

Bon Secours Richmond
Pharmacy and Therapeutics Committee
Voriconazole (VFEND)
1/2003

Recommendations: (All MEC Approved)

- Voriconazole is recommended for addition to the formulary restricted in use to the FDA approved indications.
 - Treatment of invasive aspergillus
 - Treatment of *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp. in patients intolerant to or refractory to other therapy.
- Oral use is recommended when possible; as oral bioavailability is 96% and pharmacokinetic profiles are similar for oral and IV administration. Cost is 4.85 times less, \$36.75-\$73.50 for oral versus \$333.20 per day for IV.
- Oral voriconazole dosage should be weight adjusted, rounded to the nearest dose divisible by 50 mg (as serum levels are equivalent to IV). Voriconazole is supplied as 200 and 50 mg tablets.
- Oral voriconazole is recommended for use in place of IV voriconazole in patients with calculated creatinine clearance < 50 ml/min to prevent accumulation of the intravenous vehicle (sulfobutyl ether beta-cyclodextrin 3200 mg per 200 mg voriconazole) per manufacturer recommendations. VFEND is not recommended in dialysis patients as the solubilizing agent is not removed.
- Automatic conversion to the oral route is recommended for patients who are able to take oral medicines.
- Oral tablets should be scheduled one hour before meals as high fat meals decrease its absorption.
- Voriconazole should be avoided during pregnancy as it is classified as Pregnancy Category D: can cause fetal harm.
- Voriconazole requires close monitoring for drug interactions: it is contraindicated in patients receiving carbamazepine, long acting barbiturates, sirolimus, rifabutin, rifampin, terfenadine, astemizole, cisapride, pimozide, quinidine, and ergot alkaloids and requires increased monitoring with numerous other agents (see table below).
- Voriconazole may not be infused concomitantly in the same line or cannula with other drugs or parenteral nutrition.

Findings:

- Action: Voriconazole is a triazole antifungal agent derived from fluconazole that inhibits the fungal cytochrome P-450-mediated 14- α -lanosterol demethylation like fluconazole and itraconazole, an essential step in fungal ergosterol biosynthesis. The accumulation of 14- α -methyl sterols correlates with the loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole. Voriconazole also inhibits 24-methylene dihydrolanosterol demethylation in certain yeast and filamentous fungi expanding the activity of voriconazole to include molds. Voriconazole is a more potent inhibitor than fluconazole against *Candida dubliniensis*.
- FDA approved indications
 - Treatment of invasive aspergillus
 - Treatment of *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp. in patients intolerant to or refractory to other therapy.
- Therapeutic options in resistant aspergillosis are limited. Although more clinical experience with voriconazole is needed, data are sufficient to recommend its use in patients with invasive aspergillosis and other serious fungal infections due to *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp. including *Fusarium solani*, in patients intolerant of, or refractory to other therapy. The drug may also be useful in patients with therapy-limiting toxicity associated with conventional regimens.
- Data are too limited to suggest a role in candidiasis.
- Voriconazole breakpoints have not been established for any fungi.
- Voriconazole displays Non-linear pharmacokinetics, AUC (mcg*hr/ml) more than doubles when increasing the dose from 200 to 300 mg q12h orally or from 3 to 4 mg/kg IV.
- A loading dose regimen is recommended to obtain steady state serum levels within 24 hours. Without a loading dose steady state levels are achieved in 5 days.
- High fat meals reduce AUC of oral voriconazole by 24%, tablets should be give 1 hour before meals.
- Agents that altered gastric pH don't change voriconazole's absorption.
- *A pharmacokinetic-pharmacodynamic analysis of patient data from 10 trials (N=1121) demonstrated a positive association between plasma mean, maximum, or minimum plasma concentrations and efficacy.*
- *Voriconazole is metabolized by the cytochrome P450 enzymes (CYP2C19, CYP2C9, & CYP3A4) with genetic polymorphism and has multiple significant drug interactions.*
 - *Poor metabolizers have 2-4 fold increases AUCs*
 - *3-5% of caucasians and blacks are poor metabolizers*
 - *Asians: 15-20% are poor metabolizers*
- *Young females receiving multiple oral doses have plasma levels 83% higher Cmax and 113% higher AUC than males (18-45 years old).*
 - *Elderly females have similar Cmax and AUC as young females.*
- *Elderly males (\geq 65 years old) had a 61% higher Cmax and 86% higher AUC than young males (18-45 years).*
- *Liver dysfunction*

- Child-Pugh class A: AUC is increased 2.3 fold higher
- Child-Pugh class B: AUC is increased 3.2 fold higher
- Renal Dysfunction does not affect C_{max} or AUC of voriconazole, but the solubilizing agent, sulfobutyl ether betacyclodextrin, C_{max} is 50% higher and AUC is 4 fold higher.
- IV voriconazole should be avoided in patients with moderate to severe renal dysfunction (Cl_{cr} < 50 ml/min). Oral voriconazole may be used as no solubilizing agent is in the tablet.
- Hemodialysis does not remove sufficient amount of voriconazole to warrant dosage adjustment.
- Cross-resistance to azoles (fluconazole, itraconazole, and voriconazole) can occur.
- Side effects: visual disturbances (perception, blurred vision, color changes, photophobia, eye hemorrhage) 30%, fever, rash, vomiting, nausea, hepatotoxicity (jaundice, hepatitis, and hepatic failure leading to death)

Dosing Recommendations From Package Insert			
Route	IV	Oral	Oral
Patients 18 years old and older		≥ 40kg	< 40kg
Loading dose IV	6mg/kg q12h x 2		
Maintenance dose IV	4mg/kg q12h	200 q12h	100 q12h
If inadequate response Increase dose up to:	---	300 mg q12h	150mg q12h
If intolerant decrease dose to	3 mg/kg q12h	250 or 200 mg q12h	100 mg q12h
Concurrent Phenytoin Therapy	5 mg/kg q12h	400 mg q12h	200 mg q12h
Moderate to Severe Renal Insufficiency (creatinine clearance < 50 ml/min)	Oral is recommended to prevent accumulation of sulfobutyl ether beta-cyclodextrin. The solubilizing agent in the IV formulation.		
Dialysis	IV NOT RECOMMENDED, as solubilizing agent is not cleared substantially in 4 hours.	No Change	No Change
Child-Pugh Class A or B*	Reduce maintenance dose by 50%	Reduce maintenance dose by 50%	Reduce maintenance dose by 50%
Child-Pugh Class C or Chronic Hepatitis B or C	Not Studied	Not Studied	Not Studied

*Patients were included in clinical studies with baseline LFT (ALT, AST) up to 5 times the ULN without dosage adjustment.

Drugs Contraindicated with voriconazole		
Drug	Effect on voriconazole	Effect on drug in 1 st column
Astemizole		Increased drug level
Carbamazepine	Decreased drug level	
Cisapride		Increased drug level
Ergot Alkaloids		Increased drug level
Long-acting Barbiturates	Decreased drug level	
Pimozide		Increased drug level
Quinidine		Increased drug level
Rifabutin	Decreased drug level ↓ AUC 79%	Increased drug level 400% ↑ AUC
Rifampin	Decreased drug level 96% ↓ AUC	
Sirolimus		Increased drug level 700% ↑ AUC
Terfenadine		Increased drug level

Voriconazole Drug Interactions requiring dosage change and/or monitoring		
Agent	Dose change	Monitor
Phenytoin	Increase Voriconazole IV dose from 4 to 5mg/kg IV or double oral dose	Phenytoin plasma level AUC ↑ 80%, adverse events (Aes)
Tacrolimus	Decrease tacrolimus dose to one third	Drug level
Cyclosporine	Decrease cyclosporine dose to one half	Drug level
Omeprazole (doses > 40mg)	Decrease omeprazole dose to one half	
Statins	Consider	Drug toxicity, AEs
Calcium Channel Blockers	Consider	Drug toxicity, AEs
Benzodiazepines	Consider	Drug toxicity, AEs
Vinca alkaloids	Consider	Drug toxicity, AEs
Sulfonylureas	Consider	Blood glucose, hypoglycemia
Warfarin	Consider	Prothrombin time
HIV protease inhibitor (except indinavir)	None	Drug toxicity, AEs
NNRTIs	None	Drug toxicity, AEs

Comparative Pharmacokinetics for Voriconazole, Itraconazole, and Fluconazole

Parameter	Fluconazole	Itraconazole	Voriconazole
Cmax	200 mg q12h 1.7 mcg/ml		
AUC			
Tmax (h)	1-3	3-4	1-2
Oral Bioavailability(%)	93	55	96
Half-life (h)	31	24	6-24 dose dependent
Protein binding (%)	11-12	99.9	51-67
Volume of distribution (L/kg)	0.7-1.2	10-11	4.6
Primary route of elimination	Renal excretion	Hepatic	Hepatic

Aspergillosis

Herbrecht R. Voriconazole versus Amphotericin B for Primary Therapy of Invasive Aspergillosis (in immunocompromised patients). NEJM, 2002;347:408-15

In one *opened label* randomized, multicenter, controlled study of the efficacy of voriconazole compared to amphotericin B for the treatment of acute invasive aspergillosis, 277 patients treated for 12 weeks demonstrated increased efficacy with voriconazole. In patients with invasive aspergillosis initial therapy with voriconazole led to better responses and improved survival and resulted in fewer severe side effects than the standard approach of initial therapy with amphotericin B. *Note 24% of voriconazole patients received amphotericin B or a lipid amphotericin B product. The study does not describe if they were given concurrently or sequentially. Should they have been included in analysis? Thirty-five percent (35%) of amphi B patients received a lipid product.*

Overall efficacy and success by species in the Primary Treatment of Acute Invasive Aspergillosis

Voriconazole Versus Amphotericin B for Primary Therapy of Invasive Aspergillosis			
	Voriconazole	Amphotericin B followed by other licensed therapy	Difference (95% CI)
	6 mg/kg IV q12h x2 then 4 mg/kg q12h x ≥ 7 days	1-1.5 mg/kg/day followed by other licensed therapy	
Median duration IV therapy	10 days (2-90)	12 (1-85)	
Median duration of therapy	76 days (2-232) oral voriconazole	<i>Not stated</i>	
Other licensed therapy	52/144 20 amphotericin B deoxycholate 14 Lipid amphi B 17 itraconazole 1 combination	107/133 47 lipid amphi B 38 itraconazole 22 combination	
Efficacy as Primary Therapy Modified Intention to Treat**			
Satisfactory global response	76/144 (53%)	42/133 (32%)	21.8%
Complete response*	20.8%	16.5%	p < 0.0001
Partial response*	31.9%	15%	
Unsuccessful outcome	47.2%	68.4%	
Failure of therapy	38.2%	58.6%	
Survival at day 84	102/144 (71%)	77/133 (58%)	13.1%
Success by species			
Overall success	76/144 (53%)	42/133 (32%)	
Mycologically confirmed	37/84 (44%)	16/67 (24%)	
<i>Aspergillus spp.</i>			
<i>A. fumigatus</i>	28/63 (44%)	12/47 (26%)	
<i>A. flavus</i>	3/6	4/9	
<i>A. terreus</i>	2/3	0/3	
<i>A. niger</i>	1/4	0/9	
<i>A. nidulans</i>	1/1	0/0	
Adverse Reactions			
	N=194	N=185	
Visual Disturbances	44.8%	4.3%	P < 0.001
Hallucinations	6.7% (13/194)	2.7% (5/185)	P = 0.09
Fever or Chill or both	3.1%	24.9%	P < 0.001
Skin reactions	8.2%	3.2%	P = 0.05
Liver function abnormalities	3.6% (7/194)	2.2% (4/185)	P = 0.54
Renal Impairment	1% (2/194)	10.3% (19/185)	P < 0.001

*Complete response: resolution of all clinical signs and symptoms and more than 90% of the lesions due to invasive aspergillosis that were visible on radiology. Partial response: clinic improvement and greater than 50% improvement in findings on radiology.

** Included only patients with confirmed diagnosis (definite and probable) of invasive aspergillosis at base line. Intention to treat analysis was similar 49.7% versus 27.8% successful outcome in voriconazole versus amphotericin B deoxycholate.

Febrile Neutropenia Empiric Therapy

Walsh TJ, Pappas P, Winston DJ et al: Voriconazole compared with liposomal amphotericin B (AmBisome) for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002; 346:225-234.

An *open-label*, multicenter trial randomized neutropenic febrile patients (n=837) to either voriconazole or liposomal amphotericin B (AmBisome). The following doses were used, intravenous voriconazole 6 milligrams/kilogram (mg/kg) every 12 hours for 2 doses then 3 mg/kg every 12 hours (switch to 200 mg orally every 12 hours was allowed after a minimum of 3 days of intravenous therapy) and intravenous AmBisome 3 mg/kg/day. Antifungal therapy was continued for up to 3 days after neutrophil recovery or up to a maximum of 12 weeks in those with documented invasive fungal infections. Approximately 50% to 60% of patients in each group were receiving systemic antifungal prophylaxis prior to randomization. The overall success rate was 26% and 30.6% (95% confidence interval, -10.6% to 1.6%) for the voriconazole group and AmBisome group, respectively. Eight patients compared with 21 patients (p =0.02) in the voriconazole and AmBisome groups, respectively, experienced a breakthrough fungal infection. The overall mortality was not different between the two groups. More patients in the voriconazole group discontinued primarily due to a lack of efficacy and persistent fever. AmBisome was associated with significantly more cases of severe infusion-related reactions (p less than 0.01) and nephrotoxicity (p < 0.001); while, voriconazole was associated with significantly more cases of transient visual changes (p < 0.001) and hallucinations (p < 0.001). **CONCLUSION:** *Per-protocol analysis, voriconazole was inferior to liposomal amphotericin B based on overall response.*

	Voriconazole (IV to PO) N=415	Amphotericin B Liposomal N=422
Dose	6 mg/kg x 2 LD 3 mg/kg q12h	3 mg/kg/day
Median Duration of Therapy (days)	7	7
Range	1-113	1-81
Overall Response (Modified Intention to treat)	26%(108/415)	30.6% SS
No breakthrough fungal infections within 7 days of end of therapy	98.1%	95% P= 0.02
Survival 7 days after end of therapy	92%	94.1% NS
Discontinued due to toxicity	4.6% (19/415)	5.5% (23/422)
Discontinued due to lack of efficacy before recovery from neutropenia	5.3% (22/415)	1.2% (5/422) p =0.001
Fever resolution during neutropenia	32.5%	36.5% NS
Complete or partial response of patients with base-line fungal infections by end of treatments	46.2%	66.7% NS
Visual Hallucinations	4.3%	0.5% p <0.001
Nephrotoxicity Scr 1.5 x baseline Scr 2 x baseline	10.4% 7%	19% p <0.001 7.6%
Transition to Oral Voriconazole	22% (92/415)	
Mean Serum Levels during IV	2-4 mcg/ml 75% 1-7 mcg/ml	

Candidiasis

A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin Infect Dis 2001 Nov 1;33(9):1447-54

The efficacy, safety, and tolerability of voriconazole (200 mg bid) and fluconazole (400 mg x1 then 200 mg qd) were compared in 391 immunocompromised patients with mycology- and biopsy-proven esophageal candidiasis. Ninety four percent (94%) of patients had AIDS and approximately 60% had CD4 counts < 50 cells/mm³. Primary efficacy analysis (256 patients) of esophageal treatment as assessed by esophagoscopy revealed success rates of 98.3% with voriconazole and 95.1% with fluconazole, not statistically significant. The 95% confidence interval for the difference in success rates ranged from -1.0% to 7.5%. The overall safety and tolerability of both antifungals were acceptable. *Fewer patients discontinued voriconazole treatment because of insufficient clinical response (4 patients [2.0%] vs. 5 patients [2.6%]). More patients discontinued voriconazole than fluconazole treatment because of laboratory test abnormalities (7 patients [3.5%] vs. 2 patients [1.0%]) or treatment-related adverse events (5 patients [2.5%] vs. 1 patient [0.5%]). Adverse effects occurred more frequently with voriconazole 30% versus 14% for fluconazole. Drug therapy stopped secondary to ADRs 2.5% voriconazole and 0.5% fluconazole. Therapy discontinued secondary LFT abnormalities 3.5% voriconazole and 1.1% fluconazole. The most frequent adverse events (18%) with voriconazole were mild, transient visual disturbances.*

Voriconazole (200 mg, b.i.d.) was shown to be at least as effective as fluconazole in the treatment of biopsy-proven esophageal candidiasis in immunocompromised patients, but had higher adverse event rates.

In other studies, voriconazole was shown to be effective against *Scedosporium apiospermum* (63%; 15/24 patients) and *Fusarium* spp. (43%; 9/21 patients).

Voriconazole 200 mg twice daily orally was evaluated in 12 patients with AIDS and fluconazole-refractory esophageal candidiasis. All patients had endoscopically documented fluconazole-refractory esophageal candidiasis that had persisted after at least 7 days therapy with fluconazole 400 mg daily. Complete clinical response (total disappearance of signs and symptoms) occurred in six patients after 7 days of therapy and in one additional patient after 2 weeks of therapy. Marked improvement was observed in an additional three patients, while two patients were unchanged on therapy at 7 days. The duration of clinical response ranged from 1 to 40 weeks. Mycological response (no *Candida* growth after 7 days of therapy) occurred in five patients, with mycological eradication lasting from 2 to 14 weeks.

In a blinded, dose-finding study assessing voriconazole 50 mg once daily, 200 mg once daily, and 200 mg twice daily for 7 days in HIV-infected patients with oropharyngeal candidiasis, a clinical efficacy rate of 80% to 100% was reported for the 200 mg once-daily and 200 mg twice-daily doses. Efficacy was also reported in six patients with HIV infection and fluconazole-refractory esophageal candidiasis treated with oral voriconazole 200 mg twice daily.

Table 2: Incidence of Adverse Events ($\geq 1\%$) Reported in All the Voriconazole Clinical Studies:

Adverse Event	Voriconazole Therapy (n=1493)
Abnormal vision	20.6%
Fever	6.2%
Nausea	5.9%
Rash	5.8%
Vomiting	4.8%
Chills	4.1%
Alkaline phosphatase increased	3.6%
Headache	3.2%
Liver function tests abnormal	2.7%
Hallucinations	2.5%
Tachycardia	2.5%
Photophobia	2.4%
Hepatic enzyme increased	1.9%
Hypertension	1.9%
SGOT increased	1.9%
SGPT increased	1.8%
Abdominal pain	1.7%
Hypotension	1.7%
Hypokalemia	1.6%
Vasodilatation	1.5%
Chromatopsia	1.3%
Dizziness	1.3%
Cholestatic jaundice	1.1%
Diarrhea	1.1%
Hypomagnesemia	1.1%
Maculopapular rash	1.1%
Peripheral edema	1.1%
Pruritus	1.1%
Dry mouth	1%

Table 3: Comparison of the Alterations in Selected Laboratory Tests with Voriconazole, Fluconazole, and Amphotericin B Therapy:

Laboratory test	Criteria	Study 305		Study 307/602	
		Voriconazole	Fluconazole	Voriconazole	Fluconazole
Total bilirubin	>1.5x ULN	4.3%	3.8%	19.4%	26.6%
Aspartate transaminase (AST)	>3x ULN	20.3%	8.1%	11.7%	10.3%
Alkaline transaminase (ALT)	>3X ULN	10.7%	6.5%	18.9%	23.1%
Alkaline phosphatase	>3 ULN	10.2%	7.5%	16%	22%
Creatinine	>1.3X ULN			21.4%	57.6%
Potassium	<0.9X LLN			16.6%	39.3%

ULN = upper limit of normal

LLN = lower limit of normal

Cost Analysis Per Day of Therapy

Drug	mg	Cost/Dose	Dose mg/kg/day	Dose mg/kg/day	Low Dose	High Dose
					Cost per day for 80 kg	Cost per day for 80 kg
Amphotericin B Deoxycholate (Fungizone)	50	\$6.13	1.0	1.5	\$12.26	\$18.39
Amphotericin B Cholesteryl Sulfate Complex (Amphotec)	50	\$46.06	3.0	4.0	\$230.30	\$322.42
Amphotericin B Cholesteryl Sulfate Complex (Amphotec)	100	\$78.40	3.0	4.0	\$235.20	\$313.60
Amphotericin B Liposome (Ambisome)	50	\$153.37	3.0	5.0	\$766.85	\$1,226.96
Amphotericin B Lipid Complex (Abelcet)	50	\$98.98	5.0	5.0	\$791.84	\$791.84
Amphotericin B Lipid Complex (Abelcet)	100	\$156.80	5.0	5.0	\$627.20	\$627.20
Caspofungin Acetate (Cancidas)	70	\$352.67	70 x1	50 qd	\$352.67	\$273.77
Caspofungin Acetate (Cancidas)	50	\$273.77	50 qd	70 qd	\$273.77	\$352.67
Itraconazole (Sporanox)	250	\$149.47	200 mg q12h x 4	200 qd	\$298.94	\$149.47
Itraconazole (Sporanox capsule)	100	\$6.53	200 mg TID x 3 days	200 qd	\$39.18	\$13.06
Voriconazole (VFEND)	200	\$83.30	6 mg/kg q12h x2	4 mg/kg q12h	\$499.80	\$333.20
Voriconazole (VFEND tablet)	200	\$24.50	200 mg bid	300 mg bid	\$49.00	\$73.50
Voriconazole (VFEND tablet)	50	\$6.13	100 mg bid	150 mg bid	\$24.50	\$36.75