

# Drug Monograph

Drug/Drug Class: Voriconazole (Vfend<sup>®</sup>) / Antifungal

Prepared for: Missouri Medicaid

Prepared by: Heritage Information Systems, Inc.

**New Criteria**

**Revision of Existing Criteria**

## Purpose

The purpose of this monograph is to provide an extensive review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug or not (open access). While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

## Introduction <sup>1-3</sup>

On May 28, 2002, voriconazole (Vfend<sup>®</sup>) was approved by the Food and Drug Administration (FDA) for the treatment of deadly fungal infections. Voriconazole is classified as a triazole antifungal agent. Other agents in this class are fluconazole (Diflucan<sup>®</sup>) and itraconazole (Sporonox<sup>®</sup>). This medication is indicated for the primary treatment of acute invasive aspergillosis. Additional agents include intravenous amphotericin b and oral and/or intravenous itraconazole therapies. It has also been approved as salvage therapy for rare but serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium spp.* Unlike other agents, voriconazole has been approved in both oral and intravenous (IV) formulations.

## Dosage Form(s) <sup>2,3</sup>

Tablets:

- 50mg tablets – white, film-coated, round
- 200mg tablets – white, film-coated, capsule shaped

Powder for Solution for Injection (IV)

- supplied in a single use vial as a sterile lyophilized powder equivalent to 200mg Vfend and 3200mg sulfobutyl ether beta-cyclodextrin sodium (SBECD).

## Manufacturer <sup>1-3</sup>

Pfizer, Inc. Distributed by Roerig, Division of Pfizer, New York, New York 10017

## Indication(s) <sup>2,3</sup>

Voriconazole (Vfend<sup>®</sup>) is indicated for use in the treatment of the following fungal infections:

- Treatment of invasive aspergillosis. Treatment of invasive aspergillosis in clinical trials, the majority of isolates recovered were *Asperillus fumigatus*. There was a small number of cases of culture-proven disease due to species of *Aspergillus* other than *A. fumigatus*.
- Treatment of serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium spp.* including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy.

## Clinical Efficacy <sup>2,3</sup>

### Mechanism of action/Pharmacology

- Voriconazole (Vfend<sup>®</sup>) is a triazole antifungal agent. The primary mode of action or voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlated with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

## Contraindications <sup>2,3</sup>

Vfend<sup>®</sup> is contraindicated in patients with:

- Known hypersensitivity to voriconazole or its excipients. (There is no information regarding cross-sensitivity between Vfend and other azole antifungal agents.)
- Coadministration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozone, or quinidine can lead to QT prolongation.
- Coadministration with sirolimus – will significantly increase sirolimus concentrations (in healthy subjects).
- Coadministration with rifampin, carbamazepine, and long-acting barbiturates – will significantly decrease plasma voriconazole concentrations.
- Coadministration with rifabutin – significantly increases rifabutin plasma concentrations and rifabutin also significantly decreases voriconazole plasma concentrations.
- Coadministration with ergot alkaloids – may increase the plasma concentration of ergot alkaloids, which may lead to ergotism.



## Warnings <sup>2,3</sup>

### Visual disturbances

- The effect of Vfend<sup>®</sup> on visual function is not known if treatment continues beyond 28 days. If treatment continues beyond 28 days, visual function including visual acuity, visual field, and color perception should be monitored.

### Hepatic toxicity

- In clinical trials, there have been uncommon causes of serious hepatic reactions during treatment with Vfend<sup>®</sup> (including clinical hepatitis, cholestasis, and fulminant hepatic failure, including fatalities).
- Liver function tests (LFTs) should be evaluated at the start of and during the course of Vfend<sup>®</sup> therapy. Patients who develop abnormal liver function tests during therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly LFTs and bilirubin). Discontinuation of therapy must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to Vfend<sup>®</sup>.

## Adverse Effects <sup>2,3</sup>

The most frequently reported adverse events (all causalities) in the Vfend<sup>®</sup> therapeutic trials were:

- Visual disturbances
- Headache
- Abdominal pain
- Respiratory disorder
- Fever
- Sepsis
- Nausea
- Vomiting
- Rash
- Peripheral edema
- Diarrhea

The treatment-related adverse events that most often led to discontinuation of Vfend<sup>®</sup> (voriconazole) therapy were:

- Elevated liver tests
- Rash
- Visual disturbances

*Lab test abnormalities.* The overall incidence of clinically significant transaminase abnormalities in the voriconazole clinical program was 13.4% if patients treated with voriconazole. Increased incidence of liver function test abnormalities may be associated with higher plasma concentrations or doses. The majority of abnormal liver function tests either resolve during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.



## Drug Interactions <sup>2,3</sup>

Precipitant Drug	Object Drug*		Description
Barbiturates, long acting Carbamazepine	Voriconazole	↓	Coadministration may decrease voriconazole plasma concentration caused by CYP450 induction. Coadministration is contraindicated.
Cimetidine	Voriconazole		Cimetidine increased voriconazole C <sub>max</sub> and AUC by an average of 18% and 23%, respectively. No dosage adjustment is required.
Phenytoin	Voriconazole	↓	Phenytoin may increase the metabolism of voriconazole via CYP450 induction, therefore, decreasing the C <sub>max</sub> and AUC.
Voriconazole	Phenytoin	↑	Voriconazole may increase the C <sub>max</sub> and AUC of phenytoin up to 2 times. Monitor for adverse reactions and phenytoin plasma concentrations.
Rifampin Rifabutin	Voriconazole	↓	Voriconazole plasma concentrations are significantly reduced during coadministration. Voriconazole may increase the C <sub>max</sub> and AUC of rifabutin by an average of 3 and 4 times, respectively. Coadministration is contraindicated.
Voriconazole	Rifabutin	↑	
Protease inhibitors	Voriconazole	↑	Voriconazole may inhibit the metabolism of protease inhibitors. The metabolism of voriconazole may be inhibited by protease inhibitors. Monitor closely for toxicity. Coadministration with indinavir showed no significant effects on voriconazole or indinavir exposure.
Voriconazole	Protease inhibitors	↑	
Nonnucleoside reverse transcriptase inhibitors	Voriconazole	↑↓	Coadministration may induce or inhibit the metabolism of voriconazole. Monitor for toxicity and effectiveness of voriconazole. Voriconazole also may inhibit the metabolism of an NNRTI. Monitor for drug toxicity.
Voriconazole	Nonnucleoside reverse transcriptase inhibitors	↑	
Proton pump inhibitors	Voriconazole	↑	Omeprazole may increase the C <sub>max</sub> and AUC of voriconazole by an average of 15% and 40%, respectively. No dosage adjustment is recommended. Voriconazole may increase the C <sub>max</sub> and AUC of omeprazole by an average of 2 and 4 times, respectively. When initiating voriconazole in patients already receiving omeprazole doses of 40mg or greater, reduce the dose of omeprazole by 50%. Voriconazole also may inhibit the metabolism of other proton pump inhibitors that are CYP2C19 substrates.
Voriconazole	Proton pump inhibitors	↑	
Voriconazole	Benzodiazepines	↑	Voriconazole may increase the plasma concentrations of benzodiazepines that are metabolized by the CYP3A4 (ie, midazolam, triazolam, alprazolam). Adjust benzodiazepine dose if needed.
Voriconazole	Calcium channel blockers	↑	Voriconazole may inhibit the metabolism of calcium channel blockers that are metabolized by CYP3A4 (ie, felodipine). Adjust calcium channel blocker dose if needed.



Precipitant Drug	Object Drug*	Description
Voriconazole	Cyclosporine	↑ Coadministration or oral voriconazole increased cyclosporine C <sub>max</sub> and AUC an average of 1.1 and 1.7 times, respectively. When initiating voriconazole, therapy in patients already receiving cyclosporine, reduce the dose of cyclosporine to 50% the original dose. Frequently monitor cyclosporine levels during coadministration and when voriconazole is discontinued.
Voriconazole	Ergot alkaloids	↑ Voriconazole may increase the plasma concentrations of ergot alkaloids and lead to ergotism. Coadministration is contraindicated.
Voriconazole	HMG-CoA reductase inhibitors	↑ Voriconazole has been shown to inhibit lovastatin metabolism. Voriconazole may increase the plasma concentrations of statins that are metabolized by the CYP3A4. Consider dosage adjustment of the statin during coadministration.
Voriconazole	Pimozide Quinidine Cisapride	↑ Voriconazole may inhibit the metabolism of these drugs. Increased plasma concentration may lead to QT prolongation and rare occurrences of torsades de pointes. Coadministration is contraindicated.
Voriconazole	Prednisolone	↑ Voriconazole may increase the C <sub>max</sub> and AUC of prednisolone by an average of 11% and 34%, respectively. No dosage adjustment recommended.
Voriconazole	Sirolimus	↑ Voriconazole can significantly increase the C <sub>max</sub> and AUC of sirolimus by an average of 7-fold and 11-fold, respectively. Coadministration is contraindicated.
Voriconazole	Sulfonylureas	↑ Voriconazole may increase plasma concentrations of sulfonylureas. Monitor for hypoglycemia. Dose adjustment of the sulfonylurea may be needed.
Voriconazole	Tacrolimus	↑ Voriconazole can significantly increase the C <sub>max</sub> and AUC of tacrolimus an average of 2-fold and 3-fold, respectively. When initiating voriconazole therapy in patients already receiving tacrolimus, reduce the dose of tacrolimus to 33% the original dose. Frequently monitor tacrolimus levels during coadministration and when voriconazole is discontinued.
Voriconazole	Vinca alkaloids	↑ Coadministration may increase the plasma concentrations of the vinca alkaloids and lead to neurotoxicity. Consider adjusting the dose of the vinca alkaloid and monitor for toxicity.
Voriconazole	Warfarin	↑ Coadministration significantly increased maximum prothrombin time about 2 times. Closely monitor coagulation tests and adjust warfarin dose accordingly. Voriconazole may also increase the PT in patients receiving other coumarin anticoagulants.

\*↑ = Object drug increased

↓ = Object drug decreased

*Drug/Food interactions:* When multiple doses of voriconazole are administered with high-fat meals, the mean C<sub>max</sub> and AUC are reduced by 34% and 24%, respectively.



## Cost Comparison (at commonly used dosages) <sup>4</sup>

### Initial / Loading Dose

Drug <sup>®</sup>	Strength	Cost per Unit <sup>*</sup>	Route	Dose	Cost per Day <sup>*</sup>	Cost per Load <sup>**</sup>
Vfend <sup>®</sup> (Voriconazole)	200mg/20mL vial	\$ 0.53/mg	Intravenous	6mg/kg every 12 hours for 2 doses	\$ 446.26	\$446.26
Sporonox <sup>®</sup> (Itraconazole)	250mg/25mL vial	\$ 0.74/mg	Intravenous	200mg twice a day	\$295.80	N/A
Sporonox <sup>®</sup> (Itraconazole)	200mg Capsule	\$ 8.16	Oral	200mg twice a day	\$ 32.64	N/A
Amphotericin B (generic) <i>Geneva Brand</i>	50mg/10mL vial	\$ 0.38/mg	Intravenous	1.0 – 1.5 mg/kg/day <sup>⊗</sup>	\$ 26.60 - \$39.90	N/A
Abelcet <sup>®</sup> (Amphotericin B)	50mg/10mL vial	\$ 2.70/mg	Intravenous	5.0 mg/kg/day <sup>⊗</sup>	\$ 945.00	N/A
Ambisome <sup>®</sup> (Amphotericin B)	50mg/10mL vial	\$ 3.77/mg	Intravenous	3.0 – 5.0 mg/kg/day <sup>⊗</sup>	\$ 791.70 – \$969.50	N/A
Amphotec (Amphotericin B)	50mg/10mL vial	\$ 1.87/mg	Intravenous	3.0 – 4.0 mg/kg/day <sup>⊗</sup>	\$ 392.70 – 523.60	N/A

\* Priced at Average wholesale price (AWP) utilizing the RedBook Update – September 2002. New Jersey: Thompson Medical Economics.

<sup>⊗</sup> Dose and cost calculated utilizing an estimated patient weight of 70kg. Dose and Cost will vary with actual patient weight.

### Maintenance Therapy

Drug	Strength	Cost per Unit <sup>*</sup>	Route	Dose	Cost per Day <sup>*</sup>	Cost per Week <sup>**</sup>
Vfend <sup>®</sup> (Voriconazole)	200mg/20mL vial	\$ 0.53/mg	Intravenous	4mg/kg every 12 hours	\$297.50	\$2082.50
Vfend <sup>®</sup> (Voriconazole)	50mg Tablet	\$ 7.81	Oral	100mg every 12 hours	\$31.24	\$ 218.68
Vfend <sup>®</sup> (Voriconazole)	200mg tablet	\$31.25	Oral	200mg every 12 hours	\$62.50	\$ 437.50
Sporonox <sup>®</sup> (Itraconazole)	250mg/25mL vial	\$ 0.74/mg	Intravenous	200mg twice a day	\$295.80	\$ 2070.60
Sporonox <sup>®</sup> (Itraconazole)	200mg Capsule	\$ 8.16	Oral	200mg twice a day	\$ 32.64	\$228.48
Amphotericin B (generic) <i>Geneva Brand</i>	50mg/10mL vial	\$ 0.38/mg	Intravenous	1.0 – 1.5 mg/kg/day <sup>⊗</sup>	\$ 26.60 - \$39.90	\$186.20 - \$ 279.30
Abelcet <sup>®</sup> (Amphotericin B)	50mg/10mL vial	\$ 2.70/mg	Intravenous	5.0 mg/kg/day <sup>⊗</sup>	\$ 945.00	\$ 6615.00
Ambisome <sup>®</sup> (Amphotericin B)	50mg/10mL vial	\$ 3.77/mg	Intravenous	3.0 – 5.0 mg/kg/day <sup>⊗</sup>	\$ 791.70 – \$969.50	\$ 5441.90 – \$ 6786.50
Amphotec (Amphotericin B)	50mg/10mL vial	\$ 1.87/mg	Intravenous	3.0 – 4.0 mg/kg/day <sup>⊗</sup>	\$ 392.70 – 523.60	\$2748.90 – \$ 3665.20

\* Priced at Average wholesale price (AWP) utilizing the RedBook Update – September 2002. New Jersey: Thompson Medical Economics.

# Duration of therapy should be based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response

<sup>⊗</sup> Dose and cost calculated utilizing an estimated patient weight of 70kg. Dose and Cost will vary with actual patient weight.



## Dosage and Administration <sup>2,3</sup>

### Administration

- Vfend tablets should be taken at least one hour before, or one hour following a meal.
- Vfend IV for injection requires reconstitution to 10mg/mL and subsequent dilution to 5mg/mL or less prior to administration as an infusion, at a maximum rate of 3 mg/kg per hour over 1-2 hours.

### Use in Adults

- Therapy must be initiated with the specified loading dose regimen of intravenous Vfend<sup>®</sup> to achieve plasma concentrations of Day 1 that are close to steady state. On the basis of high oral bioavailability, switching between intravenous and oral administration is appropriate when clinically indicated.
- For the treatment of adults with invasive aspergillosis due to *Fusarium* spp. and *Scedosporium apiospermum*, the recommended dosing regimen of Vfend is as follows:

Loading dose:

- 6mg/kg Vfend<sup>®</sup> IV every 12 hours for two doses, followed by

Maintenance dose:

- 4mg/kg Vfend<sup>®</sup> IV, every 12 hours

- Once the patient can tolerate medication given by mouth, the oral tablet form of Vfend<sup>®</sup> (voriconazole) may be utilized.

Oral maintenance dose

- ≥ 40kg – 200mg every 12 hours
- < 40kg – 100mg every 12 hours

### Dosage Adjustment

- If patient response is inadequate, the oral maintenance dose may be increased to:
  - ≥ 40kg – 300mg every 12 hours
  - < 40kg – 150mg every 12 hours
- If patients are unable to tolerate treatment, reduce the dose to:
  - Intravenous maintenance dose
    - ♦ 3 mg/kg every 12 hours
- Oral maintenance dose by 50mg steps to a minimum of
  - ≥ 40kg – 200mg every 12 hours
  - < 40kg – 100mg every 12 hours



- Phenytoin may be coadministered with Vfend<sup>®</sup> if the maintenance dose of Vfend<sup>®</sup> is increased to:
  - Intravenous maintenance dose
    - ♦ 5 mg/kg every 12 hours
  - Oral maintenance dose
    - ♦ ≥ 40 kg – 200mg to 400mg every 12 hours
    - ♦ < 40kg – 100mg to 200mg every 12 hours

Duration of therapy should be based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

#### Use in Geriatric Patients

- No dose adjustment is necessary for geriatric patients.

#### Use in Patients With Hepatic Insufficiency

- In the clinical program, patients were included who had baseline LFTs (AST, ALT) up to 5 times the upper limit of normal. No dose adjustment is necessary in patients with this degree of abnormal liver function, but continued monitoring of LFTs for further elevation is recommended.
- It is recommended that the standard loading dose regimens be used, but that the maintenance dose be *halved* in patients with *mild to moderate hepatic cirrhosis*.

## Conclusion <sup>2,3</sup>

Vfend<sup>®</sup> (voriconazole) is a new primary treatment option for acute invasive aspergillosis, available in both an oral and an intravenous formulation. In clinical trials, both voriconazole formulation (intravenous and oral) have proven to be somewhat effective in comparison to both intravenous amphotericin B and oral itraconazole therapies. Only one study (Study 307/602) evaluated the comparative efficacy between amphotericin B and voriconazole therapy in 277 patients with acute invasive aspergillosis. The mean duration of voriconazole dosing was 76 days (range 2-232 days) as compared 12 days (range 1-85 days) with amphotericin B. A 71% survival rate was seen with voriconazole as compared to 58% with amphotericin B at Day 84.

It is recommended that the patient be initiated on the intravenous formulation of voriconazole for the loading dose portion the treatment and based on clinical response, may then be switched to the oral formulation for maintenance therapy. Duration of therapy with voriconazole is based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response. From a cost comparison standpoint, oral voriconazole is priced similarly to both oral itraconazole and generic amphotericin B intravenous therapy. Likewise, the intravenous voriconazole formulation carries a significant cost as do the other intravenous formulations. Although if the typical treatment duration is as stated in





the above trial, it would cost approximately \$22,610 to treat a 76-day course with voriconazole as compared to approximately \$11,340 to treat a 12-day course with the most expensive amphotericin B product. Further studies are warranted as to the cost and clinical effectiveness of voriconazole therapy.

## Recommendation(s)

It is recommended that oral Vfend be subject to step-wise therapy following clinical edits.

## References

1. Newly approved drug therapies: Vfend (voriconazole). CenterWatch Clinical Trials Listing Service – Patient Resources. <http://www.centerwatch.com/patient/drugs/dru784.html>. Available via Internet. Accessed 2002 September 18.
2. Vfend® package insert. New York, NY: Pfizer; 2002 May.
3. Short RM, Burnham TH, et al., editors. Facts and Comparisons. Missouri: Facts and Comparisons.
4. RedBook Update – September 2002. New Jersey: Thompson Medical Economics.

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