drug/drug class	Mechanism of interaction by voriconazole	Voriconazole plasma exposure ( $C_{max}$ and $AUC_t$ )	Recommendation for voriconazole dosage adjustment/comments
Rifampin/rifabutin	CYP induction	Significantly reduced	Contraindicated
Carbamazepine	CYP induction	Plasma exposure likely to be significantly reduced (based on available data, not studied)	Contraindicated
Long-acting barbiturates	CYP induction	Plasma exposure likely to be significantly reduced (based on available data, not studied)	Contraindicated
Phenytoin	CYP induction	Significantly reduced	Increase voriconazole maintenance dose from 4 to 5 mg/kg every 12 hours or from 200 to 400mg orally every 12 hours (100 to 200mg orally for patients weighing <40kg)
HIV protease inhibitors	CYP3A4 inhibition	No significant effect on indinavir exposure. <i>In vitro</i> studies show potential for inhibition of voriconazole metabolism (increased plasma voriconazole exposure)	No dosage adjustment in the voriconazole dosage when coadministered with indinavir; frequent monitoring for adverse events and toxicity related to voriconazole when coadministered with other HIV protease inhibitors
Non-nucleoside reverse transcriptase inhibitors	CYP3A4 inhibition or CYP induction	<i>In vitro</i> studies show potential for inhibition of voriconazole metabolism (increased plasma voriconazole exposure)	Frequent monitoring for adverse events and toxicity related to voriconazole

**AUC<sub>t</sub>** = area under the concentration-time curve over the dose administration interval; **C<sub>max</sub>** = maximum concentration; **CYP** = cytochrome P450.

A retrospective series of five patients with documented invasive aspergillosis treated with combination voriconazole and caspofungin demonstrated efficacy with responses in all five, and no deaths attributable to aspergillosis. Companion *in vitro* studies showed additive interactions by fractional inhibitory concentration indices.<sup>[143]</sup>

A retrospective survey of invasive aspergillosis due to *A. terreus* compared voriconazole with other systemic antifungal therapy, mostly with amphotericin B formulations, in terms of survival at 12 weeks.<sup>[144]</sup> In this group, 30 of 83 survived (36%); 16 of 34 voriconazole patients (47%) and 14 of 49 patients (29%) who received other antifungal therapy, thus supporting the role of voriconazole in treating infections due to *A. terreus*.<sup>[144]</sup> Troke et al.<sup>[145]</sup> presented the results of a large retrospective study (n = 86) of voriconazole therapy in documented CNS invasive aspergillosis at the 43rd ICAAC, Chicago, IL, USA, in September 2003. In this heavily pretreated population (96% patients received a median 31 days of prior systemic antifungal therapy), success (complete or partial response) was seen in 35% and survival in 31% (22 patients lived

>3 months, 30 patients lived >1 year).<sup>[145]</sup> Another small study of 19 patients with documented bone aspergillosis demonstrated success (complete or partial response) in 10 of 19 patients (52%) and an acceptable safety profile.<sup>[146]</sup>

In a large international collaborative study of voriconazole versus liposomal amphotericin B for empirical therapy, voriconazole did not meet the prespecified statistical endpoint for non-inferiority in a composite endpoint but was associated with significantly fewer breakthrough invasive fungal infections, particularly invasive aspergillosis.<sup>[147]</sup> In a prespecified secondary efficacy analysis, voriconazole was comparable with liposomal amphotericin B and resulted in a significant reduction of invasive fungal infections among high-risk neutropenic patients. This study has been the focus of debate over the design of empirical therapy trials.<sup>[106,148-150]</sup> Marty and colleagues<sup>[151]</sup> reported on the development of breakthrough zygomycosis in 4 of 24 allogeneic bone marrow or stem cell transplant patients (3%) receiving voriconazole as empirical antifungal therapy or prophylaxis between September 2002 and June 2003. Of note, only two cases

of zygomycosis were recorded in the same institution in the 2 years prior to the availability of voriconazole. This correlates with the lack of *in vitro* activity of voriconazole against zygomycetes and emphasises the importance of pursuing diagnosis of resistant fungal infections in patients at continued risk.<sup>[151,152]</sup>

#### Clinical Safety

Voriconazole is well tolerated, as demonstrated by its improved tolerability compared with amphotericin B deoxycholate and liposomal amphotericin B.<sup>[125,147]</sup> Three specific safety concerns should be considered: visual adverse events; liver function test abnormalities; and skin reactions.

Visual adverse events are the most frequent adverse events associated with voriconazole exposure. Approximately 30% of healthy volunteers or patients experience visual adverse events when exposed to either oral or intravenous voriconazole. Most individuals report transient altered perception of light, photopsia, chromatopsia or photophobia. The visual events typically begin approximately 30 minutes after dose administration and last about 30 minutes. They tend to be reported early in therapy, with few patients reporting events after several days of therapy. The events are mild and led to discontinuation in <1% of patients treated in the clinical development programme.<sup>[92]</sup> Abnormalities in electroretinograms occur with voriconazole therapy, persist for the duration of therapy (studied for 28 days) and completely reverse within 2 weeks of discontinuation of therapy.<sup>[92]</sup>

Hepatic enzyme abnormalities are the dose-limiting adverse event for voriconazole and occur in 12–20% of patients treated with voriconazole.<sup>[92]</sup> Abnormalities of alanine aminotransferase and aspartate aminotransferase are most frequent, but elevations of alkaline phosphatase and total bilirubin have also been reported. Enzyme abnormalities have been seen to normalise in the face of continued dose administration or upon discontinuation of voriconazole, but serious events including hepatic failure and death have been reported. Thus, current recommendations include routine monitoring of hepatic enzymes during therapy. Pharmacokinetic analyses show that the risk of developing hepatic enzyme elevations increases with increasing plasma

voriconazole concentrations.<sup>[153]</sup> Retrospective clinical data from 16 liver transplant patients treated with voriconazole as salvage therapy for invasive fungal infections demonstrate that voriconazole is well tolerated in this population, with a median duration of therapy of 49 days (range 7–439 days), few discontinuations (3 of 16, two of which were treatment related) and is associated with successful outcomes in 9 of 16 patients (56%).<sup>[154]</sup>

Skin rashes were reported in 19% of patients treated in the voriconazole clinical studies. Most were mild and rarely led to discontinuation. Several cases of severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis were reported. In addition, reports have been made about photosensitivity reactions in patients receiving voriconazole.<sup>[155]</sup> The mechanism is unclear as neither voriconazole nor its major metabolite demonstrate absorption in the UVA spectrum. Patients should be advised to avoid sun exposure during voriconazole therapy.

#### 2.2.2 Posaconazole

Posaconazole was developed from itraconazole and, like the other second-generation triazoles, has a broad spectrum of activity against yeasts and moulds. Of note, posaconazole has *in vitro*, *in vivo* and clinical efficacy in treatment of infections due to zygomycetes, organisms for which there are currently limited options. Unlike the other azoles, posaconazole is only available in an oral formulation and requires frequent dose administration.

#### *In Vitro* Activity

Posaconazole demonstrates potent *in vitro* activity against *Candida* spp. (including clinical isolates and non-albicans species), *Aspergillus* spp., *Scedosporium* spp., *Fusarium* spp., *C. neoformans*, *Coccidioides* spp., *Histoplasma* spp., *Trichosporon* spp. and many other yeasts, moulds and dematiaceous moulds.<sup>[95,96,113,115-117,156-161]</sup>

Like voriconazole, posaconazole demonstrates *in vitro* fungicidal activity against *Aspergillus* spp.<sup>[100]</sup> Importantly, posaconazole also demonstrates activity against zygomycetes.<sup>[97,99]</sup> In comparative studies, posaconazole was more potent than voriconazole, fluconazole, itraconazole, and is at least as potent as amphotericin B, distinguishing it from all available azoles.

### In Vivo Activity

Posaconazole has demonstrated activity in a number of animal models of invasive fungal infection. In rabbit models of invasive aspergillosis, including *A. terreus*, an organism inherently resistant to amphotericin B, posaconazole was associated with improved survival, decreased severity of pulmonary infection, significantly decreased tissue burden of *Aspergillus* spp., as well as decreases in galactomannan antigenaemia.<sup>[162-164]</sup> Compared with itraconazole and amphotericin B in a model of invasive pulmonary *A. fumigatus* infection in neutropenic rabbits, posaconazole was associated with significantly greater survival, reduction in pulmonary injury, lower residual fungal burden and lower levels of galactomannan antigenaemia than was itraconazole at similar dosages and plasma concentrations.<sup>[163]</sup> Administered in combination, posaconazole and caspofungin demonstrated survival greater to that seen with each single agent in an immunocompetent mouse model of invasive aspergillosis.<sup>[165]</sup>

Posaconazole was compared with itraconazole and amphotericin B in a neutropenic mouse model of zygomycosis using three clinical *Mucor* isolates. In this setting, posaconazole demonstrated a dose-dependent survival advantage and decrease in residual tissue fungal burden compared with itraconazole, which was associated with survival and residual tissue fungal burden similar to that of control animals. At the doses tested, posaconazole was comparable with amphotericin B in terms of survival and efficacy.<sup>[166]</sup>

In other models, posaconazole demonstrated efficacy in treatment of *P. boydii*, histoplasmosis (survival advantage compared with itraconazole and amphotericin B in a T-cell-depleted mouse model) and cryptococcosis (survival advantage, decreased tissue burden compared with amphotericin in brain tissue in mouse model).<sup>[156,158,167,168]</sup>

### Pharmacokinetics and Tissue Distribution

In a healthy volunteer study of posaconazole in the fasted state, splitting the dose significantly increased exposure. Thus, the current recommended dose is 200mg orally four times each day.<sup>[169]</sup> Posaconazole in single and multiple doses in healthy

adults was well tolerated and demonstrated dose-proportional AUC between 50 and 800mg.<sup>[170]</sup> Saturation of absorption was observed at doses above 800mg, presumably because of the poor solubility of posaconazole.

The apparent volume of distribution is large (343–1341L) with a long-terminal phase  $t_{1/2}$  (25–31 hours), suggesting extensive distribution in to tissues and supporting once or twice daily dose administration.<sup>[170]</sup> A human case report documented presence of posaconazole in vitreous fluid (plasma concentration 1.2 µg/mL, vitreous concentration 0.25 µg/mL).<sup>[171]</sup>

Bioavailability of posaconazole increases with high-fat meals or nutritional supplements:  $C_{max}$  increased 3.4-fold and AUC 2.6-fold with Boost Plus™ 1.<sup>[172]</sup> Posaconazole interacts with tacrolimus, causing increased tacrolimus  $C_{max}$  (2.2-fold) and AUC<sub>τ</sub> (4.5-fold); this is likely to be because of the inhibition of CYP3A4 metabolism and P-glycoprotein transport of tacrolimus by posaconazole.<sup>[173]</sup>

### Clinical Efficacy

Posaconazole capsules and suspension demonstrated comparable efficacy to fluconazole in phase II studies of oesophageal candidiasis.<sup>[174,175]</sup> In an open-label, noncomparative, multicentre study of posaconazole as salvage therapy for invasive fungal infections, posaconazole was associated with success at week 4 in 8 of 15 patients with invasive aspergillosis (53%), three of four patients with candidiasis, three of four patients with fusariosis and seven of ten patients with infections due to other fungal pathogens.<sup>[176]</sup> Posaconazole demonstrated success in 9 of 21 patients (43%) treated for refractory invasive fungal infections in a recently presented open-label pharmacokinetic study.<sup>[177]</sup> In a multicentre study of posaconazole therapy for chronic pulmonary or nonmeningeal disseminated coccidioidomycosis, 15 of 20 patients completed ≥23 weeks of therapy.<sup>[178]</sup>

An open-label study of posaconazole as salvage therapy for fungal infections of the CNS (n = 49) demonstrated success in 40% of patients with brain infection due to filamentous fungi and 59% of those with HIV-associated cryptococcal meningitis.<sup>[179]</sup>

1 The use of trade names is for product identification purposes only and does not imply endorsement.



A pooled analysis of patients from two open-label studies of posaconazole for salvage therapy (75% patients refractory to prior therapy, 25% intolerant) of zygomycosis demonstrated success in 17 of 24 patients (71%) and survival in 16 of 24 (67%) after a mean duration of 137 days (6–352 days) of therapy.<sup>[180]</sup> Results of an open-label, uncontrolled study of posaconazole as salvage therapy for invasive fungal infections in patients with chronic granulomatous disease demonstrated complete response in six of seven patients refractory to (n = 6) or intolerant of (n = 1) previous voriconazole therapy.<sup>[181]</sup>

Among seven patients with histoplasmosis refractory to or intolerant of licensed antifungal therapy, posaconazole as salvage therapy was associated with success in six, including one with documented CNS histoplasmosis and stable disease in one.<sup>[182]</sup> Posaconazole has been reported to be effective in cases of *Acremonium strictum* pulmonary infection failing amphotericin B,<sup>[183]</sup> *S. apiospermum* brain abscess failing therapy with amphotericin B and ketoconazole,<sup>[184]</sup> ocular and systemic invasive *F. solani* infection of the eye,<sup>[171]</sup> and mucormycosis in a heart-kidney transplant patient.<sup>[185]</sup> In a series of 13 patients with chronic indolent infections with mycetoma (n = 7) or chromoblastomycosis (n = 6) refractory to or intolerant of standard therapy, posaconazole was tolerated for long durations (>6 months in ten patients, >1 year in five patients) and success was documented in 11 of 15 patients (73%).<sup>[186]</sup>

#### Clinical Safety

In comparative studies versus fluconazole for the treatment of oesophageal candidiasis, posaconazole was not associated with any increased or different adverse events.<sup>[175]</sup> In a noncomparative multicentre study of posaconazole as salvage therapy for invasive fungal infections, the most commonly reported adverse events were diarrhoea, asthenia, flatulence and eye pain.<sup>[176]</sup>

### 2.2.3 Ravuconazole

Ravuconazole is a derivative of fluconazole with an expanded spectrum of activity *in vitro*. It is available in oral form. A di-lysine phosphoester prodrug has been developed to facilitate intravenous administration.

#### *In Vitro* Activity

Ravuconazole demonstrates potent *in vitro* activity against *Candida* spp. (including the more resistant species *C. glabrata* and *C. krusei*), *Aspergillus* spp., *Scedosporium* spp. and *Fusarium* spp., *C. neoformans*, *Coccidioides* spp., *Histoplasma* spp. and *Trichosporon* spp., as well as other yeasts and moulds.<sup>[96,117,187-191]</sup> Like voriconazole, ravuconazole is fungicidal *in vitro* against *Aspergillus* spp.<sup>[100]</sup> Ravuconazole is active against *S. apiospermum*,<sup>[113]</sup> but less potent against *Fusarium* spp.<sup>[116]</sup>

#### *In Vivo* Activity

Ravuconazole demonstrates activity in experimental models of infections due to *Candida*, *Aspergillus* and *Cryptococcus* spp., including in immunocompromised models.<sup>[192-194]</sup> Efficacy was better than anidulafungin in a comparative rabbit model of disseminated aspergillosis where improved survival and decreased *Aspergillus* antigenaemia were observed, along with an elimination of organisms from tissue.<sup>[86]</sup> In a model of invasive pulmonary aspergillosis due to *A. fumigatus* in persistently neutropenic rabbits, ravuconazole demonstrated significant dose-dependent improvement in survival, and reduction in residual tissue fungal burden, pulmonary injury, and decrease in organisms recovered by bronchoalveolar lavage and serum galactomannan index compared with untreated controls.<sup>[195]</sup>

#### Pharmacokinetics and Tissue Distribution

In humans, ravuconazole has been studied in single- and multiple-dose studies in healthy volunteers. In these settings, ravuconazole was well tolerated to dosages of 800mg once daily or 400 mg/day for 14 days.<sup>[196,197]</sup> Single parenteral doses of 25–600mg BMS-379224, the water-soluble prodrug of ravuconazole, were well tolerated, demonstrated rapid conversion to ravuconazole and linear plasma pharmacokinetics.<sup>[198]</sup>

## 3. Future Directions

The last few years have seen the availability of several new antifungal agents that provide increased efficacy and safety to immunosuppressed patients. The echinocandins and second-generation triazole antifungal agents bring new choices and advances in our ability to treat invasive yeast and mould infec-

tions. However, the morbidity and mortality from these infections remains unacceptable, especially for the patients at highest risk, those with prolonged immunosuppression, haematological malignancy or bone marrow transplantation. Unanswered questions include: what role will the new diagnostic tools, especially the galactomannan antigenaemia assay, play in our ability to diagnose infection earlier and adapt our treatment strategies? Will newer classes of antifungal agents prove to be more active and safer than triazoles or echinocandins? Will the addition of recombinant cytokines to the newer antifungal agents improve outcome? Which drugs should be used in what combinations and how should they best be studied? The answers to these and other questions will define the future directions and advances in antifungal therapy.

## Acknowledgements

The authors have provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

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