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POSACONAZOLE (NOXAFIL®): A NEW BROAD SPECTRUM TRIAZOLE ANTIFUNGAL

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Patients with cancer, AIDS, recipients of bone marrow or solid organ transplant, and other immunodeficient patients are all at increased risk of acquiring life-threatening invasive fungal infections (IFI) caused by various pathogens, such as *Candida* spp, *Aspergillus* spp, *Cryptococcus, Mucormorales*, among others. Approximately 11 to 28% of transplant recipients acquire fungal infections at some point. Usually opportunistic fungal infections are not life threatening, but in infected bone marrow transplant patients mortality rates can be as high as 60 to 75%.[1] Treatment options for IFI include four classes of antifungal drugs: the polyenes (eg, amphotericin B), the azoles (eg, ketoconazole, itraconazole, fluconazole, and voriconazole), flucytosine, and the echinocandins (eg, caspofungin). Emergence of drug resistance, extensive side effect profile, and relatively low efficacy of established antifungals created a demand for a new agent in high-risk patients.

Posaconazole (pō´ sə kŏn´ ā zôl], or Noxafil® (nŏks´ ə fil), a new molecular entity structurally related to a family of azole antifungals, was developed by Schering Corporation and approved by the FDA on September 18, 2006. Posaconazole is indicated for prophylaxis of fungal infections caused by *Aspergillus sp.* and *Candida sp.* in immunocompromized patients and treatment of oropharyngeal candidiasis. This article will review the pharmacology, pharmacokinetics, dosing, toxicity, and clinical trials of posaconazole.

Pharmacology and pharmacokinetics

Posaconazole works similar to other azole agents by inhibiting 14-alpha-demethylase (CYP51 or Erg 11p) and blocking ergosterol synthesis. Ergosterol molecules serve as building blocks for the fungal cell membrane and imbalance between its production and degradation will results in growth inhibition and cell death. Posaconazole has an extended side chain which makes it different from other azoles. This addition provides higher binding affinity to 14-alpha-demethylase and potentially makes posaconazole less susceptible to mutations. Posaconazole is eliminated by CDR1 and CDR2 encoded pumps, but resistant to efflux by pumps encoded by FLU1 and MDR1.[2]

In vitro and in vivo activity

The minimum inhibitory concentration (MIC_{90}) is usually used to assess *in vitro* or *in vivo* antifungal activity. *In vitro* activity does not always

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correctly reflect *in vivo* response and clinical efficacy. Posaconazole has a broad and potent activity against *C. albicans* and *A. fumigatus in vitro.* Its activity is comparable to or better than that of voriconazole, itraconazole, and amphotericin B.[3] *In vivo* activity was studied in immunocompromised animal models to reflect a potential patient target population. Administration of posaconazole resulted in reduction or clearance of *A. fumigatus, A. flavus*, and *C. albicans* and increased survival, which could be suggestive of fungicidal activity. Similar finding were discovered when posaconazole was used prophylactically.

Administration

Increases in single oral doses from 50 mg to 800 mg and multiple-daily doses from 50 mg BID to 400 mg BID resulted in proportional increases in plasma concentrations and total drug exposure, expressed as area under the curve (AUC). However, total daily doses of pocasonazole exceeding 800 mg did not result in increased plasma concentrations. Posaconazole reaches peak plasma concentration (C_{max}) in 3 to 5 hours and about 7 to 10 days for steady state concentrations. Mean AUC and C_{max} increased by 3-fold when administered with nonfat meals and by 4-fold with high-fat meals. Administration as a suspension resulted in increased exposure by 37% compared to the tablet form. Pocasonazole's oral bioavailability increases when administered in divided doses. Oral bioavailability is increased by 58% when posaconazole was administered 200 mg 4 times daily instead of 400 mg twice daily.[3] Posaconazole is significantly bound to plasma proteins (>98%), especially to albumin. Based on a volume of distribution of 1774 L, it is highly likely that posaconazole distributes beyond the plasma and easily penetrates tissues. Posaconazole is not extensively metabolized by any of CYP P450 enzymes; however, it undergoes glucuronidation mediated by UDP-glucuronosyltransferase (UDP-G). Parent drug is the major form found in circulation. About 17% of a radiolabeled dose is metabolized and excreted primarily as inactive glucuronide conjugates. Elimination of posaconazole occurs primarily via the fecal route (71%) and to a smaller degree via renal (13%).[3] After administering a single radiolabeled dose, 66% was detected in feces as unchanged posaconazole, 13% was present in urine as glucuronide conjugates, and trace amounts of parent form. Posaconazole has a half-life of 35 hours (range, 20-66 hours) suggesting slow elimination. Total body clearance is 32 L/h. Posaconazole is a P-glycoprotein substrate, an ATP-dependent drug efflux transporter. However, some clinical data suggests that posaconazole could be reabsorbed into the systemic circulation.[3] Posaconazole inhibits CYP 3A4 and increases plasma concentrations of CYP 3A4 substrates. Inhibitors or inducers of UDP-glucuronidation and P-glycoprotein efflux could alter posaconazole pharmacokinetics. Rifabutin and phenytoin cause UDP-G induction and decrease posaconazole AUC by 49% and 50%. Cimetidine alters gastric pH and decreases AUC by 39%. The concomitant use of rifabutin, phenytoin, or cimetidine with posaconazole should be avoided. Posaconazole increases AUC of tacrolimus, rifabutin, midazolam and phenytoin by 358%, 72%, 83%, and 16%, respectively.[3] A dose reduction of 29% with cyclosporine is necessary with concomitant posaconazole use. The increase of AUC in the elderly and African American subjects is not clinically significant and no dose adjustment is necessary. Posaconazole is not removed by hemodialysis, probably, due to high protein binding.[3]

Clinical trials

Posaconazole vs. fluconazole for prophylaxis in severe graft-versus-host disease (GHVD)

An international, phase 3, randomized, double-blind trial was conducted by Ullmann and colleagues to compare oral posaconazole and oral fluconazole for prophylaxis against invasive fungal infections in patients with graft-versus-host disease (GVHD) on immunosuppressive therapy.[2] The primary outcome of the study was the incidence of proven or probable invasive fungal infections from randomization to the fixed 112th day of treatment. The exposure period was identified as the period from the first dose to 7 days after the last dose. Of a total of 600 patients, 301 were randomized to receive posaconazole oral suspension at a dose of 200 mg three times daily and 299 to fluconazole 400 mg encapsulated tablet orally once daily. Posaconazole was equally effective to fluconazole in preventing all invasive fungal infections, and superior in preventing proven or probable invasive aspergillosis (**Table 1**). Fewer patients receiving posaconazole acquired breakthrough invasive fungal infections during the exposure period (**Table 2**). The Kaplan-Meier method was used to analyze the time to IFI (**Figure 1**). There was a delay in the onset of infections in the

Table 1. Posaconazole vs. fluconazole for prophylaxis against IFI in patients with graft-versus-host disease (GVHD)[4]

Pathogen or Pathogen Group Fixed treatment period	Posaconazole Group (N=301) No. (%)	Fluconazole Group (N=299) No. (%)	Odds Ratio (95%CI)	P Value
All proven and probable invasive fungal infections	16 (5.3)	27 (9.0)	0.56 (0.30-1.07)	0.07
All invasive aspergillosis	7 (2.3)	21 (7.0)	0.31 (0.13-0.75)	0.006

IFI: invasive fungal infections

Table 2. Posaconazole vs. fluconazole for prophylaxis against IFI in patients with graft-versus-host disease (GVHD)[4]

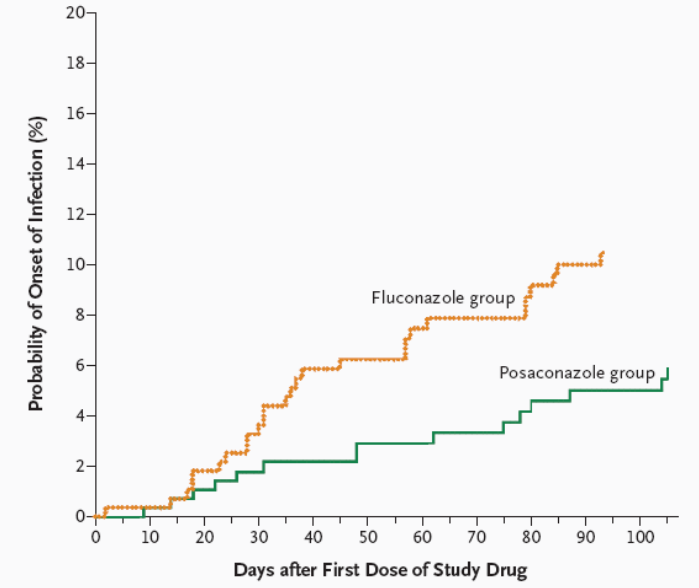
Pathogen or Pathogen Group Exposure period	Posaconazole Group (N=291) No. (%)	Fluconazole Group (N=288) No. (%)	Odds Ratio (95%CI)	P Value
All proven and probable invasive fungal infections	7 (2.4)	22 (7.6)	0.30 (0.12-0.71)	0.004
All invasive aspergillosis	3 (1.0)	17 (5.9)	0.17 (0.05-0.57)	0.001

IFI: invasive fungal infections

posaconazole group versus the fluconazole group during the fixed treatment period (P=0.048).[4] Overall mortality and the incidence of treatment-related adverse events were similar between groups.

Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia.

Figure 1. Posaconazole vs fluconazole: Time to proven or probable IFI



Adopted from Ullmann et al.[4] IFI: invasive fungal infections

Cornely et. al. compared the efficacy and safety of posaconazole, fluconazole or intraconazole for prophylaxis in patients with prolonged neutropenia.[5] A total of 602 patients participated in this prospective, randomized, evaluator-blinded, multicenter study. Patients (n=304) received 200 mg of posaconazole oral suspension TID and 298 patients received 400 mg of fluconazole oral suspension once daily (240 patients) or 200 mg of itraconazole oral solution BID (58 patients). The primary endpoint of the study was the incidence of proven or probable IFI during treatment. Prophylaxis was administered with each cycle of chemotherapy until recovery from neutropenia and complete remission, until occurrence of an invasive fungal infection, or for up to 12 weeks, whichever came first. Proven or probable IFI, especially invasive aspergillosis, occurred in fewer posaconazole recipients than in the fluconazole or itraconazole group (**Table 3**). Administration of posaconazole resulted in significantly longer survival (P=0.004). According to the Kaplan-Meier analysis for time to death from any cause at the end of the 100-day period after randomization, posaconazole resulted in a significant survival benefit (P=0.04) (**Figure 2**).

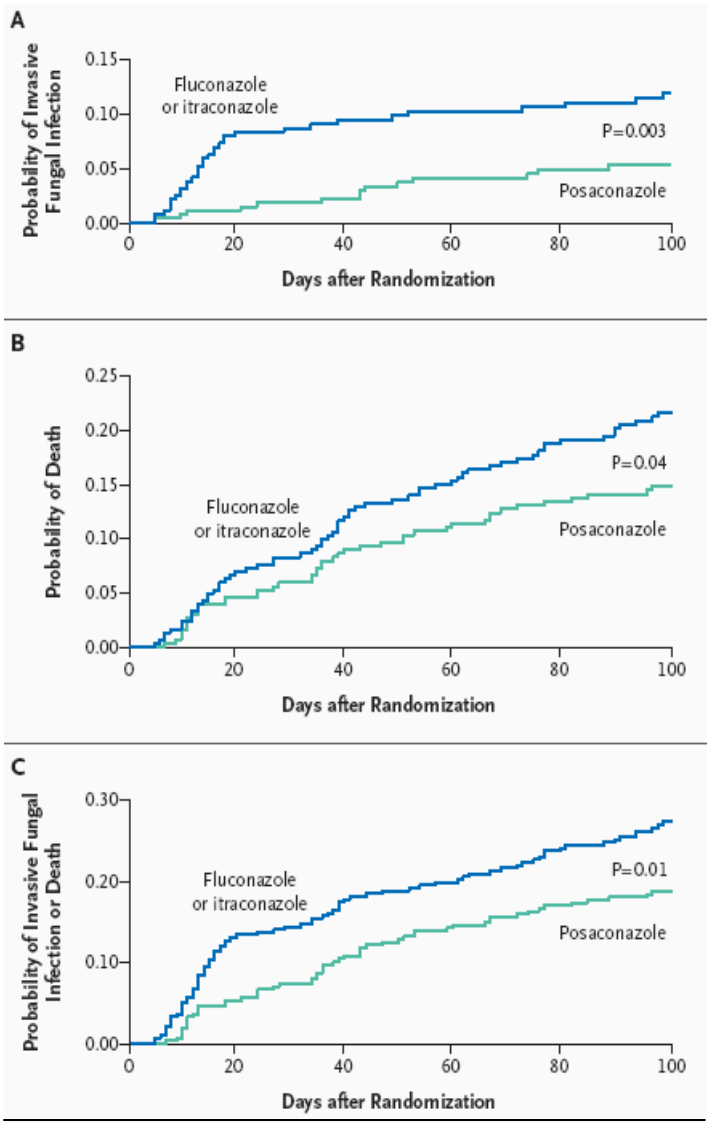
Posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS

Table 3. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia

IFI during treatment phase*	Posaconazole (N=304) No. (%)	Fluconazole or Itraconazole (N=298) No. (%)	Fluconazole (N=240)	Itraconazole (N=58)	P Value**	95 % CI
Proven or probable	7 (2)	25 (8)	19 (8)	6 (10)	<0.001	-9.7 to -2.5
Invasive aspergillosis	2(1)	20 (7)	15 (6)	5(9)	<0.001	-9.1 to -3.1

Adopted from Cornely et al.[5] *The treatment phase was defined as the period from randomization to 7 days after the last dose of the study drug had been administered during the last cycle of chemotherapy. **P values and 95% confidence intervals (CIs) are reported for the posaconazole group compared with the pooled fluconazole and itraconazole groups.; IFI: invasive fungal infections

Figure 2. Kaplan–Meier curves for time to IFI (Panel A), death from any cause (Panel B), and IFI or death (Panel C) over the 100-day period after randomization



Adopted from Cornely et al.[5]; IFI: invasive fungal infections

In this multicenter, evaluator-blinded study, Vasquez et. al. randomized 350 patients with HIV infection and oropharyngeal candidiasis to two groups: 178 in the posaconazole group and 172 in the fluconazole group.[6] Patients received either 200 mg of posaconazole or fluconazole oral suspension on day 1, followed by 100 mg/day for 13 days. The primary outcome was clinical cure or improvement on day 14. The robustness of the data was evaluated on day 42. Clinical success occurred in 155 (91.7%) of 169 posaconazole recipients and in 148 (92.5%) of 160 fluconazole recipients (95% confidence interval, 6.61% to 5.04%), indicating that posaconazole was not inferior to fluconazole. Posaconazole was more effective in sustaining clinical success after treatment was discontinued. . On day 14, mycological success was 68% in both arms, but by day 42, significantly more posaconazole recipients continued to have mycological success (40.6% vs. 26.4%).

Pooled data from other recent clinical trials reflecting posaconazole use in refractory treatment patients

Studies suggest that resistant fungi can be successfully treated with posaconazole, despite the cross-resistance between posaconazole and the older generation azoles.[8-13] Skiest et al. showed in an open-label trial that posaconazole was effective in 75% of HIV-infected patients with oropharyngeal and oesophageal candidiasis refractory to fluconazole or itraconazole.[8] Posaconazole could be used as alternative therapy for invasive aspergillosis caused by *A fumigatis* and *A terreus* refractory to amphotericin B. An open-label trial performed by Walsh et al. showed that the overall success rate was 42% in refractory or intolerant to conventional therapy pa-

Table 4. Recent clinical trials of posaconazole as salvage therapy against difficult-to-treat fungal infections.

Reference	Fungal Infection	Number of patients treated	Predominant underlying condition (proportion of patients affected)	Response Rate (%)
Skiest et al.[8]	Oropharyngeal and oesophageal candidiasis	199	HIV/AIDS (100%)	75
Walsh et al.[9]	Invasive aspergillosis	107	Haematological malignancy (74%)	42
Hachem et al.[10]	Invasive aspergillosis due to *Aspergillus fumigatus*	8	Haematological malignancy (100%)	50
Hachem et al.[10]	Invasive aspergillosis due to *Aspergillus terreus*	9	Haematological malignancy (100%)	44
Raad et al.[11]	Fusariosis	20	Haematological malignancy (75%)	45
Greenberg et al.[12]	Zygomycosis	23	Haematological malignancy (61%)	70
Restrepo et al.[13]	Histoplasmosis	7	HIV/AIDS (43%)	83

Adopted from Torres et al[7]

tients treated with posaconazole compared with 26% in the control group.[9] Posaconazole appears to be a valuable therapeutic option in patients with fusariosis, zygomycosis and histoplasmosis.[11-13] A summary of posaconazole use as salvage therapy is located in **Table 4.**

Dosing and Administration

Posaconazole is supplied as a cherry-flavored suspension containing 40 mg of posaconazole per ml. Each dose of posaconazole should be administered with a full meal or a liquid nutritional supplement. Patients with diarrhea, vomiting, and concomitant medications should be monitored for breakthrough fungal infections. The duration of treatment depends on recovery from neutropenia or immunosuppression. Posaconazole is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections at dose of 200 mg (5 ml) TID in patients 13 years of age or older, who are severely immunocompromised. An additional indication is for the treatment of oropharyngeal candidiasis for which posaconazole is administered on the first day at a loading dose of 200 mg once a day, then 100 mg once a day for 13 days. For oropharyngeal candidiasis refractory to itraconazole and fluconazole, the dose is higher at 400 mg twice a day. The duration of treatment for oropharyngeal candidiasis should be based on the severity of the patient's underlying disease and clinical response. In patients with hepatic impairment, posaconazole should be used with caution. No dose adjustment is warranted in patients with renal insufficiency.[3]

Toxicity and Safety

The safety of posaconazole has been evaluated in 605 patients in the prophylaxis studies and 1239 patients treated for other indications. In the prophylaxis study of patients with neutropenia, the safety and tolerability of the study drugs were evaluated in 602 patients.[5] Investigators found that 34% of patients in posaconazole group experienced an adverse event related to the study drug. Gastrointestinal adverse events such as diarrhea, nausea, and vomiting were reported most frequently. Rash and QTc prolongation were also commonly reported side effects. Another prophylaxis study was conducted in HSCT recipients with GVHD.[4] In the posaconazole group, 36% of patients experienced a treatment-related adverse event. Gastrointestinal adverse events were the most frequently reported. Hypertension (1%), tremor (1%) and sensory disturbances such as blurred vision and taste perversion (both 1%) were reported by HSCT recipients.[3] Side effects that occurred in > 2% of patients in both prophylaxis studies are presented in **Table 5**.

The most common adverse events associated with both prophylaxis studies were bilirubinemia, increased hepatic enzyme levels, hepatocellular damage, nausea and vomiting.[3] Serious and medically

Table 5. Treatment-related adverse events with a 2 % or greater incidence

	Patients with Neutropenia[5] N (%)		HSCT Recipients with GVHD[4] N (%)	
Adverse Events	**Posaconazole (N=304)**	**Fluconazole/Itraconazole (N=298)**	**Posaconazole (N=301)**	**Fluconasole (N=299)**
Subjects reporting any adverse event.	102 (34)	101 (34)	107 (36)	115 (38)
Body as a whole: general disorders				
Headache	5 (2)	1(<1)	3 (1)	8 (3)
GI system disorders				
Nausea	22 (7)	25 (8)	22 (7)	28 (9)
Diarrhea	20 (7)	21 (7)	8 (3)	12 (4)
Vomiting	14 (5)	20 (7)	13 (4)	15 (5)
Abdominal Pain	9 (3)	9 (3)	4 (1)	7 (2)
Heart Rate and rhythm disorders				
QT/QTc prolongation	12 (4)	9 (3)		
CV Disorders, general				
HTN			2 (1)	5 (2)
Liver and biliary system disorders				
Bilirubinemia	7 (2)	8 (3)	8 (3)	5 (2)
Hepatic Enzymes increased	7 (2)	3 (1)	8 (3)	7 (2)
Metabolic and nutritional disorders				
Hypokalemia	9 (3)	6 (2)		
Alkaline phosphatase			5 (2)	5 (2)
Skin and subcutaneous tissue disorders				
Rash	9 (3)	11 (4)		
Renal and urinary system disorders				
Serum creatinine increase			6 (2)	5 (2)

significant adverse events such as adrenal insufficiency, allergic and/or hypersensitivity reactions are uncommon and rare. Patients on concomitant cyclosporine or tacrolimus therapy were reported to have rare cases of hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and pulmonary embolus.[3]

Cost

Posaconazole is supplied as a 4-ounce (123 mL) bottle containing 105 mL of suspension (200 mg of posaconazole per 5 mL). As of April of 2007, the average retail price of Noxafil® is $685 per bottle ($676 - $692), or approximately $27.40/200 mg dose.

Summary

Posaconazole is a new triazole antifungal that blocks ergosterol synthesis. Posaconazole is indicated for prophylaxis of IFI primarily caused by *Aspergillus sp.* and *Candida sp.* in immunocompromised patients. Posaconazole represents a valuable

therapeutic alternative to fluconazole and itraconazole in refractory patients with oropharyngeal candidiasis. Posaconazole has been studied in patients with human immunodeficiency virus (HIV), hematopoietic stem cell transplantation (HSCT) recipients with GHVD, and neutropenic patients and considered to be equally effective to fluconazole in these patient populations. Posaconazole changes the metabolism of CYP 3A4 substrates and itself is subject to changes from inducers or inhibitors of UDP-G and/or P-glycoprotein. The adverse event profile of posaconazole includes common side effects such as bilirubinemia, increased hepatic enzyme levels, hepatocellular damage, nausea and vomiting. Serious and rare treatment-related adverse events are adrenal insufficiency, allergic and/or hypersensitivity reactions.

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