Posaconazole (Noxafil), an Extended-Spectrum Oral Triazole Antifungal Agent

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INTRODUCTION

The incidence of fungal infections has dramatically increased in the past few decades.1,2 These infections contribute significantly to morbidity and mortality in hospitalized patients.1,2 The high prevalence of infection is primarily attributable to an increase in the number of immunocompromised patients, such as those with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS); to hematological malignancies; and to transplant recipients, who are susceptible to invasive fungal infections (IFIs). Severely ill critical-care patients are also at high risk.1,2 Even with the addition of newer antifungal agents to the current list of available medications, the rise in resistant mycoses has led to challenges in how to manage these infections. The most common clinical pathogens include resistant organisms from Candida and Aspergillus species.1,2,5

The current management of IFIs is challenging because of the relative unavailability of tools to test the resistance of fungal isolates in microbiological laboratories and because of the development of resistance among Candida species. Clinically available antifungal agents include amphotericin B, anidulafungin (Eraxis, Pfizer), caspofungin (Cancidas, Merck), micafungin (Mycamine, Astellas), fluconazole (Diflucan, Pfizer), itraconazole (Sporanox, Janssen), voriconazole (Viend, Pfizer), and posaconazole (Noxafil, Schering-Plough). The triazoles include fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole (Basilea Pharmaceuticala), and pamiconazole (Barrier Therapeutics).

Although amphotericin B is considered the gold standard and is recommended as a first-line therapy for severe mycoses, its use is limited by its toxicities of the conventional formulation and by the high cost of the lipid emulsions.1,2 Echinocandins such as anidulafungin, caspofungin, and micafungin have comparable activity against many species of fungi. Echinocandins also have improved toxicity profiles, compared with amphotericin B; however, no oral formulations are available.

Fluconazole, itraconazole, posaconazole, and voriconazole make up the currently available triazole antifungals. Both fluconazole and voriconazole offer favorable safety profiles and are available in oral and intravenous (IV) forms.1 Itraconazole has a broad spectrum of activity, but its use is limited by the poor oral absorption.1

The U.S. Food and Drug Administration (FDA) approved posaconazole in September 2006. It is the newest orally administered triazole antifungal with an extended spectrum of activity. Posaconazole is indicated for the prophylaxis of invasive Aspergillus and Candida infections in severely immunocompromised patients 13 years of age or older.1 Immune compromised patients are identified as hematopoietic stem-cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematological malignancies with prolonged febrile neutropenia from chemotherapy.1 Posaconazole is also indicated for the treatment of oral candidiasis, including cases refractory to itraconazole and fluconazole.1 Among the extended-spectrum triazoles, posaconazole has proved to be a promising addition to the antifungal group of medications for the treatment and prophylaxis of IFIs.

Although posaconazole is structurally related to itraconazole, it is a more potent inhibitor of ergosterol synthesis (Figure 1).

PHARMACOLOGY

Similar to the other triazole antifungal medications, posaconazole alters the fungal cell membrane by inhibiting ergosterol synthesis via an interaction with 14α-demethylase.4 Ergosterol is an important component of the fungal cell membrane; inhibition of its biosynthesis...
PHARMACOKINETICS

Available as an oral suspension, posaconazole is administered with food or a nutritional supplement to attain adequate plasma concentrations. Ezzet et al., evaluating the effect of a high-fat meal on the drug’s bioavailability, concluded that administering posaconazole with high-fat content food ensured four-fold greater systemic exposure than ingesting a posaconazole suspension or tablet with a low-fat meal.

Ezzet et al. evaluated the bioavailability of posaconazole in a fasting state at different dosing intervals. The drug’s bioavailability was increased by 98% when the dose was administered every 12 hours and by 220% when it was given every six hours.

Sansone-Parsons et al. assessed the effect of nutritional supplementation with Boost Plus (Novartis), an oral drink, on posaconazole’s pharmacokinetics. They determined that the study drug’s peak concentration ($C_{\text{peak}}$) and area-under-the-curve (AUC) concentration were higher in subjects taking posaconazole with the drink than in participants who did not get the supplement.

The drug’s volume of distribution is large (1,774 liters), indicative of its extensive extravascular distribution and tissue penetration. It is more than 98% protein-bound, mainly to albumin.

Posaconazole undergoes glucuronidation in the liver, but it circulates primarily in the plasma as an unchanged compound. It does not undergo oxidative metabolism by the cytochrome P450 (CYP 450) enzyme system. Like other azoles, however, it inhibits the CYP 450 3A4 enzyme. Approximately 17% of the dose is excreted as metabolites in the urine and feces. Posaconazole should be used with caution in patients with severe hepatic impairment.

The drug’s elimination half-life is 35 hours (range, 20–66 hours), and its total body clearance is 32 L/hour. Posaconazole undergoes fecal elimination; approximately 66% is excreted in the feces as the parent drug. The renal elimination pathway accounts for about 13% of the administered dose; therefore, no dose adjustment is indicated in patients with renal disease. Comparative pharmacokinetic parameters of the azoles are reviewed in Table 1.

IN VITRO MICROBIOLOGICAL ACTIVITY

Sabatelli et al., 2005

The in vitro activity of posaconazole was tested against approximately 19,000 clinically important strains of yeasts and molds, according to Clinical and Laboratory Standards Institute (CLSI) guidelines. The activity of posaconazole was compared with that of itraconazole, fluconazole, voriconazole, and amphoteri-

The minimum inhibitory concentration (MIC$_{50}$) and the MIC$_{90}$ for posaconazole against Candida species were 0.063 and 1 mcg/mL, including C. glabrata, 1 and 2 mcg/mL; C. albicans, 0.031 and 0.063 mcg/mL; and Candida krusei, 0.5 and 1 mcg/mL, respectively. The MIC$_{50}$ and MIC$_{90}$ against Aspergillus species were 0.125 and 0.5 mcg/mL, respectively. The MIC$_{50}$ and MIC$_{90}$ against zygomycetes were 0.5 and 4 mcg/mL, respectively.

In comparison, posaconazole was more active than, or within one dilution of, itraconazole, fluconazole, voriconazole, and amphoterin B. Posaconazole was more active than or equal to the other antifungal agents against all molds such as Aspergillus species and was active against Candida and Aspergillus species that displayed resistance to fluconazole, voriconazole, and amphoterin B.

Torres-Narbona et al., 2007

An in vitro comparison of posaconazole, amphoterin B, itraconazole, voriconazole, and caspofungin against 45 clinical isolates of zygomycetes was evaluated on the basis of the CLSI standards. With its MIC$_{90}$ of 1 mcg/mL, posaconazole was more active than all of its comparators against zygomycetes. Posaconazole had the lowest MIC, compared with other antifungal agents, against Absidia species (at 1 mcg/mL) and against Mucor species (at more than 16 mcg/mL).

Table 1 Comparative Pharmacokinetics of Various Triazole Antifungal Agents

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Posaconazole (Noxafil)</th>
<th>Itraconazole (Sporanox)</th>
<th>Voriconazole (Vfend)</th>
<th>Fluconazole (Diflucan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>Variable</td>
<td>Variable</td>
<td>96%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>465–1,774 liters</td>
<td>796 liters</td>
<td>350 liters</td>
<td>180 liters</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic glucuronidation</td>
<td>Major: cytochrome (CYP) 3A4</td>
<td>Major: CYP 2C19, CYP 2C9 Minor: CYP 3A4</td>
<td>11% metabolized hepatically</td>
</tr>
<tr>
<td>Excretion</td>
<td>Feces, 71%–77%</td>
<td>Feces, 3%–18%</td>
<td>Urine</td>
<td>Urine, 80%</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>35 hours</td>
<td>21–64 hours</td>
<td>Variable</td>
<td>Approx. 30 hours</td>
</tr>
</tbody>
</table>
IN VIVO ANIMAL EFFICACY STUDIES

Cacciapuoti et al., 200610

Potential, theoretical, and different but complementary mechanisms of action of posaconazole and caspofungin were investigated. Immunocompetent mice infected with *Aspergillus fumigatus* and *Aspergillus flavus* were treated with a combination of posaconazole and caspofungin (Cancidas).

The MIC<sub>90</sub> of posaconazole ranged from 0.03 to 0.125 mcg/mL against all strains of *Aspergillus* species. The MIC<sub>90</sub> for caspofungin ranged from 32 to 128 mcg/mL, and minimum effective concentrations (MECs) ranged from 0.03 to 0.06 mcg/mL. The combination of posaconazole and caspofungin was synergistic or indifferent for *A. fumigatus* and was indifferent for *A. flavus* isolates. No antagonism was observed with the concomitant use of posaconazole and caspofungin in mice infected with *Aspergillus* species.

Barchiesi et al., 200711

Zygomycosis manifests as rhinocerebral, pulmonary, gastrointestinal, and cutaneous disseminated disease. It is a rare but highly aggressive fungal infection associated with a high mortality rate. Most common zygomycetes that are identified as etiological pathogens in humans are *Rhizopus, Rhizomucor, Mucor,* and *Absidia* species. Zygomycosis usually affects immunocompromised hosts, including patients with diabetes mellitus or neutropenia and those taking chronic corticosteroids.

Therapy usually includes surgical debridement and high doses of IV amphotericin B. Because posaconazole has shown activity against zygomycetes in *vitro*, it was compared with amphotericin B for prophyaxis against *Rhizopus oryzae* and *Absidia corymbifera* in an experimental model of neutropenic mice. In *vitro* susceptibilities of *Rhizopus* species for posaconazole and amphotericin B ranged from 1 to 2 mcg/mL and from 0.5 to 4 mcg/mL, respectively. The susceptibilities for *A. corymbifera* were 0.25 to 2 mcg/mL for posaconazole and 1 to 2 mcg/mL for amphotericin B, respectively.

The survival rate for mice that were infected with *R. oryzae* and treated with posaconazole was not improved, but mice treated with amphotericin B had significantly prolonged survival rates, compared with control mice (*P* = 0.001). Mice that were infected with *A. corymbifera* and that were treated by both posaconazole and amphotericin B had longer survival rates than controls (*P* < 0.05).

Prophylaxis with both drugs was effective at reducing the size of foci in kidneys infected by *R. oryzae* (*P* < 0.05), but neither drug was effective in the brain. Both drugs reduced the numbers and sizes of infectious foci in kidneys and brain tissues of mice infected with *A. corymbifera,* suggesting a prophylaxis potential of posaconazole for zygomycosis.

IN VIVO HUMAN EFFICACY STUDIES

Prophylaxis for Febrile Neutropenia and Invasive Fungal Infections

Ullmann et al., 200612

The efficacy and safety of different dosing regimens of posaconazole oral suspension were evaluated in a multicenter, randomized, open-label, parallel-group study in patients with possible, probable, and proven refractory invasive fungal infections (IFIs) or febrile neutropenia (FN). Overall, 66 subjects with FN and 32 patients with IFIs were randomly assigned to one of three posaconazole schedules:

- 200 mg four times a day for nine doses, followed by 400 mg twice daily (regimen 1)
- 400 mg four times a day for nine doses, followed by 600 mg twice daily (regimen 2)
- 800 mg twice a day for five doses, followed by 800 mg once daily (regimen 3)

Therapy was continued for up to six months in patients with IFIs or until neutrophil count recovery in patients with FN. In all, successful clinical responses were observed in 43% of patients with IFIs: 56% with regimen 1, 17% with regimen 2, and 50% with regimen 3. The overall successful response rate in patients with FN was 77%; 74% of patients receiving regimen 1, 78% receiving regimen 2, and 81% receiving regimen 3. Treatment-related adverse events occurred in 24% of recipients and were mostly gastrointestinal.

Cornely et al., 200713

Patients with FN caused by aggressive chemotherapy for acute myelogenous leukemia and myelodysplastic syndrome are at increased risk for fatal IFIs. In this randomized, multicenter, single-blinded study, the investigators compared the efficacy and safety of posaconazole with that of fluconazole or itraconazole. A total of 304 subjects received antifungal prophylaxis by each cycle of chemotherapy until recovery from neutropenia and complete remission. If fungal infection occurred during therapy, antifungal treatment was continued for up to 12 weeks. The incidence of proven or probable IFIs was compared for posaconazole versus fluconazole or itraconazole-treated groups. Proven or probable fungal infections were reported in seven patients (2%) in the posaconazole group and in 25 patients (8%) in the fluconazole or itraconazole group, thus revealing the superiority of posaconazole: absolute reduction, –6%; 95% confidence interval (CI), –9.7 to –2.5% (*P* < 0.001).

Significantly fewer patients in the posaconazole group (two patients, 1%) had invasive aspergillosis (20 patients, 7%) (*P* < 0.001). Survival was significantly higher among the posaconazole-treated subjects than among recipients of fluconazole or itraconazole (*P* = 0.04).

Ullmann et al., 200714

In an double-blind, randomized, international trial, the Ullmann team investigated the incidence of IFIs in 600 patients after allogeneic hematopoietic stem-cell transplantation (HSCT). Oral posaconazole or fluconazole was administered as prophylaxis against IFIs in patients with graft-versus-host disease (GVHD) who were receiving immunosuppressive therapy. The incidence of proven or probable IFIs was recorded for up to 112 days. Posaconazole was found to be as effective as fluconazole in preventing all IFIs, with an incidence of 5.3% and 9%, respectively (*P* = 0.07). It was also superior to fluconazole in preventing proven or probable invasive aspergillosis (2.3% vs. 7%, respectively) (*P* = 0.006).

Overall mortality rates were similar in the two groups, but the number of deaths from IFIs was lower with posaconazole treatment (1%) than with fluconazole (4%) (*P* = 0.046).
Candidiasis
Vazquez et al., 2006\textsuperscript{15}

Oropharyngeal candidiasis is a common opportunistic infection in patients with HIV infection. In a multicenter, randomized, single-blinded study, the efficacy of posaconazole versus fluconazole was compared in subjects with HIV and oropharyngeal candidiasis. The posaconazole dose was 200 mg daily, and the fluconazole dose was 100 mg daily for 13 days. Clinical success, including cure or improvement on day 14, was assessed in 329 subjects. The durability of clinical success was evaluated on day 42.

Clinical success was noted in 91.7% of posaconazole patients and in 92.5% of fluconazole subjects (95% CI, –6.61% to 5.04%), indicating the non-inferiority of posaconazole. After 14 days of therapy, mycological success was described in 68% of patients in both groups, and by day 42, significantly more posaconazole recipients than fluconazole recipients experienced continuous mycological success (40.6% vs. 26.4%) (\textit{P} = 0.038).

Skiest et al., 2007\textsuperscript{16}

The efficacy and safety of posaconazole in oropharyngeal and esophageal candidiasis were evaluated in patients with HIV infection who had been clinically unresponsive to fluconazole or itraconazole. The subjects were given one of two different regimens of posaconazole:

- 400 mg twice daily for three days, followed by 400 mg once daily for 25 days (regimen 1)
- 400 mg twice daily for 28 days (regimen 2)

Clinical response was detected in 75% of both treatment groups. Response rates were similar between regimen 1 (75.3%) and regimen 2 (74.7%). Of those subjects with disease resistant to fluconazole, 73% responded and 74% of those with infection resistant to itraconazole achieved clinical cure. Overall, 74% of all subjects with resistant isolates were cured with posaconazole. Of those patients with esophageal candidiasis, 74.4% responded to posaconazole.

Aspergillosis
Walsh et al., 2007\textsuperscript{17}

The efficacy and safety of posaconazole monotherapy were evaluated in an open-label, multicenter study of patients with invasive aspergillosis and other mycoses who did not respond to or who were intolerant of conventional antifungal therapy. The controls constituted a retrospectively retrieved reference group of patients who had been treated with other antifungals. The data were reviewed by committee-assessed global responses generated by 15 experts in antifungal therapy and by two radiologists who evaluated posaconazole-treated subjects and controls in a parallel, blinded fashion using predefined methods to determine evaulability and outcomes. Overall, 107 posaconazole-treated subjects and 86 controls were enrolled. Demographics and disease assessments were similar between the groups. At the end of treatment, the success rates were 42% for the posaconazole recipients and 26% for the control subjects, with an odds ratio of 4.06 (95% CI, 1.50–11.04) (\textit{P} = 0.006).

Zygomycosis
Greenberg et al., 2006\textsuperscript{18}

The investigators reported the results from the first 24 patients with active zygomycosis who were enrolled in compassionate trials evaluating oral posaconazole as salvage therapy for IFIs. Of the 24 patients exposed to posaconazole, 79% survived the infection. Survival was also linked to surgical resection as well as stabilization and improvement of the patients’ underlying illnesses.

Coccidioidomycosis
Catanzaro et al., 2007\textsuperscript{19}

The safety and tolerability of posaconazole were reviewed in 20 patients with chronic pulmonary or nonmeningeal disseminated coccidioidomycosis. The efficacy of posaconazole was also evaluated as a secondary endpoint in this trial. Overall, 70% of patients completed the study and showed a positive response.

Stevens et al., 2007\textsuperscript{20}

The efficacy of posaconazole was evaluated in 15 patients with chronic refractory coccidioidomycosis. The sites of infection were pulmonary in origin in seven patients and of disseminated origin in eight patients. The participants in this analysis had infection that had been refractory to previous therapy, including amphotericin B with or without a triazole. After treatment with posaconazole for a duration of 34 to 365 days, 73% of the patients achieved therapeutic success.

Other Fungal Infections
Histoplasma capsulatum is an endemic dimorphic fungus commonly found in the midwestern U.S. It is difficult to treat because of granulomatous tissue lesions and the requirement for long-term therapy. Several case reports and series describe successful eradication of \textit{H. capsulatum} with posaconazole.\textsuperscript{21,22} In immunocompetent patients who were previously unresponsive to itraconazole therapy, posaconazole was effective in treating this infection.\textsuperscript{21} Another case series of six patients described success with posaconazole in patients who had been unresponsive to other antifungal regimens.\textsuperscript{22}

\textit{Fusarium}, a filamentous fungus and an opportunistic pathogen, is generally resistant to most antifungal agents. One case report described \textit{Fusarium proliferatum} infection in a patient with chronic rejection after lung transplantation who had received posaconazole and improved after four months of treatment.\textsuperscript{21} In a case series that included three patients with refractory disease, \textit{Fusarium keratitis} was successfully treated with posaconazole.\textsuperscript{24}

Other rare superficial and subcutaneous mycotic infections (e.g., chromoblastomycosis, hyalohyphomycosis, or phaeohyphomycosis) have been successfully treated with posaconazole.\textsuperscript{25}

SAFETY PROFILE
Raad and associates collected the overall long-term safety data of posaconazole in 428 patients with IFIs and 66 patients with FN.\textsuperscript{26} Overall, treatment-related adverse effects were reported in 38% of patients. The most common adverse drug effects reported were nausea (8%) and vomiting (6%). Treatment-related prolongation of the corrected QT interval (QTC) occurred in 1% of patients, and 2% of patients had elevated hepatic enzymes. Overall, the long-term safety of posaconazole of six months or longer revealed a favorable adverse-effect profile in seriously ill immunocompromised patients.

In clinical reports, the tolerability of posaconazole was acceptable and comparable to other triazoles.\textsuperscript{13–26} Common adverse events included fever, nausea, vomiting, diarrhea, abdominal pain, dry
mouth, headache, and fatigue (Table 2). Some of the less common but more notable events reported with posaconazole administration included hypokalemia, rash, anemia, thrombocytopenia, and QTc prolongation.

In rare instances, severe adverse events have also been reported, including cholestasis, hepatic failure, adrenal insufficiency, allergic or hypersensitivity reactions, hemolytic-uremic syndrome, thrombotic thrombocytopenia purpura, pulmonary embolism, and torsades de pointes.

Posaconazole is an inhibitor of CYP 3A4 hepatic enzymes. Drugs undergoing metabolism by the CYP 3A4 pathway may be associated with significant drug–drug interactions with posaconazole. In one study, concentrations of tacrolimus (Prograf, Astellas) were double what they were when taken with posaconazole. Another report noted a 30% increase in cyclosporine concentrations with posaconazole administration.

Concomitant posaconazole administration is contraindicated with terfenadine (Seldane, Hoechst), astemizole (Hismanal, Janssen), pimozide (Orap, Gate), cisapride (Propulsid, Janssen), quinidine, and ergot alkaloids because of their increased potential for QT prolongation.

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Table 2: Treatment-Related Adverse Effects in Patients Treated with Posaconazole (Noxafil)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>45</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>30</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>29</td>
</tr>
<tr>
<td>Headache</td>
<td>28</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>27</td>
</tr>
<tr>
<td>Anemia</td>
<td>25</td>
</tr>
</tbody>
</table>

Posaconazole is the newest triazole antifungal agent approved for the management of resistant and difficult-to-eradicate fungal infections. It is available as an oral suspension. The daily dose must be divided and administered with a nutritional supplement to improve absorption. For patients who cannot take an oral suspension, posaconazole may be given via nasogastric tubes.

In case reports and series, in vitro studies, and clinical trials, posaconazole was active against common as well as emerging, resistant, and rare fungal pathogens, including Candida, Aspergillus, Coccidioides, Rhizopus, Cryptococcus, Fusarium, Mucor, Scedosporium, and Absidia species, among others.

Posaconazole is approved by the FDA for preventing invasive Aspergillus and Candida infections in patients at high risk for these opportunistic infections, including stem-cell recipients with graft-versus-host disease or those with chemotherapy-induced FN. It is also approved for treating oropharyngeal candidiasis that is refractory to itraconazole and fluconazole.

Posaconazole can become an important treatment option for patients with resistant opportunistic fungal infections when other antifungal options fail or are not tolerated. It has a favorable safety profile in short-term and long-term experimental studies. Although posaconazole has promising clinical efficacy against life-threatening fungal infections that are often refractory to the other antifungal agents, it is still considered an alternative option, because potential cost savings are associated with currently available antifungal therapies.

REFERENCES
12. Ulluman AJ, Cornely OA, Burchardt A, et al. Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory...


