National PBM Drug Monograph
Posaconazole (Noxafil®)

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

EXECUTIVE SUMMARY

Posaconazole is approved for prophylaxis of invasive Aspergillus and Candida infections in patients 13 years of age and older who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

- In a large randomized double-blind trial, prophylaxis with posaconazole 200mg TID was compared to fluconazole 400mg once daily in patients who have undergone allogeneic HSCT and have GVHD. There were fewer cases of proven/probable invasive fungal infections (IFIs) in patients receiving posaconazole (5% vs. 9%) at 16-weeks post-randomization. Specifically, the incidence of infection with aspergillus was 2% with posaconazole and 7% with fluconazole. The incidence of candidal infections was 1% in both groups.

- In a large randomized, open-label trial, prophylaxis with posaconazole 200mg TID was compared to fluconazole suspension 400mg once daily or itraconazole oral solution 200mg BID in neutropenic patients receiving cytotoxic chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS). There were fewer cases of proven/probable IFIs in patients receiving posaconazole (5% vs. 11%) at 100days post-randomization. The incidence of infection with aspergillus was 1% with posaconazole and 9% with fluconazole/itraconazole. The incidence of candidal infections was higher in the posaconazole group (3% vs. 1%).

Posaconazole is also approved for treatment of oropharyngeal candidiasis, including those refractory to itraconazole and/or fluconazole. It is not presently approved for treatment of esophageal candidiasis.

- Patients who were HIV positive and had clinical evidence of pseudomembranous oropharyngeal candidiasis were randomized to receive posaconazole or fluconazole suspension 100mg daily (200mg loading dose) for 14 days. Posaconazole was found to be non-inferior to fluconazole.

- Posaconazole was studied in 2 trials in patients with HIV and oropharyngeal or esophageal candidiasis that was refractory or resistant to fluconazole or itraconazole. In the first study, clinical cure or improvement at 28-days was 75%. In the second study, clinical cure or improvement at 3 months was 86%.

Posaconazole has also been evaluated for patients with invasive fungal infections caused by *Aspergillus, Fusarium, Zygomycetes, Chromoblastomycosis, Mycetoma, Coccidioides, Candida, Cryptococcus,* and other less common fungi that were refractory to or intolerant of standard therapy.

Posaconazole is only available orally as a suspension. Each dose of posaconazole should be administered with a full meal or with a liquid nutritional supplement in patients who can not eat a full meal. For patients who are unable to consume/tolerate a full meal or oral nutritional supplement, another antifungal should be considered.

- Prophylaxis of invasive fungal infections: 200 mg (5 mL) three times daily. The duration of therapy is based on recovery from neutropenia or immunosuppression.
- Oropharyngeal candidiasis: Loading dose of 100mg (2.5mL) twice daily on first day, then 100mg once daily thereafter for 13 days.

- Oropharyngeal candidiasis refractory to itraconazole and/or fluconazole: 400mg (10mL) twice daily. Duration of therapy is based on severity of patient's underlying disease and clinical response.

In vitro studies have shown that posaconazole is an inhibitor of CYP3A4; therefore, the plasma concentration of other drugs metabolized via CYP3A4 may be increased. Dosage reduction of cyclosporine, sirolimus, and tacrolimus is required.

As with other azoles, posaconazole can increase the QTc or QT-interval. Do not administer posaconazole in patients with potentially proarrhythmic conditions including co-administration with other drugs known to prolong the QTc interval and are metabolized via CYP3A4. Co-administration with CYP3A4 substrates (terfenadine, astemizole, cisapride, pimozide, halofantrine, and quinidine) is contraindicated.

As with other azoles, posaconazole has been rarely associated with hepatoxicity; therefore, liver function tests and bilirubin should be monitored at the start of and during the course of posaconazole therapy.

INTRODUCTION

Posaconazole is a second-generation extended-spectrum triazole antifungal. It is the only azole demonstrating activity against Zygomycetes. Posaconazole is the only antifungal agent FDA-approved for the prevention of invasive fungal infections (IFIs) caused by Aspergillus species.

PHARMACOLOGY

Posaconazole blocks the synthesis of ergosterol, the primary sterol in the fungal cell membrane. Specifically, it inhibits lanosterol 14α-demethylase (CYP51) encoded by *ERG11* gene for *Erg11p*.

PHARMACOKINETICS[1]

The plasma concentration of posaconazole increases in a dose-proportional fashion (doses 50-800mg) and appears to plateau with doses above 800mg.

After single-dose administration of 200mg, both the Cmax and AUC of posaconazole were approximately 3x and 4x higher when administered with a nonfat meal and high fat meal respectively compared to the unfed state. After single-dose administration of 400mg, both the Cmax and AUC was approximately 3x higher when administered with a liquid nutritional supplement containing 14gms of fat compared to the unfed state.

Table 1: Pharmacokinetics in healthy volunteers

Cmax (single-dose)	378ng/ml (200mg- nonfat meal); 512ng/ml (200mg – high fat meal); 355ng/ml (400mg- nutritional suppl)
Tmax (single-dose)	3-5 hours
AUC (ng•hr/mL) (single-dose)	10,753(200mg- nonfat meal); 15,059 (200mg – high fat meal); 11,295 (400mg- nutritional suppl)
Clearance	32L/h
Half-life	35h (range 20-66h)
Volume of distribution	1774L
Protein binding	>98% primarily to albumin
Metabolism	Predominantly circulates as the parent compound Some metabolites formed via UDP glucuronidation There are no major metabolites formed via CYP450 pathway
Elimination	71% of dose eliminated in the feces (with 66% as the parent drug) 13% eliminated renally

In patients who were taking posaconazole 200mg TID or 400mg BID, the mean AUC was (9093 and 15,900 ng•hr/mL), mean clearance (51.2 and 76.1L/h), mean volume of distribution (2425 and 3088L), and average concentration (583 and 723ng/mL) respectively.

Gender, race, and age (<65 and ≥ 65 years) did not affect the pharmacokinetic profile of posaconazole; therefore dosing adjustment based on these variables is not needed.

There are insufficient pharmacokinetic data on use of posaconazole in patients with hepatic impairment. Use with caution in these patients.

Based on a single-dose study (400mg), the pharmacokinetics of posaconazole were not significantly altered in patients with mild to moderate renal insufficiency (CLcr 20-80 mL/min/1.73m^2); therefore, dosage adjustment is not needed.

In patients with severe renal insufficient (CLcr <20 mL/min/1.73m^2), the range of AUC estimates was highly variable; therefore, these patients should be monitored closely for breakthrough fungal infections.

MICROBIOLOGY

Please note that the results of *in vitro* susceptibility testing do not necessarily correlate with clinical outcome and that interpretive breakpoints have not yet been established for posaconazole.

Posaconazole is slightly less potent than voriconazole against Candida spp, but is more potent than fluconazole. Posaconazole has similar potency to voriconazole against Aspergillus spp. Posaconazole is the only azole that has demonstrated activity against Zygomycetes; however, it is generally less active than amphotericin B. The data shown in table 2 were collected over a 10 year time span from 200 medical centers worldwide.[2]

Table 2: In-vitro activity of posaconazole (MIC_{90})

	# of isolates	Posaconazole	Fluconazole	Itraconazole	Voriconazole
Candida spp.					
C. albicans	3535	0.063	2.0	0.25	0.063
C. glabrata	1218	2.0	64	4.0	2.0
C. parapsilosis	970	0.25	4.0	0.5	0.125
C. tropicalis	719	0.25	4.0	0.5	0.5
C. krusei	189	1.0	64	1.0	0.5
C. lusitaniae	84	0.25	4.0	2.0	0.063
C. dubliniensis	164	0.125	32	0.5	0.125
Aspergillus spp.					
A. fumigatus	1119	0.5		1.0	0.5
A. niger	101	0.5		2.0	2.0
A. flavus	89	0.5		1.0	1.0
A. terreus	22	0.25		0.5	0.5
Zygomycetes					
Rhizopus spp.	32	8.0		32	128
Mucor spp.	18	16		32	128
Absidia spp.	16	0.25		0.5	128
Cunninghamella spp.	6	0.031-1.0		0.125-2.0	8-128
Apophysomyces spp.	5	0.031-4.0		0.031-8.0	16-128
Saksenaea spp.	4	0.016-2.0		0.016-0.125	0.5-4
Rhizomucor spp.	3	0.016-0.25		0.016-0.25	2-16
Cokeromyces spp.	2	0.25-4.0		0.25-8.0	16-64
Fusarium					
F. solani	39	32			32
F. oxysporum	12	4.0			32
F. moniliforme	2	1.0			1.0
Other *Fusarium spp.*	14	16			16
Dimorphic fungi					
Histoplasma spp.	53	0.25		0.063	
Blastomyces spp.	38	0.125		2.0	
Coccidioides spp.	25	0.25		0.25	
Paracoccidioides spp.	13	0.125		0.063	
Cryptococcus spp.	271	0.25	8.0	0.5	0.125

Units are µg/ml

Azole-resistant Candida isolates

Among the 6595 *Candida* isolates, 6.4%, 16.5%, and 3.3% were considered to be resistant to fluconazole (MIC>32mcg/ml), itraconazole (MIC > 0.5mcg/ml) and voriconazole (MIC > 2.0mcg/ml) respectively. For posaconazole, 3% of isolates had a MIC > 2µg/ml. Isolates with elevated MICs to one azole generally were generally less susceptible to all azoles.

FDA-APPROVED INDICATIONS

- Prophylaxis of invasive Aspergillus and Candida infections in patients 13 years of age and older who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

- Treatment of oropharyngeal candidiasis, including those refractory to itraconazole and/or fluconazole.

DOSAGE/ADMINISTRATION

Each dose of posaconazole should be administered with a full meal or with a liquid nutritional supplement in patients who can not eat a full meal. For patients who are unable to consume/tolerate a full meal or oral nutritional supplement, another antifungal should be considered.

Prophylaxis of invasive fungal infections: 200 mg (5 mL) three times daily. The duration of therapy is based on recovery from neutropenia or immunosuppression.

Oropharyngeal candidiasis: Loading dose of 100mg (2.5mL) twice daily on first day, then 100mg once daily thereafter for 13 days.

Oropharyngeal candidiasis refractory to itraconazole and/or fluconazole: 400mg (10mL) twice daily. Duration of therapy is based on severity of patient's underlying disease and clinical response.

AVAILABILITY/STORAGE

- Posaconazole is available as a 4-ounce Oral Suspension containing 105 mL of suspension (40 mg of posaconazole per mL). A plastic spoon, calibrated to measure 2.5 and 5mL doses, is supplied with each bottle.
- Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) DO NOT FREEZE.

EFFICACY

Use in prophylaxis of invasive Aspergillus and Candida infections

Two randomized trials were conducted in support of prophylaxis of Aspergillus and Candida infections (FDA-approved indications). These trials have not been published.

The first trial was a randomized, open-label study conducted in neutropenic patients receiving cytotoxic chemotherapy for AML or MDS. Posaconazole 200mg oral susp three times daily (n=304)was compared to fluconazole oral susp 400mg once daily **or** itraconazole oral solution 200mg twice daily (n=298).[1] The primary outcome was the composite endpoint of proven/probable invasive fungal infection, death, or treatment with systemic antifungals. Assessments were made while on treatment plus 7 days and 100 days post-randomization. Patients receiving posaconazole had fewer overall IFIs, and fewer infections due to aspergillus, and a lower rate of requiring treatment with antifungals. Additionally, the mortality rate was lower in the posaconazole group. The mean duration of prophylaxis was 80 days.

The second trial was a randomized, double-blind study conducted in patients who have undergone allogeneic hematopoietic stem cell transplant and have Graft-vs-Host Disease. Posaconazole 200mg oral suspension three times daily (n=301) was compared to fluconazole 400mg capsules once daily (n=299).[1] The primary outcome was the incidence of proven/probable IFIs at 16-week post-randomization in the intent-to treat group. Patients receiving posaconazole had fewer overall IFIs, and fewer infections due to aspergillus; however, the need for treatment with antifungals was not different between the groups. The mortality rate was slightly lower in the posaconazole group. Mean duration of prophylaxis was 29 days.

Table3: Prophylaxis of invasive aspergillus and candida infections

	Study 1 (data through 100-day post-randomization)		Study 2 (data through 16-weeks)	
	Posaconazole	**Fluconazole/ itraconazole**	**Posaconazole**	**Fluconazole**
Proven/probable IFI. due to:				
• Overall	5%	11%	5% (16/301)	9% (27/299)
• Aspergillus	1%	9%	2% (7/301)*	7% (21/299)
• Candida	3%	1%	1% (4/301)	1% (4/299)
• Other	1%	1%	2% (5/301)	1% (2/299)
Deaths due to:				
• All-cause	44 (14%)	64 (21%)	58 (19%)	59 (20%)
• IFI	2 (1%)	16 (5%)	10 (3%)	16 (5%)
Need for systemic antifungals	98 (32%)	125 (42%)	26 (9%)	30 (10%)

Use in oropharyngeal candidiasis

Posaconazole is approved for treatment of oropharyngeal candidiasis, but not for esophageal candidiasis. Patients who were HIV positive and had clinical evidence of pseudomembranous oropharyngeal candidiasis were randomized to receive posaconazole or fluconazole suspension 100mg daily (200mg loading dose) for 14 days.[3] Mean CD4 count was 137 ± 161 cells /mm^3. Approximately 91% of isolates were *C. albicans*. Only 44% of patients were receiving concomitant antiretroviral therapy. The primary endpoint was clinical success (clinical cure or clinical improvement) in the modified intent-to-treat group, which was defined as having received ≥ 1 dose of study and had a positive culture for Candida at baseline. Posaconazole was found to be non-inferior to fluconazole. Among the patients who had initially responded, clinical relapse at day 42 occurred in 31.5% and 38.2% of the posaconazole and fluconazole groups respectively. (See appendix 2 for other results)

Table 4: Clinical success in the modified intent-to-treat group

	Posaconazole	**Fluconazole**
Clinical Success	155/169 (91.7%)	148/160 (92.5%)
• Clinical cure	81.7%	82.5%
• Clinical improvement	10.1%	10%

Use in azole- refractory oropharyngeal or esophageal candidiasis

Posaconazole is approved for azole-refractory oropharyngeal candidiasis, but not for azole-refractory esophageal candidiasis.

In a non-comparative study, patients with HIV and oropharyngeal or esophageal candidiasis that was refractory or resistant to fluconazole or itraconazole received open-label posaconazole.[1] Posaconazole was administered as 400mg BID x 3 days followed by 400mg once daily for 25 days. The protocol for dosing was later amended to 400mg BID x 28 days. Patients were given an option to receive maintenance treatment with posaconazole 400mg BID 3 x weekly for 3 months. The primary outcome was clinical success (clinical cure or clinical improvement) at 28-days in the modified intent-to-treat population. Overall clinical success was 75% (132/176). For other results, see appendix 3.

In another study, posaconazole 400mg BID x 3 months was administered to patients with HIV and oropharyngeal or esophageal candidiasis that was refractory or resistant to fluconazole or itraconazole.[1] The primary outcome was clinical success (clinical cure or clinical improvement) at 3 months in the modified intent-to-treat population. Sixty-one patients from the 3-month maintenance phase described in the study above were included in this study. Overall clinical success was 86% (77/90). For other results, see appendix 3.

Use as salvage therapy

A large study evaluated the use of posaconazole for patients with invasive fungal infections who were refractory to or intolerant of standard therapy. Infections caused by *Aspergillus, Fusarium, Zygomycetes, Chromoblastomycosis, Mycetoma, Coccidioides, Candida, Cryptococcus,* and other less common fungi were treated (n=330).[1] Retrospectively collected data from patients treated with other salvage antifungal

therapy (n=279) mostly from the same center and during the same time frame as the posaconazole study served as the control group. Posaconazole was administered as 800mg daily in divided doses for a maximum of 12 months therapy. The primary endpoint was complete or partial improvement in baseline clinical signs and/or symptoms, radiological and mycological abnormalities in the modified intent-to-treat group. Complete or partial response was seen in 119/238 (50%) and 96/218 (44%) of patients in the posaconazole and control groups respectively. Results by pathogen are shown in appendix 4.

Use as salvage therapy for zygomycosis

Two studies have evaluated posaconazole as salvage therapy in patients with zygomycosis that was refractory to or intolerant of conventional or liposomal amphotericin ± azoles.[4, 5] The first evaluated a subgroup of patients with zygomycosis from 2 larger trials conducted between 2/99-4/01(n=24). The second evaluated a subgroup of patients with zygomycosis from a compassionate use trial conducted between 8/01-11/04 (n=91). Posaconazole was administered either as 400mg twice daily or 200mg four times daily.

In the first study, 19 patients were refractory to and 5 were intolerant of other antifungal treatment. Complete response was defined as resolution of signs of infection with no relapse for ≥ 30 days after discontinuing posaconazole. Partial response was defined as clinical and radiologic (if available) improvement during treatment and no further evidence of active zygomycosis while on posaconazole or no follow-up after discontinuing posaconazole. Overall (complete + partial) success was 19/24 (79%).[4]

In the second study, 48 patients were refractory, 10 were intolerant, and 33 were both refractory and intolerant to their antifungal regimen. Overall success was 55/91 (60%). Thirty-five patients died during or within a month of stopping posaconazole therapy; 15 deaths were due to zygomycosis and were mainly seen in patients receiving posaconazole for < 30days.[5]

See appendix 4 for more study details.

Salvage therapy-other (See appendix 4 for more study details)

In a retrospective analysis, 21 patients with invasive fusariosis from 3 open-label clinical trials that was refractory to or intolerant of conventional or lipid amphotericin were evaluated.[6] Posaconazole 800mg daily (in 2-4 divided doses) was administered. Other antifungal agents were not allowed. Seventeen patients were refractory and 4 were intolerant to their current therapy. Site of infection was pulmonary (n=4), extrapulmonary (n=7), disseminated with pulmonary involvement (n=3), disseminated without pulmonary involvement (n=7). In a subgroup of 16 patients with leukemia, mean duration of therapy was 83 days (range 1-300 days). Complete or partial response occurred in 48% (10/21) patients.

In a retrospective analysis of a subgroup of patients from a large salvage trial, 39 patients with CNS fungal infections that were refractory to or intolerant of amphotericin ± azoles were evaluated.[7] Twenty-nine patients had cryptococcal meningitis (26 refractory, 2 intolerant, 1 both) and 10 had CNS infections due to other fungal pathogens (*Aspergillus spp*. n=4; *P. boydii* n=2; *C. immitis* n=1; *H. capsulatum* n=1; *Ramichloridium mackenziei* n=1; *Apophysomyces elegans + Basidiomycetes sp.* n=1).

Among the 29 patients with cryptococcal meningitis, a complete response was seen in 4 patients, partial response in 10 patients, and a non-successful outcome in 15 patients. The mean duration of posaconazole therapy was 81 days (range 4-195 days). Among the 14 with successful outcomes, 4 died after treatment with posaconazole was complete due to other causes. Among those with unsuccessful outcomes, 8 died, 7 of which were due to cryptococcal infection.

Among the 10 patients with other fungal infections, 2 had a complete response, 3 had partial, and 5 were unsuccessful. One patient with a partial success died 1 month after posaconazole was stopped due to progressive CNS aspergillosis. Four of the 5 patients with unsuccessful outcomes died.

Use in febrile neutropenia

Sixty-six patients with febrile neutropenia were randomized to receive 1 of 3 posaconazole dosing regimens until neutrophil recovery (maximum 45 days).[8]

- 200mg QID x 9 doses, followed by 400mg BID
- 400mg QID x 9 doses, followed by 600mg BID
- 800mg BID x 5 doses followed by 800mg QD

Success was defined as all of the following: survival through 7 days after the last day of treatment, defervescence during the neutropenic period, microbial eradication of IFI (if present at baseline), no breakthrough IFI during posaconazole treatment or within 7 days of last dose, no discontinuation of posaconazole due to lack of efficacy or adverse event. In the all-patients randomized group, clinical success was 64% (42/66). There was no difference in clinical success between the 3 different dosing regimens (range 61-67%). In the efficacy evaluable population (received > 1 dose of medication and assessed at the end of treatment or 7 days post-treatment), clinical success was 77% (41/53). From the efficacy evaluable population, 47 patients were followed for 7 days post-treatment. The rate of clinical success in this group was 81% (38/47).

SAFETY

Safety of posaconazole was assessed in 1844 patients (n=605 prophylaxis studies; n=796 in oropharyngeal candidiasis studies; n=443 other). Posaconazole was administered for ≥ 6 months in 171 patients and ≥ 12 months in 58 patients.

Safety data from prophylaxis studies

In the transplant trial, the incidence of treatment-related AEs was similar for posaconazole and fluconazole (36% vs. 38%). Discontinuation of treatment due to AE was 34% and 38% for posaconazole and fluconazole respectively.

In the hematologic malignancy trial, the incidence of treatment-related AEs was 34%, which resulted in discontinuation of treatment in approximately 13% of patients. Fewer patients died due to AEs in the posaconazole group (7% vs. 10%).

The incidence of treatment-emergent adverse hepatic events was similar between posaconazole and fluconazole. However, the incidence of the following treatment related adverse hepatic events was higher with posaconazole: bilirubinemia (<1% vs. 0), hepatocellular damage (1% vs. 0), increased SGOT (2% vs. 1%), and increase SGPT (3% vs. 1%). [9]

Because visual disturbances can occur with voriconazole treatment, this AE was assessed with posaconazole. Diplopia, nystagmus, photophobia, blurred vision, reduced visual acuity, and abnormal vision occurred at the same or lower rate with posaconazole compared to fluconazole. Photopsia and scotoma were observed in 2 and 3 patients respectively in the posaconazole group; none were observed in the fluconazole group. [9]

Prolonged QTc interval of ≥60msec from baseline occurred in 5% of posaconazole, 6% of fluconazole, and 11% of itraconazole patients. A QTc value of ≥ 500msec occurred in 2%, 1%, and 2% of patients receiving posaconazole, fluconazole, and itraconazole respectively. Two cases of Torsades de Pointes occurred in patients receiving posaconazole. In both cases, the patient had underlying electrolyte disturbances that are associated with Torsades. [9]

In the post stem cell transplant patients with GVHD, there were 8 cases of hemolytic uremic syndrome (6 posaconazole and 2 fluconazole) and 8 cases of thrombotic thrombocytopenic purpura (5 posaconazole and 3 fluconazole).[9]

Seven patients receiving posaconazole (6 from the HSCT prophylaxis study) had a pulmonary embolus compared to none receiving fluconazole. Only 1 case was deemed to be possibly related to posaconazole.[9]

Please refer to Appendix 5 for other adverse events.

Safety data from oropharyngeal candidiasis study

In the comparative oropharyngeal candidiasis trial, the incidence of treatment-emergent AEs was similar for posaconazole and fluconazole (64% vs. 68%). Drug-related AEs occurred in approximately 25% of patients in each group. Treatment was discontinued due to AE in 4% of patients from either group. Deaths occurred in 2.2% and 0.5% of patients in the posaconazole and fluconazole groups respectively; none of which were thought to be related to treatment.

Elevated ALT, AST, or alkaline phosphatase that was > 3 x ULN occurred at a lower rate with posaconazole than fluconazole. Total bilirubin that was > 1.5 x ULN occurred in 3% and 2% of posaconazole and fluconazole respectively. In the OPC refractory studies, elevated values were more commonly seen than in the controlled comparative study; ALT (11%), AST 17%, alkaline phosphatase 13%, total bilirubin 5%).

In general, AEs were reported more frequently in the refractory OPC studies.

Please see Appendix 5 for other adverse events.

Safety data from salvage therapy and febrile neutropenia studies

Long-term safety data are presented for patients with febrile neutropenia (n=66) or refractory invasive fungal infections (n=362).[10] The mean duration of treatment for all patients was 115 days (range 1-609 days), median 54 days. Duration of treatment was < 6 months and ≥ 6 months in 319 and 109 patients respectively. *Aspergillus spp* was the primary pathogen identified in 37% of cases. Underlying disease was malignancy in 63% of patients and/or transplant in 35% of patients. Treatment-related adverse events occurred in 164/428 (38%) patients and were deemed as serious in 35 (8%) patients. Twenty-five (6%) patients discontinued therapy due to treatment-emergent adverse events, the majority which occurred in the < 6months group.

Prolonged QTc and or QT interval was reported in 4 (1%) and 2 (2%) of patients receiving < 6months and ≥ 6 months of therapy, which was generally considered to be mild to moderate in nature and did not result in discontinuation of therapy. However, in 2 patients, treatment was interrupted.

In patients with a baseline and at least 1 post-baseline value who received < 6 months of posaconazole, change in blood chemistry and hematologic values from Common Toxicity Criteria from grades 0, 1, or 2 to 3 or 4 occurred in the following numbers: hematocrit/hemoglobin n=25, neutrophils n= 23, platelet n=41, leukocyte n=25, AST n=13, ALT n= 21, total bilirubin n=13, alkaline phosphatase n=13, creatinine n=4.

For those receiving > 6 months of posaconazole, the number of patients with worsening values were hematocrit/hemoglobin n=20, neutrophils n= 16, platelet n=14, leukocyte n=16, AST n=4, ALT n= 8, total bilirubin n=2, alkaline phosphatase n=3, creatinine n=4.

The total number of deaths was 157/428 (37%). Seventy-five were unrelated to study treatment, 77 were related to the disease under investigation or progression of underlying disease under investigation, 3 were due to other causes, and 2 were possibly related to posaconazole.

See Appendix 5 for other adverse events.

CONRAINDICATIONS

- Co-administration with ergot alkaloids
- Co-administration with CYP3A4 substrates (terfenadine, astemizole, cisapride, pimozide, halofantrine, and quinidine) as this may result in increased concentration of these substrates and may lead to QTc prolongation.

WARNINGS/PRECAUTIONS

- There are no data regarding cross-sensitivity to other azoles and posaconazole; therefore, use with caution in patients with hypersensitivity to other azoles.

- Monitor liver function tests and bilirubin at the start of and during the course of posaconazole therapy. If abnormal LFT develop, patient should be closely monitored for more severe hepatic injury. Consider discontinuation of posaconazole if clinical signs and symptoms consistent with liver disease develop that may be attributable to posaconazole.
- Dose reduction and more frequent monitoring of cyclosporine, tacrolimus and sirolimus should be performed when posaconazole is initiated (also monitoring of levels will be needed once posaconazole is stopped).
- Do not administer posaconazole in patients with potentially proarrhythmic conditions including co-administration with other drugs known to prolong the QTc interval and are metabolized via CYP3A4.
- Correction of potassium, magnesium, and calcium should be attempted prior to initiating posaconazole.

LOOK-ALIKE/SOUND-ALIKE

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for trade name Noxafil:
Norfloxacin, NEX Avar, Amoxil, moexipril, Mexitil, Monopril, Paxil

LA/SA for generic name posaconazole:
Pantoprazole, Pediazole, propranolol, fluconazole, voriconazole, policosanol

DRUG INTERACTIONS[1]

Posaconazole is primarily metabolized via UDP glucuronidation and is a substrate for p-glycoprotein efflux; therefore, inhibitors or inducers of these pathways may affect posaconazole kinetics.

In vitro studies have shown that posaconazole is an inhibitor of CYP3A4; therefore, the plasma concentration of other drugs metabolized via CYP3A4 may be increased.

Table 5: Drug interactions

Co-administered drug	Effect	Recommendations
Cimetidine	Both Cmax and AUC of posaconazole decreased by 39%	• Avoid concomitant use unless benefit outweighs risk.
Rifabutin	• Cmax and AUC of rifabutin increased by 31% and 72% respectively • Cmax and AUC of posaconazole decreased by 43% and 49% respectively	• Avoid concomitant use unless benefit outweighs risk. • If co-administration is required, frequent monitoring of full blood counts and other adverse events of rifabutin (e.g. uveitis) is recommended.
Phenytoin	• Cmax and AUC of posaconazole decreased by 41% and 50% respectively • Both Cmax and AUC of phenytoin increased by 16%	• Avoid concomitant use unless benefit outweighs risk. • Frequent monitoring of phenytoin concentrations should be performed while co-administered with posaconazole and dose reduction of phenytoin should be considered.
Cyclosporine	• Increased cyclosporin whole blood trough concentrations • Up to 29% reduction in cyclosporin dose was required	• Reduce cyclosporin dose to ~ ¾ of the original dose • Monitor whole blood trough concentrations of cyclosporin during and at discontinuation of posaconazole and adjust dose accordingly
Tacrolimus	Cmax and AUC of tacrolimus as increased by 121% and 358% respectively	• Reduce tacrolimus dose to ~ 1/3rd of original dose • Monitor whole blood trough concentrations of tacrolimus during and at discontinuation of posaconazole and adjust dose accordingly
Midazolam	AUC of midazolam increased by 83%	Perform frequent monitoring of adverse effects of benzodiazepines metabolized via CYP3A4; consider dosage reduction of benzodiazepine
Antacids, glipizide, ritonavir, H2 antagonists other	No significant effect on posaconazole bioavailability/plasma concentration	None

than cimetidine, proton pump inhibitors		
Zidovudine, lamivudine, ritonavir, indinavir, or caffeine	Posaconazole did not have a significant effect on these co-administered drugs	None

COST

The VA cost of one 105mL bottle of posaconazole200mg/5mL is $352.88.

Table 6: Cost for antifungal prophylaxis

	Routes	Dose	Cost per day
Posaconazole§	oral only	200mg three times daily	$50.41
Fluconazole¶	oral and IV	400mg once daily	$0.37 (generic tablet) $4.10 (generic suspension) $18.75-37.50 (generic IV)
Voriconazole	oral and IV	200mg twice daily	$38.44 (tablet) $52.25 (suspension) $131.50 (IV)
Itraconazole oral solution	oral and IV	200mg twice daily	$21.24
Amphotericin B	IV only	0.1-0.25 mg/kg/day	$0.71 – 1.77*
Liposomal amphotericin B	IV only	1mg/kg/day	$73.86*
Micafungin^	IV only	50mg daily	$59.20

§Only agent approved for prophylaxis of aspergillus; however, other azoles and amphotericin are used.
¶Fluconazole does not provide coverage against aspergillus
*Cost based on 70kg patient
^Approved for prophylaxis of candida in HSCT; however, does have *in vitro* activity against aspergillus

Table 7: Cost for treatment of oropharyngeal candidiasis

	Dose	Daily cost
Posaconazole	100mg once daily (200mg LD)	$8.40
Fluconazole	100-200mg daily (200mg LD)	$1.03 – 2.05 (generic suspension) $0.13 – 0.18 (generic tablet)
Itraconazole oral solution	200mg daily	$10.62

Cost of loading dose not included

RECOMMENDATIONS

1. Fluconazole should remain the standard agent used for prophylaxis in HSCT recipients or neutropenic patients with hematologic malignancy unless non-albicans *Candida* (e.g. *C. glabrata, C. krusei*) or *Aspergillus* is prevalent at a given center or patient is at high risk for aspergillus infection. Options include posaconazole, voriconazole, amphotericin B, and the echinocandins. Posaconazole is the only agent approved for prophylaxis of *Aspergillus* in these patients.

2. Fluconazole and itraconazole remain as first line azoles for oropharyngeal candidiasis. Posaconazole should be reserved for refractory cases.

3. Posaconazole has not been evaluated for primary treatment of invasive fungal infections; however, data are available for use as salvage therapy in patients who are refractory to or intolerant of standard therapies (not FDA-approved)

    - Prior to posaconazole, the only antifungal used to treat zygomycosis was amphotericin B. Data are available showing that posaconazole can be used in patients who are refractory to or intolerant of amphotericin B. There are no data at this time with posaconazole as oral step down therapy after initial therapy with amphotericin B.

- Data are available for use of posaconazole as salvage therapy for invasive fungal infections. Other agents that are used include voriconazole, itraconazole IV, amphotericin, and the echinocandins (*Candida* and *Aspergillus*).

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Prepared December 2006
Contact Person: Deb Khachikian, Pharm D

Appendix 1: Prophylaxis of invasive Aspergillus and Candida infections

<table>
<tr><th>Study</th><th>Inclusion/exclusion criteria</th><th>Dosing</th><th>Baseline data</th><th>Results</th></tr>
<tr>
<td>Study I98-316)
R, DB, DD

n=600

ITT analysis</td>
<td>≥ 13 years old
Undergone allogeneic HSCT
Acute (grade II-IV) or chronic extensive GVHD
Receiving 1 of the following:
High-dose corticosteroids
antithymocyte globulin
steroid sparing regimens (combination of ≥ 2 immunosuppressive agents or modalities)

<u>Exclusions:</u> proven/probable mould or invasive fungal infection at baseline, use of meds known to interact with azoles, h/o hypersensitivity to azoles, use of vinca alkaloids or anthracyclines, prolonged QTc interval, neurological disorders, ALT/AST > 10 x ULN, CrCl < 20mL/min, previous use of antifungals</td>
<td>Posaconazole 200mg TID
Fluconazole 400mg once daily</td>
<td>Baseline characteristics, underlying disease and risk factors similar for both groups (data not shown)</td>
<td>
<table>
<tr><th></th><th colspan="2">On therapy + 7 days</th><th colspan="2">112 days post-randomizaiton</th></tr>
<tr><th></th><th>POS (n=301)</th><th>FLU (n=299)</th><th>POS (n=301)</th><th>FLU (n=299)</th></tr>
<tr><td>Overall clinical failure</td><td>50 (17%)</td><td>55 (18%)</td><td>99 (33%)</td><td>110 (37%)</td></tr>
<tr><td>Proven/ probable Aspergillus</td><td>3 (1%)</td><td>17 (6%)</td><td>7 (2%)</td><td>21 (7%)</td></tr>
<tr><td>Proven/ probable Candida</td><td>1 (<1%)</td><td>3 (1%)</td><td>4 (1%)</td><td>4 (1%)</td></tr>
<tr><td>Proven / probable other IFI</td><td>3 (1%)</td><td>2 (1%)</td><td>5 (2%)</td><td>2 (1%)</td></tr>
<tr><td>All deaths</td><td>22 (7%)</td><td>24 (8%)</td><td>58 (19%)</td><td>59 (20%)</td></tr>
<tr><td>Deaths due to IFI</td><td>2 (<1%)</td><td>6 (2%)</td><td>10 (3%)</td><td>16 (5%)</td></tr>
<tr><td>Need for systemic antifungal</td><td>27 (9%)</td><td>25 (8%)</td><td>26 (9%)</td><td>30 (10%)</td></tr>
<tr><td>Mean duration of therapy</td><td></td><td></td><td>80 days</td><td>77 days</td></tr>
</table>
</td>
</tr>
<tr>
<td>Study PO1899
R, OL

n=602</td>
<td>≥ 13 years old
Documented or anticipated ANC ≤ 500 cells/mm3 lasting for ≥ 7 days because of remission induction chemotherapy for newly diagnosed or first relapse of AML or MDS

<u>Exclusions:</u> recent IFI, CrCl < 20mL/min, ALT/AST/ T. bili > 3 x ULN, abnormal QTc interval, ECOG performance status score > 2, h/o AML, MDS, HSCT, hypersensitivity to any of the study drugs, use of drugs known to interact with azoles, use of AMB, FLU, or ITR within 30 days of study entry, use of any investigational or biological agent within 30 days of study entry</td>
<td>Posaconazole 200mg TID
vs.
Fluconazole 400mg once daily
OR
Itraconazole oral solution 200mg BID

Treatment given with each cycle of chemotherapy until complete remission, recovery from neutropenia, or development of IFI (maximum duration 84 days)

If unable to tolerate oral drugs the following IV alternatives were allowed:
• AMB 0.3-0.5mg/kg daily for posaconazole
• FLU 400mg IV daily/ ITR 200mg BID IV for their oral counterparts

IV tx was allowed for up to 3 days/cycle or 10 days of the total maximum tx</td>
<td>Baseline characteristics not shown</td>
<td>
<table>
<tr><th></th><th colspan="2">On therapy + 7 days</th><th colspan="2">100d post-randomization</th></tr>
<tr><th></th><th>POS (n=304)</th><th>FLU/ ITR (n=298)</th><th>POS (n=304)</th><th>FLU/ ITR (n=298)</th></tr>
<tr><td>Overall clinical failure</td><td>82 (27%)</td><td>126 (42%)</td><td>158 (52%)</td><td>191 (64%)</td></tr>
<tr><td>Proven/ probable Aspergillus</td><td>2 (1%)</td><td>20 (7%)</td><td>2 (1%)</td><td>26 (9%)</td></tr>
<tr><td>Proven/ probable Candida</td><td>3 (1%)</td><td>2 (1%)</td><td>10 (3%)</td><td>4 (1%)</td></tr>
<tr><td>Proven / probable other IFI</td><td>2 (1%)</td><td>3 (1%)</td><td>2 (1%)</td><td>3 (1%)</td></tr>
<tr><td>All deaths</td><td>17 (6%)</td><td>25 (8%)</td><td>44 (14%)</td><td>64 (21%)</td></tr>
<tr><td>Deaths due to IFI</td><td>1 (<1%)</td><td>2 (1%)</td><td>2 (1%)</td><td>16 (5%)</td></tr>
<tr><td>Need for systemic antifungal</td><td>67 (22%)</td><td>98 (33%)</td><td>98 (32%)</td><td>125 (42%)</td></tr>
<tr><td>Mean duration of therapy</td><td></td><td></td><td>29 days</td><td>25 days</td></tr>
</table>
</td>
</tr>
</table>

Appendix 2: Use in treatment of oropharyngeal candidiasis

Study	Inclusion/exclusion criteria	Dosing	Baseline data	Results
Vazquez 2006 R, evaluator-blinded, PR ITT n=350 (178 POS; 172 FLU) Non-inferiority study	≥ 18 years old confirmed HIV clinical evidence of pseudomembranous oropharyngeal candidiasis anticipated survival > 2 months Karnofsky performance score ≥ 60 **Exclusions:** systemic antifungal during the week prior to enrollment, topical oral antifungal w/i 2 days of enrollment, intolerant of azoles, protease inhibitors for the first time w/i 30days of enrollment, drugs that interact with azoles, chemotx-related mucositis, platelet <75,000, QTc prolonged > 10% of normal interval, h/o of tx failure w/ fluconazole, ALT/AST > 5xULN, T.bili> 2.5 x ULN, INR ≥ 2, SCr > 3 x ULN	Posaconazole 100mg susp (200mg on day 1) QD Fluconazole 100mg susp (200mg on day 1) QD Patients were instructed to swish and swallow the medication Duration of tx 14 days	% male: 74/ 76 % white: 37/ 39 % black: 24/ 19 % Hispanic: 29/ 30 % Asian: 10/ 9 Mean age(years): 36.4 ± 7.8/ 37.6 ± 9.1 Mean CD4 count (cell/mm3): 137 ± 170/ 132 ± 161 Concomitant antiretrovirals: %NNRTI: 8/ 8 % protease inhibitor: 26/ 22 % NRTI: 37%/ 30% %none: 63/ 70 C. albicans: 92.3%/ 90.2% C. glabrata: 7.7%/ 5.5%	**Posaconazole** / **Fluconazole** Completed tx: 157/178 (88%) / 153/172 (89%) Completed followup: 150/178 (84%) / 141/172 (82%) Clinical success (mITT-group): 155/169 (91.7%) / 148/160 (92.5%) Clinical cure/ Improvement (mITT-group): 81.7%/ 10.1% / 82.5%/ 10% Clinical success (PE- group): 139/143 (97.2%) / 130/135 (96.3%) Clinical relapse at day 42: 45/143 (31.5%) / 52/ 136 (38.2%) Mycological success (mITT): 68% / 68% Mycological eradication (mITT): 60.4% / 58.1% Mycological eradication (day 42): 41/101 (35.6%) / 22/91 (24.2%) mITT- received ≥ 1 dose of study drug and had + culture for Candida species at baseline PE-group= as in mITT group and received ≥ 7 consecutive days of study drug and had clinical response assessment on day 14.

Clinical cure= absence of plaques or ulcers and no or minimal symptoms; **Clinical improvement=** partial resolution of pretreatment signs and symptoms of candidiasis; **Failure=** no improvement or if signs and symptoms worsened after ≥ 7days consecutive days of tx and if evidence of Candida via fungal staining of specimen obtained from oropharyngeal lesion;
Clinical relapse= recurrence of signs or symptoms after initial improvement or cure on day 14; **Mycological success=** quantitative yeast culture yielding ≤ 20 cfu/mL; eradication defined as 0 cfu/mL

Appendix 3: Use in azole-refractory oropharyngeal and esophageal candidiasis

Study	Inclusion/exclusion criteria	Dosing	Baseline data	Results
Study I97-330 OL, non-comparative All patients n=199 • mITT =176 • EA = 158 Study duration 28 days	≥ 18 years old HIV-positive Refractory to treatment with fluconazole and or itraconazole Life expectancy ≥ 6 months Refractory defined as: •h/o of failure to improve/worsening of candidiasis after tx with FLU ≥ 100mg/day or ITR 200mg/day ≥ 10 consecutive days •Baseline candida isolate microbiologically resistant to FLU and or ITR •Failed FLU/ITR more than 14 days prior to POS tx who were then treated with a non-azole antifungal and still had signs/sxs and positive culture	Posaconazole 400mg BID x 3 days then 400mg QD for 25 days (protocol was later amended changing the dose to 400mg BID x 28 days) Patients were given an option to receive maintenance treatment with posaconazole 400mg BID 3 x weekly for 3 months	Not shown	**Results at day 28*** Clinical success (mITT population) • All: 132/176 (75%) • Resistant/refractory to FLU: 58/87 (66.7%) • Resistant/refractory to ITR: 10/10 (100%) • Resistant/refractory to both FLU and ITR: 59/72 (81.9%) Mycological success (mITT population): 46/126 (36.5%) • All: 28/58 (48.3%) • Resistant/refractory to FLU: 4/10 (40%) • Resistant/refractory to ITR: 13/53 (24.5%) • Resistant/refractory to both FLU and ITR % w/ clinical cure/ clinical improvement: 53.4%/ 21.6% Success in the EA population Clinical: 129/158 (81.6%) Mycological: 46/121 (38%) Clinical success in the oropharyngeal candidiasis subgroup: 66/89 (74.2%) Clinical success in the esophageal candidiasis subgroup (evaluable population): 31/34 (72%) There was no difference in outcomes between dosing used in the original and amended protocols *Results for maintenance phase shown in study P00298
Study P00298 OL, non-comparative All patients n=100 • mITT =90 • EA = 75 Study duration up to 15 months	≥ 18 years old HIV-positive Refractory to treatment with fluconazole and or itraconazole Life expectancy ≥ 6 months See study I97-330 for definition of refractory	Posaconazole 400mg BID for up to 3 months (acute phase) Clinical responders were eligible to receive maintenance therapy for an additional 12 months. **61 patients were from the 3-months maintenance from Study I97-330**	Not shown	**Results after 3 months treatment** Clinical success (mITT population) • All: 77/90 (86%) • Previously treated with POS: 52/59 (88.1%) • POS-naïve: 25/31 (80.7%) Clinical success (EA population) • All: 66/75 (88%) • Previously treated with POS: 46/50 (92%) • POS-naïve: 20/25 (80%) Mycological success (mITT population) • All: 9/51 (18%) • Previously treated with POS: 4/31 (13%) • POS-naïve: 5/20 (25%) Continued clinical success was demonstrated in 67% (10/15) of patients treated for at least 12 months of therapy

Clinical response= absence of plaques or ulcers and no or minimal symptoms (cure) or partial resolution of pretreatment signs and symptoms (improvement); **Mycological success=** ≤ 20cfu/mL *Candida* spp. **mITT population=** all treated subjects with evidence of azole-refractory Candida culture at baseline; **EA population=** all treated subjects who received < 14 days posaconazole and had clinical assessment at visit 5 or received > 3 days of posaconazole before discontinuation of drug due to lack of efficacy or AE at visit 5.

Appendix 4: Use as salvage therapy

Study	Inclusion/exclusion criteria	Dosing	Baseline data	Results
P00041 P02952 P02387 Open-label ITT n=330 (POS)/ 279 (control) mITT n=238 (POS)/ 218 (control)	≥ 13 years old Invasive fungal infection resistant to standard therapy or history of serious, severe, or life-threatening toxicity while receiving antifungal therapy or organ dysfunction precluding administration of standard antifungal therapy	Posaconazole 800mg/day in divided doses for a maximum of 12 months A control group was established using retrospectively collected data from patients treated with antifungal salvage therapy mostly at the same center and during the same time frame as the study	Not shown	**Posaconazole** / **Control** Complete or partial response (mITT): 119/238 (50%) / 96/218 (44%) Response by pathogen • Aspergillus: 45/107 (42.1%) / 22/86 (25.6%) • Candida: 11/23 (47.8%) / 16/30 (53.3%) • Fusarium: 7/18 (38.9%) / 2/4 (50%) • Cryptococcus: 15/31 (48.4%) / 37/64 (57.8%) • Coccidioides: 11/16 (68.8%) / 3/7 (42.9%) • Zygomycetes: 6/11 (54. 5%) / 4/8 (50%) • Chromoblastomycosis: 9/11 (81.8%) / 0/2 (0%) • Other fungi: 19/30 (63.3%) / 12/20 (60%) Kaplan-Meier survival analysis: Significant survival benefit with posaconazole versus control group **complete response=** resolution of all baseline attributable clinical signs and symptoms, radiological and mycological abnormalities **partial response=** clinically meaningful improvement of all baseline attributable clinical signs and symptoms, radiological and mycological abnormalities
Greenberg 2006 Case series of patients with zygomycosis (from 2 larger trials conducted from 2/99 – 4/01)	Active zygomycosis infection as determined by positive culture or biopsy Refractory to at least 7 days of standard antifungal tx or intolerant to prior antifungals	Posaconazole 400mg BID or 200mg QID Treatment duration: Mean 292 days Median 182 days Range 8-1004 days	Refractory n=19 Intolerant n=5 Mean age 46.8 years Site of infection Rhinocerebral infection n=11 Disseminated rhinocerebral infection n=4 Other sites (skin, bone, lung, abdomen, trachea) n=9 Risk factors allogeneic bone marrow transplant n=9 allogeneic peripheral-blood stem cell transplant n=2 solid organ transplant n=4 diabetes ± other risk factor n=5 non-Hodgkin lymphoma n=1 other n=3 22/24 patients received amphotericin (conventional and/or lipid formulation) ± azoles or caspofungin	Overall success: 19/24 (79%) • complete response: 11/24 (46%) • partial response: 8/24 (33%) Response in refractory patients: • overall: 15/19 (79%) • complete response: 9/19 (47%) • partial response: 6/19 (32%) Response in intolerant patients • overall: 4/5 (80%) • complete response: 2/5 (40%) • partial response: 2/5 (40%) Deaths: 9/24 (4 due to persistent zygomycosis) Failed outcome • had surgical debridement: 13% • no surgical debridement: 50% Failed outcome • disseminated infection: 3/4 (75%) • no dissemination: 2/20 (10%) **Complete response =** resolution of signs of infection with no relapse for ≥ 30 days after discontinuing posaconazole. **Partial response =** clinical and radiologic (if available) improvement during treatment and no further evidence of active zygomycosis while on

				posaconazole or no follow-up after discontinuing posaconazole.
van Burik 2006 Retrospective, questionnaire Subgroup of patients with zygomycosis from compassionate use trial conducted 8/01-11/04	Zygomycosis infection Disease progression or failure to improve after > 7d days of standard antifungal therapy or intolerant to prior antifungals zygomycosis infection document by culture (n=60), histopathologically (n=8), both (n=23)	Posaconazole 400mg BID or 200mg QID Treatment duration: At least 30 days (range 6-1005 days) in 80% of patients	Median age 47 years (range 1-80 years) Refractory n=48 Intolerant n=10 Both n=33 Proven zygomycosis n=69 Probable zygomycosis n=22 Site of infection (1 site of infection n=56/ ≥ 1 site of infection n=35) sinus (n=42); pulmonary (n=37); cutaneous (n=13); brain (n=11); orbital (n=11); palate (n=7); GI (n=2); liver (n=1); other (n=13) 1° pathogen: Mucor spp (n=17); Rhizopus spp (n=25); Rhizomucor spp (n=7); Cunninghamella spp (n=8); Absidia spp (n=2) Risk factors: diabetes (n=30); hematologic malignancy (n=48); lymphoma (n=5); neutropenia (n=29); BMT (n=27); GVHD (n=30); solid organ transplant (n=10); chronic steroids (n=31); albumin <3mg/dL (n=22)	Overall success 55/91 (60%) • complete response 13/91 (14%) • partial response 42/91 (46%) Success • Refractory patients 30/48 (62.5%) • Intolerant 6/10 (60%) • Both 19/33 (57.7%) Success • surgical debridement 39/64 (61%) • no surgical debridement 16/26 (62%) All-cause deaths 35/91 (38%) Deaths attributable to zygomycosis 15/35 (43%) **complete response=** resolution **partial response=** clinically meaningful improvement
Raad 2006 retrospective analysis n=21 Subgroup of patients with fusariosis from 3 open-label trials	Proven/probable invasive fusariosis intolerant or refractory to conventional tx refractory = antifungal tx ≥ 7days or sooner if infection was progressing	Posaconazole 800mg (divided into 2-4 doses/day) Patients treated for up to 12 months concurrent use with other antifungals not allowed	mean age 44 years proven infection n=18 probable infection n=3 refractory ± intolerant n=17 (3 had also had progressing disease) intolerant n=4 Prior tx: ≤30 days of prior antifungal n=18 20/21 initially tx'd w/ lipid-based AmB Risk factors: neutropenia (n=8); hematalogic malignancy (n=16); nonhematol malignancy (n=2); HSCT (n=6); solid organ tx (n=2); diabetes (n=6) Site of infection: pulmonary (n=4); extrapulmonary (n=7); disseminated w/ pulm (n=3); disseminated w/o confirmed pulm (n=7)	Overall success 10/21 (48%) Success in those w/ • disseminated infec 3/10 (30%) • pulmonary infec 3/4 (75%) • extrapulmonary infec 4/7 (57%) Success in those w/ leukemia 7/16 (44%) Success in those w/ leukemia and received > 3d of posaconazole 7/14 (50%) • ALL 5/6 (83%) • AML or CML 2/8 (25%) • HSCT 1/6 (17%) Success • Refractory ± intolerant (progressing infection) 8/17 (47%) 2/3 (67%) • Intolerant only 2/4 (50%) Death in patients with leukemia 10/16 **Successful response =** complete or partial response of all symptoms, signs, and radiographic or bronchoscopic abnormalities associated with invasive fusariosis and negative results of followup cultures if performed.
Pitisuttithum 2005	≥ 13 years old CNS infection	Posaconazole 800mg (divided into 2-4	Age 18-74 years HIV infected: 29/39 (74%)	Clinical success in those with

n=39 Subgroup of patients with CNS infection from studies P00041 P02952 P02387	Proven/probable invasive fungal infection Intolerant or refractory to standard therapy	doses/day) Mean duration: cryptococcal meningitis 81 days (range 4-195 days) other fungal 195 days (range 4-609 days)	Cryptococcal meningitis n=29 (26 refractory, 2 intolerant, 1 both) Other fungal CNS infection n=10 (8 refractory, 2 both) Other fungal pathogens: Aspergillus n=4; P. boydii n=2; C. immitis n=1; H. capsulatum n=1; Apophysomyces elegans n=1; Basidiomycetes spp n=1 Prior tx: AmB and or fluconazole (crypto); AmB and or itraconazole, fluconazole, ketoconazole (other fungi)	cryptococcal meningitis 14/29 (48%) • complete response 4/14 (29%) • partial response 10/14 (71%) Clinical success in those with other fungal CNS infection 5/10 (50%) • complete response 2/5 (40%) • partial response 3/5 (60%) Deaths among those with crypto 12/29 (41%) • progression of fungal infection 6/12 (50%) • unrelated to treatment 6/12 (50%) Death among those with other infec 5/10 (50%) **Clinical success=** resolution of all (complete) or clinically meaningful improvement (partial) of attributable symptoms, signs and radiographic abnormalities

Appendix 5: Adverse Events

	Pooled Prophylaxis studies			Oropharyngeal candidiasis studies			Salvage studies	
	Posaconazole (n=605)	**Fluconazole (n=539)**	**Itraconazole (n=58)**	**Posaconazole (n=557)**	**Fluconazole (n=262)**	**Refractory studies (n=239)**	**< 6 months tx (n=319)**	**≥ 6 months tx (n=109)**
General disorders								
Fever	274 (45%)	254 (47%)	32 (55%)	34 (6%)	22 (8%)	82 (34%)	-	-
Headache	171 (28%)	141 (26%)	23 (40%)	44 (8%)	23 (9%)	47 (20%)	10 (3%)	10 (9%)
Rigors	122 (20%)	87 (16%)	17 (29%)	2 (<1%)	4 (2%)	29 (12%)	-	-
Fatigue	101 (17%)	98 (18%)	5 (9%)	18 (3%)	12 (5%)	18 (3%)	5 (2%)	2 (2%)
Edema-legs	93 (15%)	67 (12%)	11 (19%)	-	-	-	-	-
Anorexia	92 (15%)	94 (17%)	16 (28%)	10 (2%)	4 (2%)	31 (13%)	3 (1%)	5 (5%)
Dizziness	64 (11%)	56 (10%)	5 (9%)	-	-	-	6 (2%)	1 (1%)
Edema	54 (9%)	68 (13%)	8 (14%)	-	-	-	-	-
Weakness	51 (8%)	52 (10%)	2 (3%)	-	-	-	-	-
Asthenia	-	-	-	9 (2%)	5 (2%)	31 (13%)	2 (1%)	2 (2%)
Pain	-	-	-	4 (1%)	2 (1%)	27 (11%)	-	-
Cardiovascular								
Hypertension	106 (18%)	88 (16%)	3 (5%)	-	-	-	-	-
Hypotension	83 (14%)	79 (15%)	10 (17%)	-	-	-	-	-
Tachycardia	72 (12%)	75 (14%)	3 (5%)	-	-	-	-	-
Blood and lymphatic system								
Anemia	149 (25%)	124 (23%)	16 (28%)	11 (2%)	5 (2%)	34 (14%)	2 (1%)	2 (2%)
Neutropenia	141 (23%)	122 (23%)	23 (40%)	21 (4%)	8 (3%)	39 (16%)	-	-
Febrile neutropenia	118 (20%)	85 (16%)	23 (40%)	-	-	-	-	-
Aggravated neutropenia	-	-	-	0	0	5 (2%)	-	-
GI system								
Diarrhea	256 (42%)	212 (39%)	35 (60%)	58 (10%)	34 (13%)	70 (29%)	11 (3%)	4 (4%)
Nausea	232 (38%)	198 (37%)	30 (52%)	48 (9%)	30 (11%)	70 (29%)	27 (8%)	8 (7%)

Vomiting	174 (29%)	173 (32%)	24 (41%)	37 (7%)	18 (7%)	67 (28%)	21 (7%)	4 (4%)
Abdominal Pain	161 (27%)	147 (27%)	21 (36%)	37 (5%)	17 (6%)	43 (18%)	13 (4%)	5 (5%)
Constipation	126 (21%)	94 (17%)	10 (17%)	-	-	-	-	-
Mucositis	105 (17%)	68 (13%)	15 (26%)	-	-	-	-	-
Dyspepsia	61 (10%)	50 (9%)	6 (10%)	-	-	-	-	-
Liver and biliary								
Bilirubinemia	59 (10%)	51 (9%)	11 (19%)	6 (1%)	2 (1%)	6 (3%)	-	-
↑ hepatic enzymes			-	1 (<1%)	1 (<1%)	8 (3%)	7 (2%)	2 (2%)
Abnormal hepatic fx				8 (1%)	4 (2%)	0	-	-
Hepatitis				3 (1%)	0	5 (2%)	-	-
Hepatomegaly				0	0	8 (3%)	-	-
Jaundice				0	0	4 (2%)	-	-
↑ ALT				8 (1%)	5 (2%)	6 (3%)	6 (2%)	5 (5%)
↑ AST				6 (1%)	5 (2%)	6 (3%)	8 (3%)	1 (1%)
Metabolic/nutritional								
Hypokalemia	181 (30%)	142 (26%)	30 (52%)	6 (1%)	3 (1%)	15 (6%)	-	-
Hypomagnesemia	110 (18%)	84 (16%)	11 (19%)	-	-	-	-	-
Hyperglycemia	68 (11%)	76 (14%)	2 (3%)	-	-	-	-	-
Hypocalcemia	56 (9%)	55 (10%)	5 (9%)	-	-	-	-	-
Weight loss	-	-	-	4 (1%)	2 (1%)	33 (14%)	-	-
Dehydration	-	-	-	4 (1%)	7 (3%)	27 (11%0	-	-
Musculoskeletal								
Musculoskeletal pain	95 (16%)	82 (15%)	9 (16%)	-	-	-	-	-
Arthralgia	69 (11%)	67 (12%)	5 (9%)	-	-	-	-	-
Back pain	63 (10%)	66 (12%)	4 (7%)	-	-	-	-	-
Platelet, bleeding, clotting								
Thrombocytopenia	175 (29%)	146 (27%)	20 (34%)	4 (1%)	1 (<1%)	12 (5%)	0	2 (2%)
Petechiae	64 (11%)	54 (10%)	9(16%)	-	-	-	-	-
Psychiatric								
Insomnia	103 (17%)	92 (17%)	11 (19%)	8 (1%)	3 (1%)	39 (16%)	-	-
Anxiety	52 (9%)	61 (11%)	9 (16%)	-	-	-	-	-
Renal								
Acute renal failure	-	-	-	0	0	7 (3%)	0	2 (2%)
Respiratory								
Coughing	146 (24%)	130 (24%)	14 (24%)	18 (3%)	11 (4%)	60 (25%)	-	-
Dyspnea	121 (20%)	116 (22%)	15 (26%)	8 (1%)	8 (3%)	28 (12%)	-	-
Epistaxis	82 (14%)	73 (14%)	12 (21%)	-	-	-	-	-
Skin and subcutaneous tissue								
Rash	113 (19%)	96 (18%)	25 (43%)	15 (3%)	10 (4%)	36 (15%)	9 (3%)	1 (1%)
Pruritus	69 (11%)	62 (12%)	11 (19%)	-	-	-	-	-
Increased sweating	-	-	-	13 (2%)	5 (2%)	23 (10%)	-	-