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Pharmacologic and clinical evaluation of posaconazole.

Jason N. Moore  
*Thomas Jefferson University, jason.moore@jefferson.edu*

Jason R. Healy  
*Thomas Jefferson University, jason.healy@jefferson.edu*

Walter K. Kraft  
*Thomas Jefferson University, walter.kraft@jefferson.edu*

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Pharmacologic and clinical evaluation of posaconazole


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Jason N. Moore¹, Jason R. Healy², Walter K. Kraft³

Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University
132 South Tenth Street
Main Building, Room 1170
Philadelphia, PA 19107
Phone: 215-955-9081
Fax: 215-955-5681

¹Jason.Moore@jefferson.edu
²Jason.Healy@jefferson.edu
³Walter.Kraft@jefferson.edu

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AML</td>
<td>Acute Myeloid Leukemia</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under The Curve</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>Maximum (Peak) Serum Concentration</td>
</tr>
<tr>
<td>$C_{\text{min}}$</td>
<td>Minimum Serum Concentration</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated Growth Factor Receptor</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>GVHD</td>
<td>Graft Versus Host Disease</td>
</tr>
<tr>
<td>HSCT</td>
<td>Hematopoietic-Stem-Cell-Transplant</td>
</tr>
<tr>
<td>IFI</td>
<td>Invasive Fungal Infection</td>
</tr>
<tr>
<td>MDS</td>
<td>Myelodysplastic Syndromes</td>
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<tr>
<td>MIC</td>
<td>Minimum Inhibitory Concentration</td>
</tr>
<tr>
<td>OPC</td>
<td>Oropharyngeal Candidiasis</td>
</tr>
<tr>
<td>P-gp</td>
<td>P-Glycoprotein</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$</td>
<td>Half-life</td>
</tr>
<tr>
<td>TDM</td>
<td>Therapeutic Drug Monitoring</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>Time To Maximum Concentration</td>
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<tr>
<td>UDP</td>
<td>Uridine Disphosphate-Glucuronosyltransferase</td>
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SUMMARY

Posaconazole, a broad-spectrum triazole antifungal agent, is approved for the prevention of invasive aspergillosis and candidiasis in addition to the treatment of oropharyngeal candidiasis. There is evidence of efficacy in the treatment and prevention of rarer, more difficult-to-treat fungal infections. Posaconazole oral suspension solution has shown limitations with respect to fasting state absorption, elevated gastrointestinal pH and increased motility. The newly approved delayed-release oral tablet and intravenous solution formulations provide an attractive treatment option by reducing interpatient variability and providing flexibility in critically ill patients. On the basis of clinical experience and furthering clinical studies, posaconazole is a valuable pharmaceutical agent for the treatment of life-threatening fungal infections. This review will examine the development history of posaconazole and to highlight the most recent advances.

INTRODUCTION

Invasive fungal infections (IFIs) are problematic for critically ill patients, with increased risks of morbidity and mortality. Prophylactic treatment is often advantageous, as delayed antifungal treatment has been shown to increase mortality rates [1,2]. The Infectious Disease Society of America guidelines for the use of antimicrobial agents in neutropenic patients with cancer suggest antifungal prophylaxis be employed in high-risk patients, including hematopoietic stem-cell transplantation (HSCT) recipients or intensive chemotherapy for leukemia [3]. Unfortunately, safety and tolerability concerns often reduce the utility of antifungals in the clinic.

The currently available systemic triazoles are divided into two groups: the first generation (fluconazole and itraconazole) and the second generation (voriconazole, posaconazole, and isavuconazonium) (Figure 1). While these agents all possess the same mechanism of action, each has differing anti-fungal activity, efficacy, pharmacokinetics and safety profiles, leading to unique therapeutic niches [4,5].

Posaconazole is a triazole antifungal that boasts an extended-spectrum of activity for prophylaxis and treatment for IFIs. Posaconazole has demonstrated efficacy as an antifungal prophylactic in HSCT recipients with graft vs. host disease and in neutropenic patients with hematologic malignancy. In addition, posaconazole has been an effective salvage therapy option for patients that are nonresponsive to standard antifungal therapies [6]. Overall, posaconazole covers a wide array of IFIs; including, aspergillosis, candidiasis, fusariosis, mucormycosis, cryptococcosis, chromoblastomycosis, mycetoma and coccidioidomycosis [7]. Compared to the other azoles (fluconazole, itraconazole, and voriconazole), posaconazole has a more favorable safety profile [8]. Furthermore, posaconazole activity extends beyond that of other azoles, including voriconazole, for instance, which does not cover mucormycosis [9,10].

CHEMICAL DEVELOPMENT
Posaconazole is designated chemically as 4-[4-[4-[(3R,5R)-5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one. Its empirical formula is C_{37}H_{42}F_{2}N_{8}O_{4} with a molecular weight of 700.8. It is synthesized solely as the (R,R,S,S) enantiomer via a three-step synthesis followed by a micronization step to enhance the dissolution rate. Posaconazole is a structurally comparable to itraconazole (Figure 1). Modifications, including fluorine in place of chlorine and a furan ring in place of the dioxolane ring, result in an extended spectrum of antifungal activity [7].

**PHARMACOLOGY**

Posaconazole, in addition to other triazoles, block ergosterol synthesis through 14α-demethylase (CYP51) inhibition. Ergosterol depletion prevents proper fungal cell wall construction and, cause the accumulation of methylated sterol precursors leading to cell death [11]. Posaconazole undergoes negligible oxidative phase 1 metabolism (<2%); its metabolism is facilitated instead through a phase 2 biotransformation via uridine disphosphate-glucuronosyltransferase (UDP) enzyme pathway. No relevant active metabolites have been identified for posaconazole [12]. Posaconazole is both a substrate and inhibitor of the p-glycoprotein (p-gp) efflux transporter [13].

The Biopharmaceutics Classification System (BCS) of the U.S. Food and Drug Administration Center for Drug Evaluation and Research lists posaconazole as a Class II compound, indicating that it is well absorbed but dissolves slowly (high permeability/low solubility) [14]. The apparent volume of distribution of posaconazole ranges from 5 to 25 L/kg, indicating extensive distribution and tissue penetration [7]. Posaconazole is highly protein bound (>98%), predominately to albumin in a concentration-dependent fashion.

Posaconazole is predominately eliminated in the feces (77% of the radiolabeled dose), primarily eliminated as parent drug (66% of the radiolabeled dose) in healthy volunteers [15]. 14% of the radiolabeled dose is excreted in urine, primarily in the form of glucuronide conjugates. The mean half-life (t_{1/2}) of posaconazole ranges from 25-35 hours [16].

Posaconazole has shown *in vitro* activity against a wide variety of fungal pathogens including *Aspergillus* spp., *Candida* spp., *Coccidioides immitis* and *Fonsecaea pedrosoi*. In addition, some species of *Fusarium*, *Rhizopus* and *Mucor* are sensitive to posaconazole [17]. Clinical *Aspergillus fumigatus* isolates have been identified that demonstrate resistance to posaconazole, specifically those that harbor CYP51 mutations [18].

There are no established pharmacokinetic guidelines with respect to plasma posaconazole for breakthrough IFIs [19]. A posaconazole concentration target greater than 0.5 mg/L is recommended for prophylactic treatment, with others suggesting a concentration target greater than 0.70 mg/L. Cardiothoracic transplant patients possessing posaconazole levels consistently exceeding 0.50 mg/L had therapeutically successful outcomes [20]. One report suggests that
values exceeding 0.70 mg/L do not provide any further reduction in the clinical failure rate, as demonstrated in two randomized, active-controlled clinical studies employing posaconazole oral suspension [21].

**Oral Suspension Formulation**

The posaconazole oral suspension solution has been reviewed extensively [7,22]; its use has been eclipsed by the newer formulations. Briefly, there are several challenges with respect to the posaconazole oral suspension formulation. One, this formulation is limited by saturable absorption. In a clinical study utilizing healthy men, posaconazole oral suspension given 400 mg every 12 hours or 200 mg every 6 hours resulted in a 98% and 220% increase in bioavailability, respectively, compared to 800 mg given as a single dose [23]. Secondly, there is also significant pharmacokinetic variability in regards to nutrition, as bioavailability increases at a low gastric pH along with high-fat meals. [24,25]. Acidic carbonated beverages have been shown to increase the bioavailability of posaconazole oral suspension [26].

**Delayed-Release Oral Tablet Formulation**

The FDA approved a delayed-release oral posaconazole tablet in November 2013. This tablet was largely designed to overcome the absorption limitations associated with the oral suspension as seen in the clinic and in previous studies. The current posaconazole delayed-release tablet is designed to reduce active drug release at low gastric pH, while increasing release at the elevated pH of the intestine with an absolute bioavailability of 54% for the oral delayed-release tablet. It is suggested that the oral delayed-release tablet be taken with food, though it is not known if the oral bioavailability of the tablet improves under fed conditions [16].

A single- and multiple-dose study was performed in healthy subjects to ascertain optimal dosing and to assess pharmacokinetics of this posaconazole tablet formulation [27,28]. During the single 100 mg dose study, the delayed-release tablet formulation had a higher maximum (peak) serum concentration ($C_{\text{max}}$) compared to the oral suspension solution in the fasted state (0.39 mg/L vs. 0.08 mg/L, respectively). In the fed state, the delayed-release tablet formulation still maintained a higher $C_{\text{max}}$ compared to the oral suspension formulation (0.33 mg/L vs. 0.24 mg/L, respectively). For the multi-dose study, subjects were randomized to one of two cohorts. Cohort 1 consisted of either placebo or posaconazole 200 mg SD on day one, a 5-day washout period, and then 200 mg BID on day 6, 200 mg QD on days 7-14, and 200 mg BID on days 15-22. Cohort 2 received 400 mg, as opposed to 200 mg, and had the same schedule as cohort 1 until day 14. Median time to maximum concentration ($T_{\text{max}}$) was 4 hours for the 200 mg dose and 5 hours for the 400 mg dose, while mean $t_{1/2}$ following was similar for both doses (25 and 26 hours for the 200 mg and 400 mg dose, respectively). With the 400 mg dose, the delayed-release tablet exhibited linear pharmacokinetics and steady-state concentrations were achieved after 7 days. Greater inter-subject variability was noted in exposure values for the 400 mg dose compared to the 200 mg dose (54% vs. 32%, respectively).
A phase 1b, multicenter dose-determining trial was conducted in order to examine the pharmacokinetics of posaconazole tablets in patients with acute myeloid leukemia or myelodysplasia [29]. The two cohorts were administered posaconazole tablets, 200 mg or 300 mg daily. The 300 mg cohort reached the predefined steady-state concentration goal of 0.50 and 2.50 mg/L in 97% of patients, while 79% of patients reached the goal in the 200 mg cohort.

A phase 3, multicenter trial utilized the 300 mg delayed-release posaconazole oral tablet to further examine the pharmacokinetics in acute myeloid leukemia or myelodysplasia patients along with recent HSCT recipients [30]. During the 28-day trial period, the predefined steady-state concentration goal, set at 0.50 – 3.75 mg/L, was achieved in 96% of patients, with 81% falling in the range between 0.50 and 2.50 mg/L. These concentration goals are in line with targeted recommendations for breakthrough IFIs.

**Intravenous Formulation**

An intravenous posaconazole formulation developed as an aqueous solution containing the solubilizer sulfobutyl ether beta-cyclodextrin has also been approved for marketing in the United States [31]. Initially, a single-center, two-part rising single- and multiple-dose study in healthy adults was performed to evaluate the pharmacokinetics and safety of intravenous posaconazole [32]. For the first part of the study, six cohorts covered a single dose posaconazole range from 50 to 300 mg by 30-min peripheral infusion. Intravenous posaconazole showed a greater-than-dose-proportional increase in exposure, whereby $C_{\text{max}}$ values ranged from 0.31 mg/L to 2.84 mg/L for the 50 and 300 mg single dose administration, respectively. Part 2 was terminated early due to unacceptable rates of infusion site reactions.

To expand the pharmacokinetic and safety profile of intravenous posaconazole, a two-part study was performed, one part classified as phase 1b and the other as phase 3 in order to bridge the new posaconazole intravenous solution to the previously approved posaconazole suspension [31]. The primary purpose of the phase 1b trial was to identify the posaconazole dose that would attain an exposure target of 0.50-2.50 mg/L. A single-dose and two multiple-dose cohorts were established for the study, with the multiple dose cohorts used to evaluate the 200 mg or 300 mg once daily dose after a twice-daily loading dose on the first day. Subjects attaining steady-state exposure goals were 94% and 95% for the 200 mg and 300 mg dosing cohorts, respectively. Mean concentration average was 1.19 mg/L and 1.43 mg/L for the 200 mg and 300 mg dosing cohorts on day 14, respectively. Intravenous posaconazole demonstrated a similar safety profile to the oral suspension formulation. A 300 mg QD dose was recommended for the phase 3 study.

The pharmacokinetics and safety of the posaconazole intravenous formulations have also been investigated [33]. Patients with acute myeloid leukemia, myelodysplastic syndrome, or HSCT were enrolled into a study further examining posaconazole intravenous formulation [34]. Posaconazole was intravenously administered 300 mg twice daily on day 1 and 300 mg once daily for 4-13 days afterwards. Then, they were switched to posaconazole oral suspension 600
mg or 800 mg in divided doses for up to 23 days for a total treatment period of 28 days. The intravenous formulation resulted in higher trough concentrations of posaconazole than either of the dosages of oral suspension. Thus, this result shows that the posaconazole intravenous solution can be dosed at a level to reach satisfactory exposure for the treatment or prophylaxis of fungal infections.

SAFETY AND TOLERABILITY

In general, posaconazole has a very good safety and tolerability profile [35,36]. Courtney and colleagues demonstrated the tolerability of oral suspension posaconazole in doses up to 400 mg twice daily in a Phase I study in healthy subjects [37]. Adverse effects were mild, such as fatigue and dry mouth. In the later phase clinical trials, posaconazole was also particularly well tolerated. The main side effects experienced by the participants were gastrointestinal distress (nausea, vomiting, and diarrhea), neutropenia and elevated liver enzymes [34,38,39]. Patients suffering from mucositis, diarrhea, or are in the early post-transplant period in hematopoietic stem cell transplant therapy have reduced posaconazole levels when administered the oral suspension solution [19]. Overall, posaconazole has favorable safety profile compared to other currently approved systemic triazole antifungals (Table 2) [8].

Other than infusion site reactions, the intravenous formulation of posaconazole had few additional adverse effects. Infusion site reactions, specifically thrombophlebitis, were clinically acceptable at 30 minutes compared to 90 minutes for single-dose peripheral administration [32]. However, a decrease in infusion time from 90 minutes to 30 minutes did not reduce infusion site reactions for multiple-dose administrations. It is recommended that infusion be performed by central line when multiple-dose posaconazole administration is necessary.

Early pooled analysis of 18 controlled studies in healthy volunteers and patients receiving posaconazole oral suspension solution indicated low potential to prolong the corrected QT (QTc) interval, among other side effects [40]. An initial report identified minimal safety concerns regarding elevated hepatic function tests and QTc prolongation for the posaconazole delayed-release oral tablets [29]. However, an additional study has shown that the oral delayed-release tablet increases hepatic enzyme levels in addition to prolonging the QTc interval [41]. As such, patients need to be monitored of their hepatic enzyme levels and QTc intervals.

Drug Interactions

The other triazole antifungals have numerous drug-drug interactions as they inhibit the P-gp transporter in addition to CYP P450 enzymes, thus resulting in increased concentration of other drugs [42]. However, posaconazole and fluconazole are less potent inhibitors than voriconazole and itraconazole. Posaconazole inhibits CYP3A4 and P-gp, whereas other triazoles may also affect CYP2C9 and CYP2C19 [22]. This has important implications for therapy selection. In the GVHD patient population, immunosuppressive drugs cyclosporine and tacrolimus are commonly used; as they are CYP 3A4 substrates, posaconazole will likely increase their plasma concentration potentially resulting in toxicity (Figure 2). The co-administration of posaconazole
with several CYP3A4 substrates is contraindicated, including substrates known to prolong the QTc interval (i.e. terfenadine, cisapride), in addition to HMG-CoA reductase inhibitors (i.e. statins) and ergot alkaloids [16]. No further induction or inhibition of additional CYP450 enzymes at therapeutically relevant concentrations has been identified.

Reduced posaconazole oral suspension exposure is noted with the concurrent use of metoclopramide, phenytoin or rifampin, and the H₂ ranitidine [19]. Since the posaconazole oral suspension formulation is more readily absorbed at a lower pH, proton pump inhibitors and cimetidine have been shown to decrease the AUC of posaconazole [7,43]. Other histamine H₂ receptor antagonists and antacids had no effect on the AUC.

In contrast to the oral suspension formulation, the absorption profile of the delayed-release posaconazole tablet is not affected by gastric acidity or motility. To investigate, healthy volunteers were randomized to groups to receive a single 400 mg dose of the delayed-release posaconazole tablet alone; with metoclopramide to affect gastric motility; or with an antacid (aluminum and magnesium hydroxide), ranitidine, or esomeprazole to affect gastric acidity in a crossover trial. [44]. Exposure, $T_{\text{max}}$ and $t_{1/2}$ were comparable whether posaconazole was administered alone or in combination with medications that affect gastric pH and motility. Future studies demonstrated increased plasma concentrations associated with the delayed-release oral tablet, as leukemia patients transitioned from posaconazole oral suspension to tablets had significantly higher posaconazole concentrations (median, suspension 0.75 mg/L; tablet 1.91 mg/L without clinically relevant hepatotoxicity [45].

**Use in special populations**

Posaconazole pharmacokinetics are comparable regardless of gender and are not significantly affected by ethnicity [16]. Furthermore, posaconazole pharmacokinetics do not differ significantly with age. Posaconazole is designated pregnancy category C, such that no adequate clinical studies have examined this population [16]. Posaconazole administration has led to skeletal malformations in rats at relative concentrations lower than human therapeutic dosing. Furthermore, posaconazole administration produced higher rates of bone resorption to occur in rabbits, with higher dosages causing a reduction in body weight gain and a reduction in litter size in females. Preclinical animal models also suggest that posaconazole may excrete into breast milk of lactating females. Prophylaxis studies indicate that mean steady-state posaconazole average concentration is consistent in the pediatric population with that of adults [16].

For prophylaxis of candidiasis, posaconazole has been indicated in several clinical contexts in pediatric patients [46]. For allogenic HSCT, posaconazole oral suspension (200 mg TID) is recommended for patients greater than grade II GVHD that are at least 13 years of age. Posaconazole oral suspension (200 mg TID) is recommended for AML and recurrent leukemia patients ages 13 and older after the last dose of chemotherapy until neutrophil recovery. Delayed-release posaconazole tablets are now indicated for patients 13 years or older. However,
the use of posaconazole intravenous injection is not recommended for patients under the age of 18 due to preclinical safety concerns [16].

No posaconazole pharmacokinetic effects have been seen in patients administered 400 mg single-dose posaconazole oral suspension with mild to moderate renal impairment; thus, no further dose adjustment requirements are recommended for patients with mild-to-moderate renal impairment [16]. However, close monitoring for breakthrough IFI is recommended for patients with severe renal impairment (eGFR: <20 mL/min). Similar studies have not been conducted with the oral delayed-release posaconazole tablets; however, no dose adjustments are recommended for mild-to-moderate renal impairment. Posaconazole intravenous injection should be avoided in patients with moderate or severe renal impairment as excess accumulation of the intravenous vehicle, sulfobutylether-β-cyclodextrin, may be problematic. Accordingly, the serum creatinine levels of these patients should be closely monitored [16].

No posaconazole oral suspension dose adjustments are recommended for patients with mild to severe hepatic impairment [16]. Mean AUC values of a single dose of 400 mg posaconazole oral suspension range from 21-43% higher for patients with hepatic impairments. Respective $C_{\text{max}}$ and $t_{1/2}$ values for patients with hepatic impairments vary compared to normal individuals. Similar studies have not been performed with the oral delayed-release tablets or intravenous injection; however, no dose adjustments are recommended for either of these formulations with patients with mild to severe hepatic impairment [16].

Immunosuppressant drugs, specifically cyclosporine and tacrolimus, need to have levels monitored when given in combination with posaconazole [47]. While concurrent use of posaconazole and sirolimus is contraindicated by the manufacturer, a recent study has shown that posaconazole can be given in combination with sirolimus in a liver solid organ transplant patient. [48]. It is imperative that sirolimus concentration levels are monitored when given in conjunction with posaconazole.

**CLINICAL EFFICACY STUDIES**

**Phase 2 Clinical Studies**

Two main Phase 2 trials were completed in the clinical development program of posaconazole. For the indication of IFI prophylaxis, study P018893 was designed to establish the dose by comparing the pharmacokinetic and study P01893 examined pharmacodynamic properties of different posaconazole dosing strategies [16,49,50]. This study focused on the treatment of patients with azole-refractory IFIs or patients experiencing febrile neutropenia and requiring empiric antifungal therapy. 98 patients were randomized to receive posaconazole as an oral suspension between 800 mg and 1600 mg every day divided into different dosing schedules. Patients continued to receive the drug for a maximum of 6 months or until febrile neutropenia resolved. Posaconazole was well tolerated and was comparably effective at all dosing schedules in the treatment of the fungal infections. These results agreed with previous pharmacokinetic
data suggesting that the absorption of posaconazole is saturable and therefore limited. Beyond a certain threshold, increasing the dose does not affect posaconazole exposure preventing additional therapeutic benefit and worsened adverse effects.

For the indication of oropharyngeal candidiasis (OPC) treatment, study C/I96-209 was used to elucidate the dose while analyzing the pharmacologic profile [16,51]. This trial involved 463 HIV-infected patients with OPC. The goal of this trial was to compare treatment using various doses of posaconazole with an established dose of fluconazole, which is routinely used for this indication. Patients were randomized to receive either of the agents with posaconazole at the doses of interest and fluconazole at 200 mg once followed by 100 mg daily. Treatment was continued for a total of 14 days. Posaconazole was well tolerated and showed similarly efficacy at the dose levels and compared to fluconazole. Based on the data, the posaconazole 100 mg once daily dose was selected.

**Phase 3 Clinical Studies**

**IFI Prophylaxis**

The approval of posaconazole by the FDA was based on four pivotal clinical trials, two for each indication – IFI prophylaxis and OPC treatment. Ullmann and colleagues compared the efficacy of posaconazole versus fluconazole in preventing IFIs in a multicenter, randomized, double-blind trial [39]. 600 patients with HSCT and GVHD or patients who were being treated with highly immunosuppressive agents were randomized to receive either agent for 16 weeks. One cohort received posaconazole as a 200 mg oral suspension three times daily with placebo capsules once daily, while the second cohort received fluconazole as a 400 mg encapsulated tablet once daily with placebo oral suspension three times daily. Posaconazole was shown to be non-inferior to fluconazole in the prevention of IFIs (5.3% vs 9.0%) and was shown to be superior in the treatment of invasive aspergillosis specifically (2.3% vs 7.0%). Between both groups, adverse events were similar (36% vs 38%, respectively) as was the rate of discontinuation due to adverse events (34% vs 38%, respectively).

Cornely conducted a study comparing the efficacy of posaconazole to fluconazole and itraconazole for IFI prophylaxis in patients treated for cancer who were projected to experience neutropenia [52]. 602 patients were randomized and received 200 mg posaconazole three times daily as an oral suspension or one of the alternate azoles for up to 12 weeks during their rounds of chemotherapy; the choice of the alternate azole (400 mg fluconazole once daily or itraconazole 200 mg twice daily) was made by each investigator. Patients were monitored for fungal infections by a blinded independent data review committee. Posaconazole was shown to be superior in preventing IFIs compared to the alternate azoles (2% vs 8%, respectively). In addition, the mean time to IFI was longer with posaconazole (41 days vs 25 days, respectively). Lastly, the posaconazole group experienced lower mortality during the treatment period (16% vs 22%, respectively). Adverse effects were comparable for patients taking each agent.

**OPC Treatment**
The efficacy of posaconazole versus fluconazole for patients with HIV/AIDS in the treatment of OPC has been evaluated [53]. 350 patients were randomized and received 200 mg posaconazole or fluconazole oral suspension on the first day as the loading dose, followed by 100 mg every day of the same drug for a total of 14 days. Blinded evaluators investigated each patient for clinical success, which was specified as cure or improvement of OPC. At the end of the trial, clinical success was seen in both groups at similar rates (91.7% for posaconazole and 92.5% for fluconazole). Of the patients deemed clinically successful 42 days after trial completion, 31.5% of the posaconazole patients relapsed compared to 38.2% of the fluconazole patients. Also at the 42-day follow-up, mycological eradication was greater in patients of the posaconazole arm (35.6% vs 24.2%, respectively). Adverse events were comparable in each group.

In order to investigate the role of posaconazole in azole-refractory OPC, Skriest analyzed patients infected with HIV with oropharyngeal or esophageal candidiasis resistant to standard azole treatments of fluconazole and itraconazole [38]. Patients received 400 mg twice daily for 3 days followed by 400 mg daily for 25 days or 400 mg twice daily for 28 days. 75% of the 176 patients experienced clinical success, defined as cure or improvement. Treatment success was relatively invariable between the groups taking different regimens. Four weeks after the last dose, 74% of 80 patients who had experienced a clinical response had relapsed (80% of patients on the daily dosing regimen, 68% of patients on the twice daily dosing regimen).

Treatment of other Approved Fungal Infections

Additional studies were conducted in order to support the approval of posaconazole for the treatment of a broader range of fungal infections in Europe [17]. 330 patients with varying fungal infections, which were resistant to or intolerant of standard therapy including other azoles, echinocandins, and amphotericin, were administered posaconazole 200 mg four times daily while hospitalized and 400 mg twice daily on an outpatient basis for up to one year. Overall 50% of patients responded to posaconazole. The investigators analyzed clinical success rates for each fungal infection individually with the following infections showing the best efficacy with posaconazole: aspergillosis (42%), fusariosis (39%), chromoblastomycosis or mycetoma (82%), coccidioidomycosis (69%).

Catanzaro and colleagues investigated the role of posaconazole in treating patients with coccidioidomycosis [54]. In twenty treatment-naïve patients with nonmeningeal disseminated or chronic pulmonary coccidioidomycosis, the study investigators administered 400 mg of posaconazole daily. 85% of the patients experienced a response, defined as a 50% or greater reduction in the mycoses Study Group score from baseline. Stevens et al. further analyzed the use of posaconazole in the treatment of treatment-resistant coccidioidomycosis [55]. Fifteen patients with refractory coccidioidomycosis were recruited for this trial. Patients were administered 800 mg of posaconazole in divided doses daily for up to a year. At the end of the treatment period, 73% of the patients responded to treatment: four showed a complete eradication of disease, and seven showed a partial resolution. Posaconazole was well tolerated in both trials.
**Off-label Indications**

Posaconazole has also been studied for infections that are rarer, often as salvage therapy in smaller, less controlled trials. While clinical experience with posaconazole is limited with these indications, there is evidence to support utilization. van Burik and colleagues retrospectively analyzed the use of posaconazole in mucormycosis [56]. Information from 91 patients was included in this study. Patients were treated with posaconazole; 80% for at least 30 days. 60% of patients responded to treatment. Restrepo and colleagues investigated posaconazole’s utility as salvage treatment of histoplasmosis [57]. Six patients who had failed other treatments were placed on posaconazole 800 mg per day in divided doses. All patients responded to treatment within a month as demonstrated by clinical improvement.

Posaconazole has also demonstrated good activity in the treatment of fungal infection of the central nervous system (CNS). Pitisuttithum et al. studied 39 patients with CNS fungal infections [58]. Most of these patients had refractory disease (95%) or an HIV infection (74%). The infections were caused by a variety of fungi including *Cryptococcus*, *Aspergillus*, and a variety of rarer fungi (*P. boydii*, *C. immitis*, *H. capsulatum*, *Ramichloridium mackenziei*, *Apophysomyces elegans*, and *Basidiomycetes sp.*). Patients were administered the posaconazole oral suspension at 800 mg per day in divided doses for at least a month and up to one year. Clinical responses were seen in 48% of the patients infected with *Cryptococcus* and in 50% of the patients with the other fungal infections. This trial provides evidence that posaconazole can be useful as salvage therapy for a wider variety of fungal infections and in the CNS.

**Post-marketing Surveillance**

The FDA required pediatric studies to be completed secondary to the approval of posaconazole. Completing one study that addressed the use of posaconazole in this population, Döring and colleagues compared itraconazole, voriconazole, and posaconazole in pediatric patients with allogenic HSCT as an oral antifungal prophylactic agent [59]. 150 patients between the age of seven months and 18 years were divided evenly into three cohorts to receive 5 mg/kg twice daily itraconazole, 100 mg twice daily (or 200 mg twice daily if body weight >40 kg) voriconazole, or 200 mg thrice daily posaconazole. Patients also received antiviral and antibacterial prophylaxis for other possible infections. At the end of the observation period (maximum of 220 days after HSCT), there were no deaths due to IFIs or even any cases of “proven” or “probable” IFIs in the patients. There were several “possible” infections: two in the itraconazole group, three in the voriconazole group, and none in the posaconazole group. The differences between “proven”, “probable”, and “possible” were analyzed secondary to the National Institute of Allergy and Infectious Diseases Mycoses Study Group criteria. Ultimately, the three agents were deemed non-inferior to each other in terms of efficacy. Comparing the safety profiles, the adverse effect ratio was comparable between all three groups, with increased liver enzymes representing one of the most common events.

**REGULATORY AFFAIRS**
Posaconazole has been approved to treat fungal infections in the United States and European Union with the trade name Noxafil®. Posaconazole is marketed as Posanol in Canada [16]. Labeled indications in the US and Europe are listed in Text Boxes 1 and 2. The FDA approved posaconazole for prophylaxis of the Aspergillus and Candida IFIs in immunocompromised patients of at least 13 years of age in September 2006, and it was approved for the treatment of oropharyngeal candidiasis including those cases refractory to other azole antifungals in October 2006 [60,61]. For both indications, posaconazole was approved as a 40 mg/mL oral suspension. Posaconazole was subsequently approved as a delayed-release tablet in addition to an intravenous solution for the indication of invasive Aspergillus and Candida infection prophylaxis in November 2013 and March 2014, respectively [62,63]. In the United States, posaconazole’s patent is scheduled to expire in 2019.

The European Medicines Agency (EMA) has approved posaconazole as an oral suspension and as a gastro-resistant tablet for treatment of a wider variety of IFIs (aspergillosis, fusariosis, chromoblastomycosis and mycetoma, coccidioidomycosis, and oropharyngeal candidiasis) including those cases refractory to standard antifungal therapy. In addition, posaconazole is approved for the prevention of IFIs in patients whom are receiving immunosuppressive therapy after receiving HSCT or chemotherapy for acute myelogenous leukemia or any other myelodysplastic syndrome [64]. For all of these indications, posaconazole was approved as an oral suspension and as a gastro-resistant tablet in October 2005.

The FDA specified a number of post-marketing commitments from posaconazole. For the IFI indication, the FDA required a pediatric study in patients from age zero months to twelve years of age based on the Pediatric Research Equity Act (PREA). For the OPC indication, a pediatric study is also required but in patients from zero months to sixteen years of age. In addition, the FDA requested a study among patients receiving IFI prophylaxis at risk for low absorption in order to explore alternate dosing strategies and the utility of therapeutic drug monitoring [60,61]. These studies were originally required by 2011. Since then, the FDA has granted a deferral extension, and the studies will need to be completed by 2019 with the exception of the study involving alternate dosing strategies and TDM. The FDA has released the company from the obligation to complete that study [65]. For the new formulations, pediatric studies are also required and will need to be completed within the next ten years [62,63]. (Figure 3)

**CONCLUSION**

Posaconazole is a useful antifungal agent. This drug has shown efficacy in the role of IFI prophylaxis, the treatment of OPC and salvage treatment for refractory fungal infections. Overall, posaconazole has a favorable safety and tolerability profile. However, the initially approved oral suspension formulation has a wide interpatient variability with respect to absorption. The systemic availability of the oral suspension can be improved through administration with a high-fat meal, nutritional supplement or acidic beverage in addition to divided daily doses. The suspension has shown a reduction in systemic availability when administered with proton-pump inhibitors in addition to pharmacotherapeutics that increase
gastric motility. Diarrhea and mucositis have both also been shown to reduce the bioavailability of posaconazole.

The administration of multiple daily doses with a full meal or nutritional supplement can be difficult for patients whom have difficulties swallowing. As such, the recent approval of a delayed-release tablet that requires administration only once daily and does not appear to be clinically affected by food, alterations in gastric pH or motility represents a new option for the prophylaxis of IFI. As it achieves consistently higher average serum concentrations, the delayed-release tablet is a better option than suspension for both prophylaxis and treatment of IFI. An intravenous formulation has been recently developed and approved, which provides even greater access to patient populations.

**FIVE-YEAR VIEW**

Unlike in the United States, posaconazole has not been approved in the European Union as a delayed-release tablet or as a solution for intravenous administration. However, Merck has received “positive opinions” from the Committee for Medicinal Products for Human Use inside the EMA [66,67]. This signifies that European Commission will review the new drug formulations further and likely approve it in the near future, following the precedent set by the FDA.

Posaconazole has been increasingly studied for other fungal infections beyond those infections for which it was originally approved by the major regulatory bodies. Elewski and colleagues investigated posaconazole in the treatment of toenail onychomycosis and showed improved cure rates compared to the commonly used antifungal agent terbinafine [68]. Posaconazole has also shown some potential for use in Chagas disease and chronic granulomatous disease [69,70], a significant finding as both of these conditions currently have limited therapeutic options. With further investigation, posaconazole may be readily used for these indications in the future.

Furthermore, the effect of posaconazole in pediatric patients will become clearer as the PREA-required studies are completed in the next few years. Favorable outcomes are expected given the positive safety data of the posaconazole oral suspension in pediatric patients. Thus, the use of the posaconazole formulations will likely increase over time in this subset of patients.

Therapeutic drug monitoring (TDM) has been increasingly suggested for posaconazole oral suspension therapy, as inter-patient concentration variability is high as is the risk for under-exposure. Prophylactic target posaconazole concentrations range from at least >0.5 mg/L to >0.7 mg/L. As such, a general consensus has yet to be determined. A recent report from Hoenigl and colleagues suggests the need for therapeutic drug monitoring, as personal on-site education of low posaconazole plasma concentrations can lead to >40% increase in sufficient plasma concentrations [71]. These findings are consistent with a previously reports that found that cases of breakthrough infections were all associated with low posaconazole plasma concentrations [19,21,72]. Bryant et al. (2011) was one of the first studies to report on therapeutic drug monitoring of prophylactic posaconazole in patients with acute myelogenous leukemia or
myelodysplastic syndrome [73]. In this study, greater than 7% of patients did not reach the lower target limit of 0.7 mg/L. Of the 21 patients, three developed ‘proven’ or ‘possible’ fungal infections, all three patients having posaconazole concentrations < 0.5 mg/L. Since posaconazole is liable to interact with many other pharmaceutical agents, several sources recommend TDM for posaconazole during the duration of multimodal therapy. This may be particularly useful in cases where posaconazole is used with an agent with whom it has a drug-drug interaction, which is common as many agents used for cancer, HIV, and transplants are CYP3A4 substrates, e.g. tacrolimus and cyclosporine. With time, a consensus will be reached concerning TDM the appropriate concentration goals for effective posaconazole treatment.

Also on the horizon, isavuconazonium is a novel triazole agent, which has recently been approved by the FDA for the treatment of aspergillosis and mucormycosis and is available as its prodrug isavuconazonium [74]. Preliminary data from Phase 3 studies suggests that it may have similar efficacy as voriconazole with fewer adverse effects in treating IFIs [75,76]. Isavuconazonium had a relatively quick regulatory timeline because the prognosis of mucormycosis is so poor at the moment that the FDA labeled isavuconazonium as an orphan drug and as a Qualified Infectious Disease Product for expedited review [77]. Following the approval of isavuconazonium, it will likely influence both the European and US markets. It will present a good option for mucormycosis and may, in fact, be used instead of posaconazole for some patients suffering from invasive aspergillosis.

EXPERT COMMENTARY

Posaconazole has been recognized by the guidelines for quite a few therapeutic uses beyond its FDA approved indications. The Infectious Disease Society of America (IDSA) has included them in their guidelines for aspergillosis, cryptococcosis, candidiasis, skin and soft tissue infections, and antimicrobial prophylaxis in neutropenia [3-5,78,79]. The IDSA guidelines on skin and soft tissue infections specifically recommend posaconazole for the treatment of aspergillus, mucormycosis, and fusariosis. Posaconazole is also recommended for the general prophylaxis and treatment of IFIs in the respective guidelines for patients affected by HIV, hematopoietic cell transplantation, and cancer [80-82] (Figure 5).

Numerous favorable pharmacoeconomic analyses have been published for posaconazole [83-86]. In these studies, the usage of posaconazole was primarily studied for the prevention of IFIs secondary to HSCT or secondary to febrile neutropenia in acute myeloid leukemia or myelodysplastic syndrome. Lyseng-Williamson (2011) specifically suggested that posaconazole was the dominant option compared to standard antifungal therapy in many markets if not simply a cost-effective choice [86]. Compared to the otherazole antifungals, posaconazole occupies a unique place in therapy. It can be used in fungal infections resistant to fluconazole and itraconazole. Posaconazole can also be used for prophylaxis of a wider variety of fungal infections than voriconazole. As the newest agent in a long-standing class of pharmaceuticals, there will be some time before prescribing healthcare providers accumulate enough clinical experience with this agent and become accustomed to it. However, the addition of the delayed-
release tablet, and potentially an intravenous formulation, as options will certainly accelerate this process as it allows for more convenient dosing.
KEY ISSUES

- Invasive fungal infections (IFIs) are a significant cause of morbidity and mortality for immunocompromised patients; unfortunately, the clinical usefulness of many antifungal agents is limited by safety and tolerability.
- Posaconazole is a relatively safe and well-tolerated broad-spectrum azole antifungal agent.
- Newer posaconazole formulations, oral tablet and intravenous, increase its availability to larger patient population.
- Posaconazole is a cost-effective and dominant option compared to standard antifungal therapy in many markets.
- Posaconazole continues to be studied for additional fungal infections beyond original approval, including toenail onychomycosis, Chagas disease and chronic granulomatous disease.
- Success of posaconazole has spurred enhanced development of future azole antifungal agents, including isavuconazonium.
Supplementary Material Located in Separate Files

Text Box 1: Labeled FDA Indications for use (Posaconazole Text Boxes.docx)
Text Box 2: Labeled EMA Indications for use (Posaconazole Text Boxes.docx)

Figure 1: Chemical structures of common triazole anti-fungal drugs and isavuconazonium. (ChemDraw files)

Figure 2: Key Patient Populations with Posaconazole Drug Interactions (Posaconazole Figures.pptx)
Figure 3: Regulatory History of Posaconazole (Posaconazole Figures.pptx)

Figure 4: Posaconazole Therapy Algorithm (Posaconazole Figures.pptx)

Table 1: (Posaconazole Tables.docx)
Table 2: (Posaconazole Tables.docx)
REFERENCES

Papers of particular interest have been highlighted as:
* of interest
** of considerable interest


30. Cornely OA, Duarte R.F., Haider S., et al. Phase 3 pharmacokinetics (PK) and safety study of posaconazole (POS) tablet in patients at risk for invasive fungal infection. 23rd European congress of clinical microbiology and infectious diseases; Berlin, Germany; 2013.


Pettit N.N. SJL, Han Z., delaCruz J., Landon E., Pisano J. Posaconazole (PCZ) Tablet Formulation Therapeutic Drug Monitoring (TDM) and Toxicity Analysis. Interscience conference on antimicrobial agents and chemotherapy; Washington, D.C.; 2014.


45. Jung DS, Tverdek FP, Kontoyiannis DP. Switching from posaconazole suspension to tablets increases serum drug levels in leukemia patients without clinically relevant hepatotoxicity. *Antimicrobial agents and chemotherapy*, 58(11), 6993-6995 (2014).


78. Potential future direction of azole antifungal therapeutics.


