



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Voriconazole (Vfend®)**

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## Hyperlink to Related Coverage Policies

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

CIGNA covers voriconazole (Vfend®) as medically necessary for ANY of the following indications:

- treatment of invasive aspergillosis
- treatment of any of the following when there is failure, contraindication, or intolerance to fluconazole:
  - candidemia
  - severe candida infections (e.g., skin, abdomen, kidney, bladder wall)
  - esophageal candidiasis
- empiric therapy of presumed fungal infections in a febrile neutropenic, high-risk individual (e.g., recipients of bone marrow transplantation, individual with relapsed leukemia)
- treatment of fungal infection caused by *Scedosporium apiospermum* and *Fusarium* spp.
- aspergillosis prophylaxis post transplantation

## FDA Approved Indications

Vfend is a triazole antifungal drug indicated for use in the treatment of:

- Invasive aspergillosis
- Candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds
- Esophageal candidiasis
- Serious infections caused by *Scedosporium apiospermum* and *Fusarium* spp. including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy

## FDA Recommended Dosing

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

## Drug Availability

### Powder for Solution for Injection

Vfend I.V. for Injection is supplied in a single use vial as a sterile lyophilized powder equivalent to 200 mg Vfend and 3200 mg sulfobutyl ether beta-cyclodextrin sodium (SBECD). Individually packaged vials of 200 mg Vfend I.V.

### Tablets

Vfend 50 mg tablets; white, film-coated, round, debossed with "Pfizer" on one side and "VOR50" on the reverse in bottles of 30. Vfend 200 mg tablets; white, film-coated, capsule shaped, debossed with "Pfizer" on one side and "VOR200" on the reverse in bottles of 30.

### Powder for Oral Suspension

Vfend for Oral Suspension is supplied in 100 mL high density polyethylene (HDPE) bottles. Each bottle contains 45 g of powder for oral suspension. Following reconstitution, the volume of the suspension is 75 mL, providing a usable volume of 70 mL (40 mg voriconazole/mL). A 5mL oral dispenser and a press-in bottle adaptor are also provided.

## General Background

### Pharmacology

Voriconazole is a broad-spectrum triazole antifungal which inhibits fungal cytochrome P450 mediated 14 alpha-lanosterol demethylation and disrupts the synthesis of ergosterol, resulting in abnormal fungal cell membrane. The pharmacokinetic properties of voriconazole are similar following administration by either the intravenous (IV) or oral route. Peak plasma concentrations are achieved within 1–2 hours of dosing. Voriconazole is extensively distributed into tissues with volume of distribution estimated to be 4.6 L/kg. Approximately 58% of voriconazole is protein bound.

### Guidelines

According to the the Infectious Diseases Society of America (IDSA) clinical guidelines for the treatment of candidiasis (2009), the usual drug of choice for the treatment of candidemia is IV amphotericin B, IV or oral fluconazole, or IV caspofungin, and on the basis of efficacy, safety, and cost considerations, fluconazole is the agent of choice for the empirical treatment of disseminated candidiasis in non-neutropenic, hemodynamically stable patients. Voriconazole is effective for candidemia (A-I), but it offers little advantage over fluconazole and is recommended as stepdown oral therapy for selected cases of candidiasis due to *Candida krusei* or voriconazole-susceptible *C. glabrata* (BIII).

Based on the recommendations from the IDSA clinical guideline (2009), fluconazole is the treatment of choice for esophageal candidiasis. Ketoconazole and itraconazole capsules are less effective than fluconazole because of variable absorption. Voriconazole is as effective as fluconazole but is associated with more adverse events. A randomized, double-blind, double-dummy, multicenter study (Ally et al., 2001) compared the efficacy and tolerability of voriconazole with fluconazole in the treatment of 487 patients. Of these, 250 patients were diagnosed with esophageal candidiasis at screening. *C. albicans* was the most common pathogen isolated at screening. The immunocompromised patients were randomized to treatment of either voriconazole 200 mg twice daily or fluconazole 400 mg on day one, followed by 200 daily. The duration of treatment ranged from 2–6 weeks. The primary objective of the study was to demonstrate equivalent efficacy between voriconazole and fluconazole. The primary efficacy outcome analysis was based on the response to treatment as assessed by esophagoscopy on day 43 or the end of treatment. The cure rate was 95% for patients receiving voriconazole and 98% for patients receiving fluconazole. Therefore, similar cure rates were observed, and voriconazole was shown to be equivalent to fluconazole in the treatment of proven esophageal candidiasis. A similar number of patients receiving voriconazole and fluconazole experienced adverse events (79.5% vs. 74%). Visual side effects were experienced more frequently in patients taking voriconazole than with fluconazole (18% vs. 5%).

According to the 2008 IDSA guideline, antifungal therapy is appropriate in neutropenic patients who have persistent unexplained fever, despite receipt of 4–7 days of appropriate antibacterial therapy. Although the data are controversial because some analyses show that voriconazole was, overall, slightly inferior to liposomal amphotericin, voriconazole has been shown to be superior to liposomal amphotericin B in the prevention of breakthrough fungal infections in high-risk patients (e.g., recipients of bone marrow transplants and individuals with relapsed leukemia). Thus, use of this compound should be limited to allogeneic bone marrow transplant recipients and individuals with relapsed leukemia.

### **Clinical Efficacy**

To evaluate the efficacy and safety of voriconazole in the treatment of invasive aspergillosis (IA), an open, noncomparative multicenter study was conducted. One hundred and sixteen patients were evaluated for efficacy, while 137 patients were evaluated for tolerability to treatment of voriconazole. Treatment of the immunocompromised patients was initiated with 6 mg/kg twice daily for two doses, then 3 mg/kg twice daily for 6–27 days, followed by 200 mg twice daily orally for up to 24 weeks. Response was assessed by clinical and radiographic change. Of the 116 patients, 56 patients (48%) had either a partial or complete response, 24 patients (21%) had a stable response, and 36 patients (31%) failed to respond to therapy. The underlying disease, such as hematologic disorder, solid organ transplantation, or AIDS was considered to be the most important parameter for the development of IA. Of the 67 patients with hematologic disorders, 39 patients (58%) had a complete or partial response, 10 patients (15%) had a stable response, and 18 patients (27%) failed to respond to therapy. Complete responses were only seen in patients with hematologic disorders. Four patients were diagnosed with AIDS, one patient (20%) had a partial response to therapy, and four patients (80%) failed therapy. In addition, the 84 patients with pulmonary and tracheobronchial infection responded better to voriconazole treatment than patients with other sites (cerebral, disseminated, or sinus) of infection ( $p < 0.001$ ). The most common adverse events were rash, visual disturbance, and elevated liver function tests. Of the 137 patients evaluated for adverse effects, 15 patients (11%) developed abnormal vision, described as blurry or seeing zigzag lines. The overall response rate indicates that voriconazole is an effective agent in the treatment of IA, particularly in patients with hematologic disorders and in sites of infection located in the lung.

A single-center, retrospective, sequential study (Husain et al., 2006) was designed to evaluate fungal infection rates in lung transplant recipients who were managed with either universal prophylaxis with voriconazole ( $n=65$ ) or targeted prophylaxis ( $n=30$ ) with itraconazole +/- inhaled amphotericin in patients at high risk. The rate of IA at one year was better in lung transplant recipients receiving voriconazole prophylaxis as compared to the cohort managed with targeted prophylaxis (1.5% vs. 23%;  $p=0.001$ ). Twenty-nine percent of cases in the targeted prophylaxis group were in patients colonized with *A. niger* who did not receive itraconazole. Threefold increase of liver enzymes was noted in 37–60% of patients receiving voriconazole prophylaxis as compared to 15–41% of patients in the targeted prophylaxis cohort. Compared to 8% in the targeted prophylaxis group, 14% of patients in the voriconazole group had to discontinue antifungal medications due to side effects. Based on these results, voriconazole prophylaxis can be used in preventing IA in lung transplant recipients. However, regular monitoring of liver enzymes is required to avoid hepatotoxicity.

### **Adverse Reactions**

Visual disturbance within 30 minutes of dosing during the first week of therapy occurred in about 30% of patients. Abnormalities in hepatic transaminase level occurred in 13%, which led to treatment discontinuation. Dermatological reactions were reported by 6% of patients, with the majority of reactions being rashes of mild to moderate severity. Voriconazole can cause the development of retinoid-like side effects and facial erythema. As a consequence of extensive hepatic metabolism by cytochrome P450 enzymes, there is potential for numerous drug-drug interactions. Voriconazole is contraindicated with rifampin, rifabutin, sirolimus, carbamazepine, long-acting barbiturates, St. John's Wort, and ergot alkaloids. Other interacting drugs may require dosage adjustments.

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## **Coding/Billing Information**

**Note:** This section is not in use.

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## References

1. Ally R, Schurmann 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 Infect Dis* 2001; 33:1447-54.
2. Apisarnthanarak A, Little JR, Tebas P. Voriconazole versus liposomal amphotericin B for empirical antifungal therapy. *N Engl J Med* 2002; 346:1745-7; author reply 1745-7.
3. Brad J. Spellberg, Scott G. Filler, and John E. Edwards, Jr. Current Treatment Strategies for Disseminated Candidiasis. *Clinical Infectious Diseases*, volume 42 (2006), pages 244–251.
4. Breit SM, Hariprasad SM, Mieler WF, et al. Management of Endogenous Fungal Endophthalmitis With Voriconazole and Caspofungin. *Am J Ophthalmol* 2005;139:135-140.
5. Carrillo AJ, Guarro J. In vitro activities of four novel triazoles against *Scenedosporium* spp. *Antimicrob Agents Chemother* 2001; 45:2151-3.
6. Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2009; 48:503–535.
7. Cornely, O. A., Ullmann, A. J. & Karthaus, M. (2003). Evidence-based assessment of primary antifungal prophylaxis in patients with haematological malignancies. *Blood*. 2003, 101;9: 3365-3372
8. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis* 2002; 34:563-71.
9. Espinel-Ingroff A, Bartlett M, Chaturvedi V, et al. Optimal susceptibility testing conditions for detection of azole resistance in *Aspergillus* spp.: NCCLS collaborative evaluation. National Committee for Clinical Laboratory Standards. *Antimicrob Agents Chemother* 2001; 45:1828-35.
10. Harari S. Current strategies in the treatment of invasive *Aspergillus* infections in immunocompromised patients. *Drugs* 1999; 58:621-31.
11. Husain S, D. L. Paterson DL, Studer S, et al. Voriconazole Prophylaxis in Lung Transplant Recipients. *American Journal of Transplantation*. December 2006. 6;12:3008-3016.
12. Johnson JR. Voriconazole versus liposomal amphotericin B for empirical antifungal therapy. *N Engl J Med* 2002; 346:1745-7; author reply 1745-7.
13. Kirkpatrick WR, Perea S, Coco BJ, Patterson TF. Efficacy of caspofungin alone and in combination with voriconazole in a Guinea pig model of invasive aspergillosis. *Antimicrob Agents Chemother* 2002; 46:2564-8.
14. Kontoyiannis DP. A clinical perspective for the management of invasive fungal infections: focus on IDSA guidelines. *Infectious Diseases Society of America. Pharmacotherapy* 2001; 21:175S-187S.
15. Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. *Lancet*. 2005;366(9495):1435-42.
16. Lazarus HM, Blumer JL, Yanovich S, Schlamm H, Romero A. Safety and pharmacokinetics of oral voriconazole in patients at risk of fungal infection: a dose escalation study. *J Clin Pharmacol* 2002; 42:395-402.
17. Morgenstern, G. R., Prentice, A. G., Prentice, H. G. et al. (1999). A randomized controlled trial of itraconazole versus fluconazole for the prevention of fungal infections in patients with haematological malignancies. *British Journal of Haematology* 105, 901–11.

18. Pappas PG, Rex JH, Sobel JD et al. Guidelines for treatment of candidiasis. *Clin Infect Dis*. 2004; 38(2):161-89.
19. Pelletier R, Loranger L, Marcotte H, De Carolis E. Voriconazole and fluconazole susceptibility of *Candida* isolates. *J Med Microbiol* 2002; 51:479-83.
20. Perea S, Gonzalez G, Fothergill AW, Kirkpatrick WR, Rinaldi MG, Patterson TF. In vitro interaction of caspofungin acetate with voriconazole against clinical isolates of *Aspergillus* spp. *Antimicrob Agents Chemother* 2002; 46:3039-41.
21. Pfaller MA, Messer SA, Hollis RJ, Jones RN. Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of *Aspergillus* spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program, 2000. *Antimicrob Agents Chemother* 2002; 46:1032-7.
22. Pfizer, Inc. VFEND® (voriconazole) package insert. New York, NY: Pfizer, Inc. Dec 2010.
23. Powers JH, Dixon CA, Goldberger MJ. Voriconazole versus liposomal amphotericin B in patients with neutropenia and persistent fever. *N Engl J Med* 2002; 346:289-90.
24. Reichenberger F, Habicht JM, Gratwohl A, Tamm M. Diagnosis and treatment of invasive pulmonary aspergillosis in neutropenic patients. *Eur Respir J* 2002; 19:743-55.
25. Sabo JA, Abdel-Rahman SM. Voriconazole: a new triazole antifungal. *Ann Pharmacother* 2000; 34:1032-43.
26. Shalit I, Shadkchan Y, Samra Z, Osherov N. In Vitro Synergy of Caspofungin and Itraconazole against *Aspergillus* spp.: MIC versus Minimal Effective Concentration End Points. *Antimicrob Agents Chemother* 2003; 47:1416-8.
27. Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2008:46.
28. Ullmann AJ, Heussel CP, Cornely OA. Voriconazole versus liposomal amphotericin B for empirical antifungal therapy. *N Engl J Med* 2002; 346:1745-7; author reply 1745-7.
29. Wheat LJ. Combination therapy for aspergillosis: is it needed, and which combination? *J Infect Dis* 2003; 187:1831-3.
30. Winston, D. J., Maziarz, R. T., Chandrasekar, P. H. et al. (2003). Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomised trial. *Annals of Internal Medicine* 138, 705–13.

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