



Therapeutic Class ReviewSM

Antifungals – Posaconazole (Noxafil[®])

April 2007

New Product for Review:

posaconazole (Noxafil[®]) [Schering-Plough]

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: 3

- 1- dossier w/missing components
- 2- all components present, except pharmacoeconomic model
- 3- all components present (comprehensive)

Executive Summary

- Transplant and oncology patients have compromised immune systems, placing them at risk for invasive fungal infections, which are associated with significant morbidity and mortality.
- The most common fungal infections affecting these populations are *Candida* and *Aspergillus*.
- Current FDA labeling for available antifungal options:

Drug	Aspergillus		Oral Candidiasis	
	Prophylaxis	Treatment	Prophylaxis	Treatment
Fluconazole (Diflucan [®])				X
Itraconazole (Sporanox [®])		X		X
Posaconazole (Noxafil [®])	X		X	X
Voriconazole (Vfend [®])		X		X

- In clinical practice, fluconazole and itraconazole have been used for antifungal prophylaxis in transplant and oncology patients.
- When given in combination with cyclosporine, posaconazole (Noxafil), like other azole antifungal agents, is associated with drug interactions (some of which have been fatal).
- Potential off-label uses of posaconazole (Noxafil) include abdominal candidiasis, zygomycosis, coccidioidomycosis, and salvage therapy for other invasive fungal infections.

Evidence

- All of the available evidence for posaconazole (Noxafil) in the treatment and prevention of fungal infections is uncertain (Grade U) or not useful (Grade X).
 - No reliable conclusions can be drawn from these trials.
 - Available evidence is not helpful in determining the superiority of posaconazole (Noxafil) over existing formulary/preferred antifungal agents.
- Nausea was the most common side effect reported during clinical trials, occurring in up to 38% of patients.

Considerations in subpopulations

- *Pediatrics*: Safety and efficacy in pediatric patients (<13 years old) have not been established. A total of 28 pediatric patients ages 8 through 17 were treated with posaconazole (Noxafil) in clinical trials.
- *Geriatrics*: No differences in efficacy and safety of posaconazole (Noxafil) were noted between older (≥ 65 years of age) and younger patients. Out of 605 patients randomized to posaconazole (Noxafil) in prophylaxis trials, 63 (10%) were 65 years of age or older.
- *Race, ethnicity*: No adjustment in the dosage of posaconazole (Noxafil) is necessary.
- *Gender*: No adjustment in the dosage of posaconazole (Noxafil) is necessary.

Decision

- Posaconazole (Noxafil) is non-preferred/non-formulary because:
 - There is no reliable evidence of posaconazole (Noxafil) efficacy in the treatment of oropharyngeal candidiasis or prophylaxis of invasive fungal infections.
 - There is no consensus on the value of *Aspergillus* prophylaxis in clinical practice.

Products

Drug Products	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^d
fluconazole (Diflucan [®]) ¹	1/1990	N/A	<ol style="list-style-type: none"> 1. Bone marrow transplant - Candidiasis; Prophylaxis 2. Candidal vulvovaginitis 3. Candidiasis 4. Candidiasis of mouth and esophagus 5. Candidiasis of urogenital site 6. Cryptococcal meningitis 	200 mg – 400 mg po/iv daily	Asthma, prophylaxis for candidiasis, coccidioidomycosis, cryptococcosis, cutaneous leishmaniasis, deep mycosis, disseminated sporotrichosis, eye infection, febrile neutropenia, histoplasmosis, aspergillosis pneumonia, <i>P. marneffe</i> , onychomycosis, perforated tympanic membrane, septic shock, tinea
itraconazole (Sporanox [®]) ²	9/1992	2014 – 2019 ^e	<ol style="list-style-type: none"> 1. Aspergillosis 2. Blastomycosis 3. Candidiasis of mouth and esophagus 4. Febrile neutropenia 5. Histoplasmosis 	200 mg – 400 mg po/iv daily	Allescheriosis, aspergillosis prophylaxis, candidal vulvovaginitis, chromomycosis, coccidioidomycosis, cryptococcosis, cutaneous leishmaniasis, fungal keratitis, disseminated <i>C. trichoides</i> , <i>Penicillium marneffe</i> , invasive fungal infection prophylaxis, mycetoma, superficial tinea, yellow nails, paracoccidioidomycosis, sporotrichosis, phaeohyphomycosis

Drug Products	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^d
			6. Onychomycosis due to dermatophyte		
posaconazole (Noxafil) ³	9/2006	9/2011	<ol style="list-style-type: none"> 1. Disseminated candidiasis in severely immunocompromised patients; Prophylaxis 2. Infection due to Aspergillus species in severely immunocompromised patients; Prophylaxis 3. Oropharyngeal candidiasis 	100 mg – 800 mg daily (in divided doses)	Fusarium infection, mycosis, disseminated zygomycosis, disseminated phaeohyphomycosis, mycotic keratitis
voriconazole (Vfend) ⁴	5/2002	5/2007	<ol style="list-style-type: none"> 1. Aspergillosis, Invasive 2. Candidal septicemia 3. Candidiasis of the esophagus 4. Disseminated candidiasis, of the skin and infections in abdomen, kidney, bladder wall, and wounds 5. Mycosis, Serious infections due to <i>Scedosporium apiospermum</i> and <i>Fusarium</i> spp. including <i>Fusarium solani</i> 	100 mg – 300 mg po/iv q12h (Dose based on 75 kg person)	Febrile neutropenia, fungal keratitis, hyalohyphomycosis

References

1. Diflucan[®] (fluconazole) Product Information. Pfizer, Inc: New York, NY, August 2004.
2. Sporanox[®] (itraconazole) Product Information. Janssen Pharmaceutica: Titusville, NJ, June 2006.
3. Noxafil[®] (posaconazole) Product Information. Schering-Plough: Kenilworth, NJ, October 2006.
4. Vfend[®] (voriconazole) Product Information. Pfizer, Inc: New York, NY, November 2006.
5. Vazquez JA, Skiect DJ, Nieto L, Northland R, Sanne I, Gogate J, et al. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. *Clin Infect Dis* 2006;42:1179-86.
6. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007;356:348-59.
7. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007;356:335-47.
8. Raad II, Graybill JR, Bustamante AB, Cornely OA, Gaona-Flores V, Afif C, et al. Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. *Clinical Infectious Diseases* 2006;42:1726-34.
9. Center for Drug Evaluation and Research. Approval package for application number NDA 22-003; Medical Review. Available at: http://www.fda.gov/cder/foi/nda/2006/022003s000_Noxafil_MedR.pdf. Accessed on 12//2006.
10. Product Dossier: Noxafil (posaconazole). Schering-Plough.; Kenilworth, NJ. Reviewed 1/12/2007.
11. Pankhurst CL. Candidiasis (oropharyngeal) [search date June 2005]. *Clin Evid*. 2006;15:1-14.
12. Playford EG, Webster AC, Sorrell TC, Craig JC. Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004920. DOI: 10.1002/14651858.CD004920.pub2.
13. Pienaar ED, Young T, Holmes H. Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD003940. DOI:10.1005/14651858.CD003940.pub2.
14. Playford EG, Webster AC, Sorrell TC, Craig JC. Antifungal agents for preventing fungal infections in solid organ transplant recipients. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004291. DOI: 10.1005/14651858.CD004291.pub2.
15. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Fever and Neutropenia – v.1.2006. Available at: http://www.nccn.org/professionals/physician_gls/PDF/fever.pdf. Accessed on 1/8/2007.
16. Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among HIV-infected persons – 2002 recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002; 51(No. RR-8).
17. Pappas PG, Rex JH, Sobel JD, Filler SG, Dismukes WE, Walsh TJ, et al. Guidelines for the treatment of candidiasis. *Clin Infect Dis* 2004 Jan 15;38(2):161-89.
18. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002 Mar 15;34(6):730-51.
19. Asciglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Rokaert F, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002;34:7-14.