Voriconazole: A New Triazole Antifungal Agent

S. Scott Sutton, PharmD

Introduction

Voriconazole (VFEND®, Pfizer) is a new wide-spectrum, second-generation triazole antifungal drug that is structurally related to fluconazole (Diflucan®, Pfizer). Voriconazole has a replacement of one triazole moiety of fluconazole by a fluoropyrimidine grouping with an additional alpha methylation. This structural modification has led to a more potent compound with fungicidal activity against Aspergillus species. As with other triazole antifungals, the primary mechanism of action is the inhibition of fungal cytochrome P-450-dependent 14α-lanosterol demethylation.

Voriconazole is indicated for the primary treatment of invasive aspergillosis (IA) and for the treatment of serious fungal infections caused by Scedosporium apiospermum and Fusarium species in patients who are intolerant of, or whose condition is refractory to, other therapies.

Pharmacokinetics

The pharmacokinetic parameters of voriconazole are nonlinear and display a disproportionate elevation of serum concentrations with increasing doses. Concentrations of the drug increase up to eight-fold after multiple doses because of a saturation of its own metabolism.

Voriconazole is rapidly absorbed after oral administration and reaches maximum plasma concentrations (Cmax) within two hours in normal, healthy, fasting volunteers. The oral bioavailability is estimated to be 96% after administration in healthy subjects, and switching from intravenous (IV) to oral voriconazole is appropriate when it is clinically indicated. Consuming a high-fat meal decreases the drug’s bioavailability, and administering voriconazole with food alters the time to maximum plasma concentration from one hour to 2.5 hours.

Steady-state trough plasma concentrations are obtained within one day following a loading dose and within five days without a loading dose. Voriconazole is metabolized by the cytochrome P-450 hepatic enzymes CYP2C19, CYP2C9, and CYP3A4. It is eliminated by hepatic metabolism, and less than 2% of the dose is excreted unchanged in the urine.

Pharmacogenomics

CYP2C19 exhibits genetic polymorphism and is extensively involved in the metabolism of voriconazole. Voriconazole levels may increase four-fold in patients who are poor metabolizers of CYP2C19 substrates. Approximately 20% of those of Asian ancestry and 3% to 5% of whites are poor metabolizers and have predictably higher voriconazole concentrations. Currently, no studies have definitively correlated voriconazole concentrations with adverse drug reactions (ADRs), although increased concentrations of this drug have been associated with ADRs.

Clinical Trials

Trials involving voriconazole have focused on primary or salvage therapy in patients with Aspergillus, Fusarium, and Scedosporium infections; esophageal candidiasis; and neutropenic

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fever. Table 1 summarizes the results of clinical trials with voriconazole.

**Invasive Aspergillosis**

**The Herbrecht Study**

Herbrecht et al. compared the efficacy, survival, and safety of voriconazole and amphotericin B deoxycholate (Amphocin®, Pharmacia & Upjohn; Fungizone®, Geneva) as the primary therapy for invasive aspergillosis. In this unblinded trial, patients were randomly assigned to receive a loading dose of IV voriconazole 6 mg/kg every 12 hours on day one, followed by a maintenance dose of 4 mg/kg every 12 hours or IV amphotericin B deoxycholate 1 to 1.5 mg/kg daily. After receiving IV voriconazole for seven days, the patients could be switched to twice-daily oral voriconazole 200 mg. Other licensed antifungal therapy (OLAT) was allowed if the initial therapy failed or if the patient was intolerant of the initial agent. Patients receiving OLAT were included in the analyses.

- A *complete* or *partial response* was considered a successful outcome; a *stable* response or disease progression was considered an unsuccessful outcome.
- A *complete response* was defined as resolution of all clinical symptoms and more than a 90% improvement in the appearance of the lesions (resulting from invasive aspergillosis) that were visible by radiology.
- A *partial response* was defined as clinical improvement and a 50% improvement in radiographic lesions.
- A *stable response* was defined as no change in clinical symptoms and less than a 50% change in radiographic lesions.
- A *treatment failure* was defined as disease progression.

Patients enrolled in the study had either definitive or probable aspergillosis. The planned duration of therapy was 12 weeks. Most patients had an allogeneic hematopoietic cell transplant, acute leukemia, or another hematological disease.

There were 144 patients in the voriconazole group and 133 patients in the amphotericin B group. The median duration of treatment with voriconazole was 77 days (range, 2 to 84 days). The median duration of IV therapy with voriconazole was 10 days (range, 2 to 78 days). The median duration of amphotericin B treatment was 10 days (range, 1 to 84 days). OLAT was given to 52 patients in the voriconazole group and to 107 patients in the amphotericin B group.

At 12 weeks, the voriconazole group experienced significantly better outcomes. The success rate for voriconazole was 52.8% (76/144) and 31.6% (42/133) for the amphotericin B group in a modified intention-to-treat population. The absolute difference was 21.2%, and the number needed to treat was 4.7. Therefore, 4.7 patients would have had to be treated with voriconazole for 12 weeks to have a successful outcome, compared with the number needed for amphotericin B. According to the study’s confidence interval (CI) (95% CI, 10.4–32.9), voriconazole was found to be superior to amphotericin B.

The intention-to-treat population demonstrated similar results. The successful outcome with voriconazole was 49.7% in this population, in contrast to 27.8% for the amphotericin B group. This represents an absolute difference of 21.9% and a number needed to treat of 4.6.

At the end of the initial period of randomized therapy, 53.5% of voriconazole patients in the modified intention-to-treat population responded satisfactorily, in contrast to 21.8% of the amphotericin B group. In the voriconazole group, the survival

### Table 1 Summary of Voriconazole Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Design</th>
<th>Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbrecht et al.</td>
<td>Invasive Aspergillosis</td>
<td>R, P, MC, OL</td>
<td>VCZ 6 mg/kg IV q12h x two doses, then 4 mg/kg IV q12h (oral 200 mg q12h allowed after day 7), AMB, 1.0–1.5 mg/kg once daily x 14 days</td>
<td>Success rate: •VCZ, 53% •AMB, 32% Complete and partial responses: 48%</td>
</tr>
<tr>
<td>Denning et al.</td>
<td>Invasive Aspergillosis</td>
<td>P, MC, NC, OL</td>
<td>VCZ 6 mg/kg IV q12h x two doses, then 3 mg/kg IV q12h for 6–27 days, then 200 mg PO q12h for 4–24 weeks</td>
<td></td>
</tr>
<tr>
<td>Walsh et al.</td>
<td>Febrile Neutropenia</td>
<td>R, P, MC, OL</td>
<td>VCZ 6 mg/kg IV q12h x two doses, then 3 mg/kg IV q12h (oral 200 mg q12h allowed after day 3), L-AMB, 3–6 mg/kg IV once daily</td>
<td>Success rate by composite outcome score: •VCZ, 26% •L-AMB, 30.6%</td>
</tr>
<tr>
<td>Ally et al.</td>
<td>Esophageal Candidiasis</td>
<td>R, P, DB, DD, MC</td>
<td>VCZ 200 mg PO b.i.d., FLU 400 mg PO x one dose, then 200 mg PO once daily</td>
<td>Esophagoscopically proven cure: •VCZ, 94.8% •FLU, 90.1%</td>
</tr>
</tbody>
</table>

AMB = amphotericin B deoxycholate; b.i.d. = twice daily; DB = double-blind; DD = double-dummy; FLU = fluconazole; IV = intravenous; L-AMB = liposomal amphotericin B; MC = multicenter; NC = noncomparative; OL = open label; P = prospective; PO = oral; R = randomized; VCZ = voriconazole; q12h = every 12 hours.

rate was 70.8%; in the amphotericin B group, it was 57.9%.

The authors concluded that voriconazole was superior to amphotericin B as initial therapy for invasive aspergillosis in terms of response rate, survival rate, and safety.

The Denning Study
Denning et al. evaluated the efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis in an open, noncomparative multicenter trial for patients older than age 14 years who had definite or probable invasive aspergillosis. Voriconazole could be given as primary therapy or as salvage therapy when amphotericin B deoxycholate, liposomal amphotericin B (L-AMB) (AmBisome®, Fujisawa) and other liposomal products, or itraconazole (Sporanox®, Janssen/Ortho Biotech) was considered ineffective or toxic. Outcomes for patients receiving voriconazole were defined as complete, partial, stable, or failed:

- A complete response indicated resolution of all clinical signs and symptoms and complete or nearly complete resolution on radiography.
- A partial response indicated major improvement or resolution of clinical signs and symptoms and at least a 50% improvement in radiographic findings.
- A stable response was defined as an intermediate response and less than a 50% improvement in radiographic findings.
- A failed response was defined as disease progression and death resulting from the infection.

A good response was used to denote both complete and partial outcomes.

The initial therapy consisted of IV voriconazole for six to 27 days. The drug was administered with two IV loading doses of 6 mg/kg every 12 hours, followed by 3 mg/kg intravenously every 12 hours, and then orally administered therapy (200 mg twice daily) for four to 24 weeks. Patients were monitored for 30 days after discontinuation of voriconazole.

The drug was assessed for efficacy in 116 patients and for safety in 137 patients. A diagnosis of invasive aspergillosis was “confirmed” in 48 (41%) and “probable” in 68 patients (59%). Voriconazole was administered as primary therapy in 60 (52%) of the patients. Patients classified as having probable aspergillosis had better response rates than those considered to have a definite diagnosis of aspergillosis (38% vs. 58%, P = .05).

Overall, 56 patients (48%) experienced a good response, 16 patients (14%) had a complete response, 40 patients (34%) had a partial response, and 24 patients (21%) had a stable response to voriconazole; 36 (31%) patients did not respond to therapy. A good response was seen in 60% of patients with pulmonary or tracheobronchial invasive aspergillosis (n = 84), 16% with cerebral invasive aspergillosis (n = 19), in 58% with hematologic disorders (n = 67), and in 26% who had undergone allogeneic stem cell transplantation (n = 23).

The authors concluded that voriconazole was efficacious for treating acute invasive aspergillosis.

Febrile Neutropenia
The Walsh Study
Walsh et al. compared voriconazole with L-AMB as empirical antifungal therapy in patients with neutropenia and persistent fever. Patients were randomly assigned to receive

### Table 2 Effect of Voriconazole on the Pharmacokinetics of Various Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Mechanism</th>
<th>Result</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (WAR) (Coumadin®, DuPont)</td>
<td>↑</td>
<td>CYP2C9 inhibition</td>
<td>↑ PT/INR</td>
<td>Monitor PT/INR; adjust WAR dose if necessary</td>
</tr>
<tr>
<td>Phenytoin (PHT) (Dilantin®, Parke-Davis)</td>
<td>↑</td>
<td>CYP2C9 inhibition</td>
<td>↑ PHT AUC ≈ 80%</td>
<td>Monitor PHT level and related PHT adverse events</td>
</tr>
<tr>
<td>Omeprazole (OME) (Prilosec®, AstraZeneca)</td>
<td>↑</td>
<td>CYP3A4 inhibition</td>
<td>↑ OME C(_{\text{max}}) × 3.8 ↑ OME AUC × 2.2</td>
<td>↓ OME dose by one-half in patients taking ≥ 40 mg when starting VCZ</td>
</tr>
<tr>
<td>Rifabutin (RIF) (Mycobutin®, Pharmacia &amp; Upjohn)</td>
<td>↑</td>
<td>CYP3A4</td>
<td>↑ RIF</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Tacrolimus (TAC) (Prograf®, Fujisawa)</td>
<td>↑</td>
<td>CYP3A4 inhibition</td>
<td>↑ TAC C(_{\text{max}}) × 2.2 ↑ TAC AUC × 3.2</td>
<td>↓ TAC dose by one-third when starting VCZ; monitor levels frequently</td>
</tr>
<tr>
<td>Sirolimus (SIR) (Rapamune®, Wyeth-Ayerst)</td>
<td>↑</td>
<td>CYP3A4 inhibition</td>
<td>↑ SIR levels</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Cyclosporine (CSA) (Gengraf™, Abbott; Neoral, Sandimmune®, Novartis)</td>
<td>↑</td>
<td>CYP3A4 inhibition</td>
<td>↑ CSA AUC ≈ 70% ↑ CSA trough × 2.5</td>
<td>↓ CSA dose by one-half when starting VCZ; monitor CSA levels frequently</td>
</tr>
</tbody>
</table>

*Please consult the most up-to-date package insert for accurate drug interactions.

AUC = area under the curve; C\(_{\text{max}}\) = maximum plasma concentration; INR = International Normalized Ratio; PT = prothrombin time; VCZ = voriconazole.

Data from VFEND® (voriconazole) package insert. New York: Pfizer; 2002.
Voriconazole or L-AMB. Voriconazole was administered as an IV loading dose of 6 mg/kg every 12 hours on day 1, followed by an IV maintenance dose of 3 mg/kg every 12 hours. Twice-daily oral voriconazole 200 mg was allowed after at least three days of IV therapy. IV L-AMB was administered in a dose of 3 mg/kg daily. Treatment was continued for up to three days after neutrophil recovery, for an absolute neutrophil count (ANC) greater than or equal to 250 cells/mm³ or up to 12 weeks in patients with documented invasive fungal infections.

The investigators measured overall success rates of voriconazole and L-AMB using a composite outcome score consisting of the following parameters:

- No occurrence of breakthrough fungal infections
- Survival of patients for seven days beyond the end of therapy
- No premature discontinuation of therapy
- Resolution of fever during the period of neutropenia
- Successful treatment of all baseline fungal infections

A total of 415 patients receiving voriconazole and 422 patients receiving L-AMB were included in the modified intention-to-treat analysis. The overall success rate was 26% (108 patients) for voriconazole and 30.6% (129 patients) for L-AMB (95% CI for the difference, −10.6 to 1.6). The only significant difference among the five components for the composite score was the frequency of breakthrough fungal infections (voriconazole with eight patients and L-AMB with 21 patients, P = .02). There were fewer cases of documented breakthrough invasive aspergillosis, candidemia, and dematiaceous mold infections among the voriconazole patients and fewer cases of zygomycosis among the L-AMB patients. The mortality rate from breakthrough fungal infections was higher than the overall mortality in the study (48.3% vs. 12.9%, P = .001).

Three hundred eighty-two voriconazole patients (92.0%) and 397 L-AMB patients (94.1%) survived for seven days after the end of therapy (95% CI for the difference, −5.5 to 1.4). Forty-one voriconazole patients and 28 L-AMB patients discontinued therapy because of toxicity or lack of efficacy before recovery from neutropenia (95% CI for the difference, −7.0 to 0.5). The number of patients who discontinued therapy as a result of toxicity was similar in both groups (19 voriconazole patients and 23 L-AMB patients). However, discontinuations from therapy were more numerous because of a lack of efficacy in the patients receiving voriconazole (in 22 vs. 5 patients). Persistent fever was the most common reason for withdrawal (in 14 vs. 2 patients).

Despite the withdrawals attributable to persistent fever, the overall frequency of, and the time to, fever resolution were nearly identical in the study groups; fever resolved in 135 voriconazole patients (32.5%) and in 154 L-AMB patients (36.5%) while they had neutropenia (95% CI for the difference, −10.4 to 2.5). The complete or partial response of patients with baseline fungal infections by the end of treatment was 46.2% (6/13) in the voriconazole group and 66.7% (4/6) in the L-AMB group (95% CI for the difference, −67.0 to 25.9).

A secondary analysis of individual composite scores showed that among patients at high risk (e.g., those with an allogeneic transplant or with relapsed leukemia), the overall success rate was 32% for the voriconazole group and 30% for the L-AMB group (95% CI for the difference, −9.0 to 12.4). Among the patients at moderate risk, the overall success rate was 23% for voriconazole and 31% for L-AMB (95% CI for the difference, −15.2 to −0.4).

This difference in the drug’s efficacy for the moderate-risk patients was a result of a disparity in mortality from progressive cancer. The moderate-risk patients had a lower risk for fungal infections but not for death from other causes. There were significantly fewer breakthrough fungal infections in high-risk patients in the voriconazole group (1.4% vs. 9.2%, P = .003); these patients had shorter hospitalization stays, with a median difference of two days (P = .03).

### Table 3 Effect of Various Medications on the Pharmacokinetics of Voriconazole*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
<th>Mechanism</th>
<th>Result</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin (Rifadin®, Aventis)</td>
<td>↓ VCZ</td>
<td>CYP-450 induction</td>
<td>↓ C&lt;sub&gt;max&lt;/sub&gt; ↓ AUC</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Rifabutin (Mycobutin®, Pharmacia &amp; Upjohn)</td>
<td>↓ VCZ</td>
<td>CYP-450 induction</td>
<td>↓ C&lt;sub&gt;max&lt;/sub&gt; ↓ AUC</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Phenytoin (Diantin®, Parke-Davis)</td>
<td>↓ VCZ</td>
<td>CYP-450 induction</td>
<td>↓ C&lt;sub&gt;max&lt;/sub&gt; ↓ AUC</td>
<td>↑ VCZ dose to 5 mg/kg IV or 400 mg PO q12h</td>
</tr>
<tr>
<td>Carbamazepine (Carbatrol®, Shire US, Inc.; Tegretrol®, Novartis) (not studied—predicted outcome)</td>
<td>↓ VCZ</td>
<td>CYP-450 induction</td>
<td>↓ C&lt;sub&gt;max&lt;/sub&gt; ↓ AUC</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Long-acting barbiturates (not studied—predicted outcome)</td>
<td>↓ VCZ</td>
<td>CYP-450 induction</td>
<td>↓ C&lt;sub&gt;max&lt;/sub&gt; ↓ AUC</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

*Please consult the most up-to-date package insert for accurate drug interactions.

AUC = area under the curve; C<sub>max</sub> = maximum plasma concentration; CYP-450 = cytochrome P-450; IV = intravenous; PO = oral; q12h = every 12 hours; VCZ = voriconazole.

Data from VFEND® (voriconazole) package insert. New York: Pfizer; 2002.
The authors concluded that voriconazole was an appropriate agent for empirical therapy in febrile neutropenia and that it could be used as an alternative to amphotericin B. Voriconazole is not currently approved as empirical therapy for febrile neutropenia.

Candidiasis
The Ally Study

Ally et al. compared the efficacy, safety, and tolerability of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Patients were randomly assigned to receive either voriconazole 200 mg twice daily or fluconazole 400 mg on day one, followed by 200 mg once daily. The duration of therapy ranged from two to six weeks, depending on the severity of the esophageal infection and the response to treatment. Treatment was continued for seven days after signs and symptoms resolved but could not exceed 42 days of therapy.

The primary efficacy analysis was the response to treatment, as assessed by esophagoscopy. The primary success rate was defined as cure plus improvement. For secondary efficacy outcomes, the authors evaluated patients’ symptomatic relief of esophageal and oropharyngeal candidiasis as well as their time to clinical cure.

In the primary efficacy analysis, a total of 94.8% (109 patients) receiving voriconazole and 90.1% (127 patients) receiving fluconazole demonstrated cure, as confirmed by endoscopy. The success rate (cure plus improvement) for esophageal candidiasis was 98.3% in the voriconazole group and 95.1% in the fluconazole group (95% CI for the difference, –1.0 to 7.5).

In the secondary efficacy analysis, 82% (164 patients) receiving voriconazole and 83.2% (159 patients) receiving fluconazole achieved symptomatic relief. The success rate (symptom relief plus improvement) was 88% in the voriconazole group and 91.1% in the fluconazole group (95% CI for the difference, –9.2 to 3.0). The success rate for oropharyngeal candidiasis, as assessed from resolution of symptoms, was 88.4% for the voriconazole patients and 93.8% for the fluconazole patients (95% CI for the difference, –12.0 to 1.0).

The authors concluded that voriconazole was at least as effective as fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Voriconazole is not indicated for the treatment of esophageal candidiasis at this time.

Clinical trials are under way to evaluate voriconazole in invasive candidiasis. In vitro studies show that voriconazole is fungistatic against Candida species and displays non–concentration-dependent pharmacodynamics. The activity of voriconazole in vitro is more potent against Candida species compared with that of fluconazole and itraconazole. It remains active in vitro against fluconazole-resistant Candida species, including C. glabrata and C. krusei. Voriconazole has higher minimum inhibitory concentrations against fluconazole-resistant Candida species, as compared with fluconazole-susceptible isolates. This finding suggests the possibility of cross-resistance between fluconazole and voriconazole.

Drug Interactions

Voriconazole is a substrate and inhibitor of CYP2C19, 2C9, and 3A4 hepatic cytochrome P-450 enzymes; thus, numerous drug interactions exist with other substrates, inhibitors, and inducers of these enzymes. Tables 2 and 3 summarize some of the clinically significant drug interactions involving voriconazole.

Adverse Drug Reactions

Voriconazole has been well tolerated with minimal ADRs in patients who received normal therapeutic doses. The most commonly reported adverse drug events (ADEs) have included dose-dependent and reversible visual disturbances, fever, rash, nausea, vomiting, diarrhea, elevated liver-function test scores, headache, sepsis, peripheral edema, abdominal pain, and respiratory disorders.

Vision Changes

Visual disturbances have been commonplace in therapeutic trials with voriconazole. Approximately 30% of patients have experienced altered or enhanced visual perception, blurred vision, changes in color vision, and/or photophobia. Visual adverse reactions were generally mild and led to discontinuation of the medication in fewer than 1% of patients. These visual changes may be associated with increased voriconazole serum concentrations and can be linked to patients who are poor metabolizers of the CYP2C19 substrate.

The mechanism behind this ADR is unknown, but is thought to involve the retina. Voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude, a decrease in the visual field, and an alteration in color perception in healthy volunteers. The visual effects typically occurred within 30 minutes after a voriconazole dose and lasted approximately 30 minutes. The ADE led to a discontinuation rate of less than 1% in one study and was most frequent during the first week of therapy.

Skin Reactions

Dermatological reactions are common with the use of voriconazole. Most of the rashes were mild to moderate and occurred in 6% of patients in clinical trials. There have been rare reports of serious reactions, such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme with voriconazole administration.

Hepatic Function

Elevated liver-function test scores (range, 4.3% to 26.5%) have been reported with voriconazole therapy. The incidence of clinically significant elevations in transaminase levels was 13.4% in clinical trials. These elevations may be related to increased serum concentrations of voriconazole and are reversible following discontinuation of the drug. This may predispose patients who are slow metabolizers of CYP2C19 substrates to a higher incidence of elevated transaminase levels. Voriconazole has been infrequently associated with hepatic toxicity, and there have been rare cases of hepatitis and hepatic failure that have resulted in death. Liver-function tests
should be monitored before voriconazole therapy begins and during the course of therapy.\(^3\)

**Dosage and Administration**

Voriconazole is administered as an IV loading dose of 6 mg/kg every 12 hours for two doses, followed by an IV maintenance dose of 4 mg/kg every 12 hours.\(^3\) When therapy is stepped down to oral voriconazole, the dosage is 200 mg every 12 hours for patients weighing more than 40 kg and 100 mg every 12 hours for patients weighing less than 40 kg.\(^3\) If patients do not respond to treatment, the oral voriconazole dose may be increased to 300 mg every 12 hours for those weighing more than 40 kg and to 150 mg every 12 hours for patients weighing less than 40 kg.\(^3\)

Dosage adjustments are recommended for patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B).\(^2,3\) A normal loading dose and one-half of the maintenance dose are recommended.\(^2,3\) No data are available for patients with severe hepatic cirrhosis (Child-Pugh Class C), chronic hepatitis B, or chronic hepatitis C.\(^3\)

The IV formulation of voriconazole is prepared with the vehicle sulfo-butyl-ether-cyclodextrin (SBECD) to increase solubility.\(^2,3\) In patients with moderate renal insufficiency (a creatinine clearance of 35–50 ml/minute), the effect on SBECD concentrations is significant.\(^2,3\) In animal studies, SBECD has been correlated with histological effects on the kidney.\(^3\) Therefore, IV voriconazole should be avoided in patients with mild to moderate renal insufficiency (a creatinine clearance of less than 50 ml/minute) unless the benefits outweigh the risks.\(^3\) The use of oral voriconazole is recommended in patients with renal insufficiency.\(^2,3\)

**Pharmacoeconomics**

For patients with invasive aspergillosis, the acquisition costs of two-week regimens can be considerable, depending on the antifungal agent selected. The treatment guidelines recommend IV therapy in acutely ill patients until progression of the disease is arrested, followed by oral therapy for prolonged treatment.\(^15\) Before the introduction of voriconazole, amphotericin B deoxycholate and lipid formulations of amphotericin B had been the standard treatment for invasive aspergillosis.\(^15\) Itraconazole had been the oral alternative to amphotericin B in patients with arrested disease.\(^15\)

Table 4 summarizes the costs of some antifungal agents. All costs are based on the average wholesale price (AWP). Some typical prices are as follows:

- IV voriconazole for a 70-kg patient for one week, followed by one week of oral voriconazole: $2,220\(^16\)
- IV amphotericin B deoxycholate for a 70-kg patient for one week, followed by oral itraconazole for one week: $357.80\(^17\)
- IV amphotericin B lipid complex (ABLC; Abelcet®, Elan) for a 70-kg patient for one week, followed by oral itraconazole for one week: $6,050.16\(^17\)
- IV L-AMB for a 70-kg patient for one week, followed by oral itraconazole for one week: $9,509.14\(^17\)

### Table 4 Daily Cost Comparison (Average Wholesale Price) of Current Aspergillosis Antifungal Drugs for a 70-kg Patient

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>1–1.5 mg/kg/day IV</td>
<td>$37.18</td>
</tr>
<tr>
<td>(Amphocin®, Pharmacia &amp; Upjohn; Fungizone®, Geneva)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>3–5 mg/kg day IV</td>
<td>$1,318.80</td>
</tr>
<tr>
<td>(AmBisome®, Fujisawa)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B lipid complex for injection (Abelcet®, Elan)</td>
<td>5 mg/kg/day IV</td>
<td>$824.66</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
<td>3–4 mg/kg/day IV</td>
<td>$480.00</td>
</tr>
<tr>
<td>(Amphotec®, InterMune)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole (Sporanox®, Janssen/Ortho Biotech)</td>
<td>200 mg IV b.i.d. x 2 days, then 200 mg IV once daily or 200 mg PO t.i.d. x 3 days, then 200 mg PO b.i.d.</td>
<td>$369.74, $1,84.87</td>
</tr>
<tr>
<td>Voriconazole (VFEND®, Pfizer)</td>
<td>6 mg/kg IV q12h x 1 day, then 4 mg/kg IV q12h, followed by: • patients ≥ 40 kg: 200 mg PO q12h; • patients &lt; 40 kg: 100 mg PO q12h</td>
<td>$340.00, $255.00</td>
</tr>
<tr>
<td>Caspofungin acetate (Cancidas®, Merck)</td>
<td>70 mg IV x 1 day, then 50 mg IV once daily</td>
<td>$463.75, $360.00</td>
</tr>
</tbody>
</table>

*This table reflects the average wholesale price of the antifungal agent only. Additional pharmaco-economic data should be incorporated when making P&T decisions. b.i.d. = twice daily; IV = intravenous; PO = oral; t.i.d. = three times a day.

Data from Drug Topics. Red Book Update and Red Book. Montvale, NJ: Thomson Medical Economics; 2002.\(^6,17\)
it is an appropriate agent to be used as primary therapy for invasive aspergillosis.

Although voriconazole appears to be effective in treating esophageal candidiasis, further studies are needed to clarify the drug’s role in this disease and to confirm it as an effective alternative to L-AMB in the empirical treatment of febrile neutropenia.

References

Disclosure
Dr. Sutton has disclosed that, in the past, he received an honorarium and research funds from Pfizer and participated on a Pfizer advisory board. He has not received an honorarium relating to the writing of this article. This article contains information on unapproved uses.
Multiple Choice
Select the one correct answer.

1. From the secondary analysis of the study by Walsh et al. that compared voriconazole with L-AMB as empirical antifungal therapy, which of the following statements is not true?
   a. Voriconazole patients at high risk had higher success rates than L-AMB patients at high risk.
   b. Voriconazole patients at moderate risk had higher success rates than L-AMB patients at high risk.
   c. The difference in efficacy for moderate-risk patients was caused by a disparity in mortality from progressive cancer.
   d. There were significantly fewer breakthrough fungal infections in high-risk patients in the voriconazole group.

2. Voriconazole, a substrate and inhibitor of several hepatic cytochrome P-450 enzymes, affects the pharmacokinetics of other medications, which are also substrates of these enzymes. As cited in Table 2, patients receiving cyclosporine are likely to have:
   a. decreased plasma levels of cyclosporine.
   b. unchanged plasma levels of cyclosporine.
   c. increased plasma levels of cyclosporine.
   d. none of the above.

3. According to previous studies mentioned in this article, which of the following is not true about adverse reactions from voriconazole?
   a. Visual disturbances occurred in approximately 30% of patients.
   b. Visual disturbances lasted approximately 30 minutes.
   c. Mild to moderate rashes occurred in approximately 6% of patients.
   d. Toxic epidermal necrolysis occurred in approximately 30% of patients.

4. Which of the following statements is false?
   a. Elevations in liver-function tests ranging from 4.3 to 26.5% have been reported.
   b. The incidence of clinically significant transaminase elevations was approximately 13.4%.
   c. Infrequent hepatic toxicity and rare cases of hepatitis or hepatic failure have been reported.
   d. Patients who are fast metabolizers of CYP2C19 substrates may experience a higher incidence of transaminase elevations.

5. Which of the following statements is true?
   a. Consuming a high-fat meal increases the bioavailability of voriconazole.
   b. The pharmacokinetic parameters of voriconazole are linear.
   c. Voriconazole is a third-generation triazole antifungal.
   d. Voriconazole is indicated for the primary treatment of invasive aspergillosis.

6. Herbrecht et al. compared voriconazole with amphotericin B deoxycholate for efficacy, survival, and safety for the primary therapy of:
   a. invasive aspergillosis.
   b. febrile neutropenia.
   c. esophageal candidiasis.
   d. oropharyngeal candidiasis.

7. According to the article, which of the following is the dosing regimen for voriconazole?
   a. a loading dose of 6 mg/kg intravenously every 12 hours for two doses, followed by a maintenance dose of 4 mg/kg intravenously every 12 hours
   b. a loading dose of 6 mg/kg intravenously every 12 hours for three doses, followed by a maintenance dose of 4 mg/kg intravenously every 12 hours
   c. a loading dose of 6 mg/kg intravenously every 12 hours for three doses, followed by a maintenance dose of 4 mg/kg intravenously every eight hours
   d. a loading dose of 6 mg/kg intravenously every 12 hours for two doses, followed by a maintenance dose of 4 mg/kg intravenously every eight hours

8. Dosage adjustments of voriconazole are recommended for patients with mild to moderate hepatic cirrhosis.
   a. True
   b. False

9. Intravenous voriconazole is recommended for patients with mild to moderate renal insufficiency.
   a. True
   b. False

10. According to this article, what is the total average cost of intravenous voriconazole for one week, followed by oral voriconazole for one week, for a 70-kg patient?
    a. $2,020
    b. $2,220
    c. $2,420
    d. $2,620
Continuing Education for Pharmacists
Examination Answer Sheet

TOPIC: Voriconazole: A New Triazole Antifungal Agent

Program #079-999-03-016-H01
Expiration Date: April 30, 2004

Complete this answer sheet (including the questions and information requested below), detach, and mail to:

Office of Health Policy and Clinical Outcomes
Thomas Jefferson University Hospital
attn: Continuing Pharmacy Education
1015 Walnut St, Suite 115
Philadelphia, PA 19107

Directions
Select the one best answer to each question and darken the appropriate circle.

1. a b c d
2. a b c d
3. a b c d
4. a b c d
5. a b c d
6. a b c d
7. a b c d
8. a b c d
9. a b c d
10. a b c d

Program Evaluation
(Circle the appropriate response):
Excellento Poor
General quality of article 1 2 3 4 5
Applicability to practice 1 2 3 4 5
Objectives met 1 2 3 4 5
Ease of comprehension 1 2 3 4 5

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Suggested topics for future consideration:
____________________________________________
____________________________________________
____________________________________________

I certify that I have completed this course independently:
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(Signature)

Date Completed ______________________________

This article is approved for continuing pharmacy education only.

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Continuing Medical Education for Physicians

**TOPIC:** Voriconazole: A New Triazole Antifungal Agent

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Date of publication: April 2003
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Authors: S. Scott Sutton, PharmD
Submission deadline: April 30, 2004

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Name: ____________________________________________________________ Degree: __________________________________
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Zip: _____________ City: _____________________________________ State: ______ Telephone: ____________________________
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Time needed to complete this CME activity: □ < 1 hr □ 1 hr

Certification: I attest to having completed this CME activity. ________________________________________________________
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Date

Evaluation
1. Rate the overall effectiveness of this CME activity. 5 4 3 2 1 (very effective) (not at all effective)

2. Circle Yes or No
A. The learning objectives were useful to me in determining whether performing this CME activity would be a worthwhile educational experience. Yes No
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C. This activity will influence how I practice medicine. Yes No
D. The activity was free from commercial bias. Yes No
E. I learned something new that was important from the article. Yes No

3. Which of the following best describes a change you might consider making in your practice as a result of something you learned from this activity? (Please circle only one response.)
A. Slightly modify what I currently do.
B. Make a major change in what I currently do.
C. Follow a procedure, use a technique/technology that is completely new to me.
D. Follow a procedure, use a technique/technology that I currently use but for a different purpose.
E. None of the above, but some change.
F. Not considering any changes.

4. Please describe any change(s) you plan to make in your practice as a result of this activity: ______________________________
____________________________________________________________________________________________________________

5. How committed are you to making these changes? 5 4 3 2 1 (very committed) (not at all committed)

6. Other comments: __________________________________________________________________________________________
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