National PBM Drug Monograph
Voriconazole (Vfend®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

Introduction

There remain relatively few agents available to treat systemic and resistant fungal infections. Amphotericin B has remained the gold standard for many years, though this agent displays significant dose and infusion related toxicity and growing resistance problems.[1] The discovery of the azole antifungals (ketoconazole and fluconazole) improved the ability to treat systemic mycosis. However, these agents lack fungicidal activity so the search has continued for an agent capable of this mechanism.[2] Additionally, the mortality and morbidity associated with the currently available antifungal remains relatively high.[3] Various alterations were made to the core compound of fluconazole in hopes of discovering such an agent. Voriconazole was the result of modifications made to fluconazole resulting in changes in efficacy and susceptible organisms.

Pharmacology/Pharmacokinetics[4567]

The mechanism of action for voriconazole involves the inhibition of a critical step in the sterol pathway. Fungal cytochrome P450- mediated 14 alpha-lanosterol demethylation is inhibited, resulting in alterations to the fungal membrane/cell wall and sustained growth[8].

Voriconazole displays nonlinear pharmacokinetics due to a saturable metabolism. This results in large intraindividual variability. Administration via oral or intravenous routes results in the same pharmacokinetic profile. The oral bioavailability of voriconazole is near 95% with maximum plasma concentrations being reached in less than 2 hours. Approximately 50-65% protein binding occurs with a volume of distribution near 2 L/kg. A single case report stated that levels in cerebrospinal fluid are near those in plasma.[9] The primary route of metabolism is the cytochrome P450 system with the principal enzymes being CYP2C9, CYP2C19 and CYP3A4. The elimination half-life of the agent is approximately 6 hours. However, with extended dosing this may lengthen, leading to accumulation of the drug with long-term exposure.

The pharmacokinetics of voriconazole in special populations has not been studied extensively. Since the agent is hepatically metabolized, caution should be exercised in individuals with hepatic impairment. A study of patients with mild and moderate (Child-Pugh Class A and B) liver dysfunction determined that the C_{max} remained the same but AUC increased. The resultant recommendation is to maintain the initial loading dose and decrease the maintenance dose by 50%. In patients with moderate renal insufficiency (CrCl 30-50 ml/min) the intravenous vehicle, SBECD, can accumulate. Voriconazole and the intravenous vehicle are removed by dialysis but not sufficiently enough to require dosage adjustment. The use of voriconazole should be carefully considered in patients with renal dysfunction since the clinical impact of SBECD accumulation is unknown.

FDA Approved Indication(s) and Off-label Uses

Voriconazole is indicated in the treatment of invasive aspergillosis and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species. Additionally, clinical trials have investigated its safety and efficacy in the treatment of candidal infections.

Current VA National Formulary Status

The systemic antifungal agents on VA National formulary include Amphotericin B injectable, Amphotericin B lipid complex injection, fluconazole oral and intravenous formulations and ketoconazole oral tablets.

Dosage and Administration

The manufacturer recommends initiating voriconazole therapy with a loading dose. The loading dose is 6mg/kg IV every 12 hours for 2 doses continuing with a maintenance dose of 4 mg/kg IV every 12 hours. There have been clinical trials that did not employ a loading dose but documented favorable patient outcomes. Therefore the optimal dosing regimen remains unknown. When patients are capable of tolerating oral therapy an oral dose of 200 mg (>40 kg) and 100 mg (< 40 kg) every 12 hours should be used. The IV dose must be infused over 1-2 hours at a concentration of 5 mg/ml or less.

In patients with an inadequate therapeutic response the oral dose of voriconazole can be increased to 300 mg (> 40 kg) and 150 mg (<40 kg) every 12 hours respectively. If patients are intolerant of voriconazole therapy the intravenous dose can be decreased to 3mg/kg every 12 hours.

Dosage adjustments are recommended in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B). Only the maintenance dose should be decreased by 50 %, the loading dose should remain the same. In patients with CrCl < 50 ml/min caution should be exercised with the intravenous formulation due to the possible accumulation of the SBECD vehicle. Oral dosing does not need to be altered.

Adverse Effects (Safety Data)

The most common adverse event reported with voriconazole therapy is a transient dose-related visual disturbance. This has included increased brightness, blurred vision, color vision change, altered visual perception and photophobia. In the clinical trials of this agent as many as 30% of patients. The mechanism for the effect is unknown.

In common with the other azole antifungals, voriconazole may elevate hepatic transaminases, resulting in discontinuation of the agent.[10] Additionally, there has been a case report of photosensitivity occurring with voriconazole therapy.[11] Further post marketing data will be required to determine the incidence of this effect. **Table 1** summarizes the major adverse events reported for voriconazole and comparators in the Phase III clinical trials.

Infusion related reactions have occurred with intravenous voriconazole administration. Symptoms include flushing, fever, sweating, tachycardia, chest tightness and dyspnea. Infusions should be discontinued if this occurs.

Voriconazole is pregnancy category D as it was shown teratogenic in rats. Safety and efficacy in children under 12 years of age has not been proven.

Further studies in the elderly are required to determine the safety of voriconazole for this population. Plasma concentrations are 80-90% higher in these patients than in younger patients.

Table 1:Voriconazole Adverse Reactions (%)

Adverse reaction	Voriconazole (n=1493)	Fluconazole (N=191)	Ampho B (N=185)	Oral voriconazole (N=200)
Headache	3.2	0.5	4.3	0
Hallucinations	2.5	0	0.5	0
Rash	5.8	0.5	3.8	1.5
Puritis	1.1	0	1.1	0
Anemia	0.1	0	2.7	0
Thrombocytopenia	0.5	0.5	1.1	0
Nausea	5.9	1.6	15.7	1
Vomiting	4.8	0.5	9.7	1
LFT abnormality	2.7	1	2.2	3
Abdominal pain	1.7	0	3.2	0
Diarrhea	1.1	0	3.2	0
Creatinine increased	0.3	0	31.9	0.5
Bilirubinemia	0.8	0	1.6	0.5
Peripheral edema	0.1	0	4.9	0.5
Hypomagnesemia	1.1	0	5.4	0
Abnormal vision	20.6	4.2	0.5	15.5
Fever	6.2	0	13.5	0
Chills	4.1	0	19.5	0.5
Chest pain	0.9	0	1.1	0

Precautions/Contraindications

Caution should be exercised when voriconazole is given with agents that are substrates for CYP3A4. Concurrent use of pimozide, cisapride and quinidine are contraindicated due to QT prolongation. Coadministration with sirolimus, rifampin, carbamazepine, rifabutin, ergot alkaloids and long-acting barbiturates is not advised.

Hypersensitivity to other azole antifungals would contraindicate the use of voriconazole.

Patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not receive the oral preparation of voriconazole due to galactose as an excipient in this formulation.

Drug Interactions

There is limited data regarding the occurrence of drug interactions with this agent. Voriconazole metabolism occurs in the cytochrome system, with the highest affinity for CYP2C19 and lowest for CYP3A4. It acts as an inhibitor of metabolism, though to a lesser degree than ketoconazole. Use with agents that are substrates for these same enzymes should be under taken cautiously, especially in agents with a narrow therapeutic index. Increased plasma monitoring and dosage adjustments may be necessary. Interactions of this nature have been studied. In a study of voriconazole and cyclosporine, the mean cyclosporine AUC was increased 1.7 fold.[12]

When administered with a high-fat meal the C_{max} and AUC of voriconazole were reduced. Therefore, the agent should be administered 1 hour before or after a meal.

Clinical Trials

<table>
<tr><td>Citation</td><td>Denning DW, Ribaud P, Milpied N, et al. Efficacy and Safety of voriconazole in the treatment of acute invasive aspergillosis. Clin Infec Disease 2002;34:563-571.</td></tr>
<tr><td>Study Goals</td><td>Evaluate voriconazole in acute IA</td></tr>
<tr><td>Methods</td><td>

Study Design

Open, non comparative multicenter study
Conducted between 1994-1996
Voriconazole 6mg/kg every 12 hours for 2 doses, then 3 mg/kg at 12 hr intervals followed by 200 mg BID orally for a total of 4-24 weeks
Response was assessed by clinical and radiographic change
Clinical, radiologic and mycologic outcomes evaluated separately. A global outcome was made after these factors were evaluated.

Data Analysis

Comparison of response rates evaluated with Chi square
Survival times were compared in those receiving salvage therapy by means of log rank test and Kaplan Meier plots

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<tr><td>Criteria</td><td>

Inclusion criteria

Definite diagnosis of IA with histopathologic evidence
Probable IA with radiographic evidence of acute infection
Halo or air crescent on CT in patients with profound neutropenia
Previous treatment with Ampho B > 10 mg/kg total dose, Ampho B lipo >40 mg/kg total dose or itraconazole ≥400 mg daily for ≥10 days could receive salvage therapy due to failure

Exclusion criteria

Transaminases > 3 times upper limit of normal
Serum creatinine > 3 times upper limit of normal
Pregnancy or currently breast feeding
Allergy to other azole drugs

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<tr><td>Results</td><td>
Response at end of therapy
<table>
<tr><th>Site</th><th>Complete</th><th>Partial</th><th>Stable</th><th>failure</th></tr>
<tr><td>Pulmonary N=84</td><td>15</td><td>35</td><td>16</td><td>18</td></tr>
<tr><td>Cerebral N=19</td><td>0</td><td>3</td><td>5</td><td>11</td></tr>
<tr><td>Disseminated N=6</td><td>1</td><td>2</td><td>0</td><td>3</td></tr>
<tr><td>Sinus N=5</td><td>0</td><td>0</td><td>2</td><td>3</td></tr>
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Response by previous therapy
<table>
<tr><th></th><th>complete</th><th>partial</th><th>stable</th><th>Failure</th></tr>
<tr><td>Primary N=60</td><td>10</td><td>25</td><td>11</td><td>14</td></tr>
<tr><td>Salvage N=56</td><td>6</td><td>15</td><td>13</td><td>22</td></tr>
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Response by patient group

	Complete	Partial	Stable	failure
Hematologic disorder N=67	16	23	10	18
Allogeneic HSCT N=23	0	6	8	9
Solid organ transplant N=6	0	3	2	1
AIDS N=5	0	1	0	4

Conclusions	Voriconazole was most efficacious as primary therapy. Patients with hematologic disorders showed the best response. Voriconazole is efficacious in treating IA. With a response rate of 48%.
Critique	• **Strengths** • multicenter • **Limitations** • Company sponsored • Nonrandomized • Patients received concurrent therapy with enzyme inducers which may have lowered voriconazole concentrations • Small sample sizes in each group • Reviewer and rater not blinded to treatment

Citation	Herbrecht R, Denning D, Patterson TF, et al. Voriconazole versus Amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347(6):408-15.
Study Goals	Demonstrate the equivalence of voriconazole and Ampho B in treatment of IA at 12 weeks
Methods	• **Study Design** ➢ Randomized, unblended stratified based on infection site, treatment center, base line neutropenic status and underlying disease ➢ Centers in US and Europe ➢ Voriconazole 6mg/kg every 12 hours for 2 doses, then 4 mg/kg at 12 hr intervals for at least 7 days followed by 200 mg BID orally versus Amphotericin B deoxycholate 1-1.5 mg/kg daily. ➢ List information on treatment groups, randomization, length of study, and efficacy measures used • **Data Analysis** ➢ Hazard ratio for death estimated using Cox proportional hazards model ➢ Intention to treat using all patients who were randomized ➢ Modified intention to treat using patients who received at least one dose of study medication ➢ Adverse events compared by Fisher exact
Criteria	• **Inclusion criteria** ➢ Definite or probable IA 12 years of age or older ➢ Immunocompromised • **Exclusion criteria** ➢ Chronic aspergillosis ➢ Receiving interacting drugs ➢ LFT > 5 times upper limit of normal ➢ Creatinine > 2.5 mg/dl

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Pregnancy or lactating
On ventilator or expected survival of less than 72 hours

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<tr><td>Results</td><td>
Response at week 12 in the modified intent to treat group
<table>
<tr><th></th><th>Complete</th><th>Partial</th><th>Stable</th><th>Failure</th></tr>
<tr><td>Voriconazole N=144</td><td>30</td><td>46</td><td>8</td><td>55</td></tr>
<tr><td>Ampho B N=133</td><td>22</td><td>20</td><td>8</td><td>78</td></tr>
</table>
Week 12 survival rate (modified intention-to-treat)

70.8% in voriconazole group vs. 57.9% in Ampho B group (hazard ratio 0.59, CI 0.4-0.88)

Week 12 survival rate (intention-to-treat)

49.7% in voriconazole group vs. 27.8% in Ampho B group (absolute difference 21.9%, CI 12.4-31.2)
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<tr><td>Conclusions</td><td>Voriconazole treated patients with IA had better responses and improved survival with fewer adverse events than those treated with Ampho B</td></tr>
<tr><td>Critique</td><td>

Strengths
United States and European sites
Randomized
Majority of male patient, mean age 50 years
Limitations
Unblinded
Majority of patients with underlying hematologic disorders
Discrepancy between investigators and review committee due to lack of radiologic evidence of IA on CT scan

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Citation	Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal Amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002;346:225-234.
Study Goals	Voriconazole in not inferior to liposomal Ampho B for empiric therapy
Methods	• **Study Design** ➢ Open label, prospective, randomized, multicenter, international ➢ Data review by blinded group of experts ➢ Voriconazole 6mg/kg every 12 hours for 2 doses, then 3 mg/kg at 12 hr intervals for at least 3 days followed by 200 mg BID orally versus liposomal Amphotericin B 3 mg/kg daily. ➢ List information on treatment groups, randomization, length of study, and efficacy measures used • **Data Analysis** ➢ Intention to treat and modified intention to treat ➢ Adverse events examined with chi square and Fischer exact ➢ Utilization of healthcare resources measured by number of inpatient days analyzed by Wilcoxon rank sum ➢ Time to defervescence by Kaplan-Meier
Criteria	• **Inclusion criteria** ➢ At least 12 years of age ➢ Had received chemotherapy or hematopoietic stem cell transplant, received 96 hours

	of antibacterial therapy but remained febrile and were neutropenic. ➢ **Exclusion criteria** ➢ Documented invasive fungal infection ➢ Liver function tests 5 times upper limit of normal
Results	• In the composite score only item to show statistical significance was frequency of breakthrough fungal infections within 7 days after completion of therapy. Time to defervescence, survival, and discontinuation were not different. • The oral formulation of voriconazole was responsible for the decrease in hospital stay by 1 day. Those patients at high risk (relapse leukemia and allogeneic transplant) had a decrease in hospital stay by 2 days.
Conclusions	Voriconazole is a suitable alternative to liposomal Ampho B in treatment of febrile neutropenic patients.
Critique	• **Strengths** • International with blinded data review • **Limitations** • Open label design may have biased towards Ampho B • Partial funding by the manufacturer

Citation	Ally R, Schürmann D, Kreisel W, et al. A randomized, double blind, double dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin Infec Dis 2001;33:1447-54.
Study Goals	Oral voriconazole and oral fluconazole are equal in treatment of esophageal candidiasis
Methods	• **Study Design** ➢ randomized, double blind, double dummy, multicenter ➢ voriconazole 200 mg PO BID, fluconazole 400 mg PO day 1then 200 mg PO QD ➢ treatment continued for 7 days after clinical resolution but not longer than 42 days total ➢ esophagoscopy, positive microscopy and mycological culture used to define disease • **Data Analysis** ➢ Time to symptomatic cure assessed by Kaplan-Meier survival curve ➢ Intention to treat, voriconazole not inferior to fluconazole if CI did not fall below –0.15 when comparing difference in success rates.
Criteria	• **Inclusion criteria** ➢ 18-75 years, male and non pregnant females ➢ clinical diagnosis of esophagitis then confirmed with esophagoscopy • **Exclusion criteria** ➢ Not listed
Results	**Resolution as measured by esophagoscopy** **Success rate** Voriconazole 98.3% Fluconazole 95.1% Difference of –3.2%, CI –1.0 to 7.5%

	Cure	Improved	failure
Voriconazole N=115	109	4	2
Fluconazole N=141	127	7	7

Conclusions	Voriconazole was shown to be at least as effective as fluconazole in the treatment of candidal esophagitis with no increase in adverse effects.
Critique	• **Strengths** • Use of esophagoscopy, mycology culture and microscopic findings for diagnosis and cure • Well defined outcomes • **Limitations** • Over 90% of study population had AIDS, other underlying diseases not well represented • No mention of blinded reviewers • Exclusion criteria not defined • No review of patient demographics • No US sites

Acquisition Costs

Drug	Dose	Cost/day
Invasive Aspergillosis		
Voriconazole IV	420 mg BID then 210mg BID	$267.24 then $133.62
Voriconazole oral	200 mg BID	$37.42
Ampho B liposome	210 mg QD	$304.50
Ampho B	70 mg QD	$6.86
Candidal Esophagitis		
Voriconazole oral	200 mg BID	$37.42
Fluconazole oral	400 mg then 200 mg QD	$14.56 then $7.28

Dosing based on 70 kg patient

Conclusions

Limited studies are available using voriconazole to treat systemic fungal infections. The in vitro susceptibility profiles of this agent appear to be wide spectrum and to possess lower MIC's than currently available agents. The clinical studies available suggest that voriconazole may be superior for the treatment of invasive aspergillosis. The oral formulation of this agent offers an acceptable alternative for prolonged therapy and may help increase patient compliance. Further studies will help elucidate if voriconazole has other therapeutic areas of superiority to currently available agents.

Voriconazole therapy is not without side effects. The occurrence of visual disturbances and hepatic transaminase elevations lead to treatment discontinuations in the clinical trials, this could limit therapy. However, therapy with Ampho B can cause adverse effects, which limit its use. Overall, the adverse effect profile of voriconazole may be more acceptable than Ampho B, especially given a broader spectrum and less resistance. One disadvantage is the twice daily dosing of voriconazole. This could impact compliance when the oral formulation is used. The drug interaction profile of voriconazole is problematic. There are many potential and proven interactions in the cytochrome P450 system that can limit therapy. The vehicle in the intravenous formulation may cause problems due to accumulation, the impact of this remains to be determined.

Recommendations

There appear to be specific areas for the use of voriconazole. The agent should be considered primary therapy for invasive aspergillosis, serious infections caused by *Scedosporium apiospermum* or *Fusarium* species, and selected other Amphotericin B resistant fungi. While the side effect profile of voriconazole may raise concern, the side effects associated with Amphotericin B are also worrisome. Further studies are

necessary to define the drug interactions, use in renal impairment, safety in the geriatric population and efficacy over other currently available antifungal agents. Given these caveats, voriconazole would not be recommended for national or VISN formulary listing at this time. The use of the Non-formulary request process in the indications defined above will help ensure that appropriate care is exercised regarding drug interactions, renal impairment and patient selection.

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Date: August 2002

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