

SCH 56592 (POSACONAZOLE) ORAL SUSPENSION
1.5.2 LABELING
FINAL – 19-OCTOBER-2006

MODULE 1

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NOXAFIL[®]

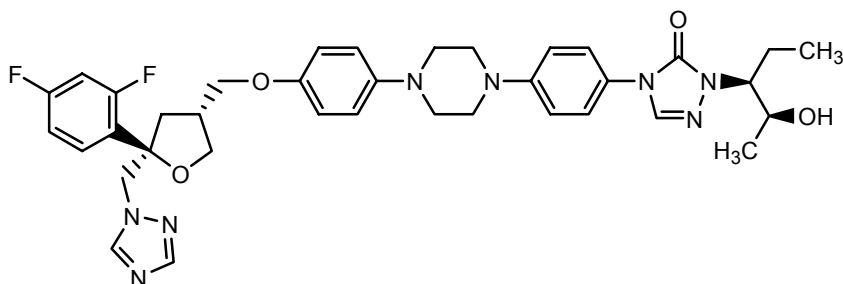
(posaconazole) ORAL SUSPENSION

PRODUCT INFORMATION

DESCRIPTION

NOXAFIL[®] (posaconazole) is a triazole antifungal agent available as a suspension for oral administration.

Posaconazole is designated chemically as 4-[4-[4-[[4-[(3*R*,5*R*)-5-(2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1*S*,2*S*)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one with an empirical formula of C₃₇H₄₂F₂N₈O₄ and a molecular weight of 700.8. The structural formula is:



Posaconazole is a white powder and is insoluble in water.

NOXAFIL Oral Suspension is a white, cherry-flavored immediate-release suspension containing 40 mg of posaconazole per mL and the following inactive ingredients: polysorbate 80, simethicone, sodium benzoate, sodium citrate dihydrate, citric acid monohydrate, glycerin, xanthan gum, liquid glucose, titanium dioxide, artificial cherry flavor, and purified water.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption

Posaconazole is absorbed with a median T_{max} of ~ 3 to 5 hours. Dose proportional increases in plasma exposure (AUC) to posaconazole were observed following single oral doses from 50 mg to 800 mg and following multiple-dose administration from 50 mg BID to 400 mg BID. No further increases in exposure were observed when the dose was increased from 400 mg BID to 600 mg BID in febrile neutropenic patients or those with refractory invasive fungal

infections. Steady-state plasma concentrations are attained at 7 to 10 days following multiple-dose administration.

Following single-dose administration of 200 mg, the mean AUC and C_{max} of posaconazole are approximately 3 times higher when administered with a nonfat meal and approximately 4 times higher when administered with a high-fat meal (~50 gm fat) relative to the fasted state. Following single-dose administration of 400 mg, the mean AUC and C_{max} of posaconazole are approximately 3 times higher when administered with a liquid nutritional supplement (14 gm fat) relative to the fasted state (See **TABLE 1**). In order to assure attainment of adequate plasma concentrations, it is recommended to administer posaconazole with food or a nutritional supplement. (See **DOSAGE AND ADMINISTRATION**.)

TABLE 1: The Mean (%CV) [Min-Max] Posaconazole Pharmacokinetic Parameters Following Single-Dose Suspension Administration of 200 mg and 400 mg Under Fed and Fasted Conditions

Dose (mg)	C_{max} (ng/mL)	T_{max} ^a (hr)	AUC(I) (ng·hr/mL)	CL/F (L/hr)	t _{1/2} (hr)
200 mg fasted (n=20) ^c	132 (50) [45-267]	3.50 [1.5-36 ^b]	4179 (31) [2705-7269]	51 (25) [28-74]	23.5 (25) [15.3-33.7]
200 mg nonfat (n=20) ^c	378 (43) [131-834]	4 [3-5]	10,753 (35) [4579-17,092]	21 (39) [12-44]	22.2 (18) [17.4-28.7]
200 mg high fat (54 gm fat) (n=20) ^c	512 (34) [241-1016]	5 [4-5]	15,059 (26) [10,341-24,476]	14 (24) [8.2-19]	23.0 (19) [17.2-33.4]
400 mg fasted (n=23) ^d	121 (75) [27-366]	4 [2-12]	5258 (48) [2834-9567]	91 (40) [42-141]	27.3 (26) [16.8-38.9]
400 mg with liquid nutritional supplement (14 gm fat) (n=23) ^d	355 (43) [145-720]	5 [4-8]	11,295 (40) [3865-20,592]	43 (56) [19-103]	26.0 (19) [18.2-35.0]

^a: Median [min-max]

^b: The subject with T_{max} of 36 hrs had relatively constant plasma levels over 36 hrs (1.7 ng/mL difference between 4 hrs and 36 hrs)

^c: n=15 for AUC(I), CL/F and t_{1/2}

^d: n=10 for AUC(I), CL/F and t_{1/2}

Distribution

Posaconazole has an apparent volume of distribution of 1774 L, suggesting extensive extravascular distribution and penetration into the body tissues.

Posaconazole is highly protein bound (>98%), predominantly to albumin.

Metabolism

Posaconazole primarily circulates as the parent compound in plasma. Of the circulating metabolites, the majority are glucuronide conjugates formed via UDP glucuronidation (phase 2 enzymes). Posaconazole does not have any major circulating oxidative (CYP450 mediated) metabolites. The excreted metabolites in urine and feces account for ~17% of the administered radiolabeled dose.

Excretion

Posaconazole is eliminated with a mean half-life ($t_{1/2}$) of 35 hours (range 20 to 66 hours) and a total body clearance (CL/F) of 32 L/hr. Posaconazole is predominantly eliminated in the feces (71% of the radiolabeled dose up to 120 hours) with the major component eliminated as parent drug (66% of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 13% of the radiolabeled dose excreted in urine up to 120 hours (<0.2% of the radiolabeled dose is parent drug).

Summary of Pharmacokinetic Parameters

The mean (% CV) [min-max] posaconazole average steady-state plasma concentrations (C_{av}) and steady-state pharmacokinetic parameters in patients following administration of 200 mg TID and 400 mg BID of the oral suspension are provided in **TABLE 2**.

TABLE 2. The Mean (%CV) [Min-Max] Posaconazole Steady-State Pharmacokinetic Parameters in Patients Following Oral Administration of Posaconazole 200 Mg TID And 400 mg BID

Dose ^a	C_{av} (ng/mL)	AUC ^e (ng·hr/mL)	CL/F (L/hr)	V/F (L)	$t_{1/2}$ (hr)
200 mg TID ^b (n=252)	1103 (67) [21.5– 3,650]	ND ^f	ND ^f	ND ^f	ND ^f
200 mg TID ^c (n=215)	583 (65) [89.7-2,200]	15,900 (62) [4100 -56,100]	51.2 (54) [10.7 -146]	2425 (39) [828 -5702]	37.2 (39) [19.1 -148]
400 mg BID ^d (n=23)	723 (86) [6.70 – 2,256]	9093 (80) [1564 -26,794]	76.1 (78) [14.9 - 256]	3088 (84) [407-13,140]	31.7 (42) [12.4-67.3]

Note: C_{av} based on observed data; other pharmacokinetic parameters based on estimates from population pharmacokinetic analyses

^a: Oral suspension administration

^b: Allogeneic hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease

^c: Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes

^d: Febrile neutropenic patients or patients with refractory invasive fungal infections, C_{av} n=24

^e: AUC (0-24 hr) for 200 mg TID and AUC (0-12 hr) for 400 mg BID

^f: Not done

The variability in average plasma posaconazole concentrations in patients was relatively higher than that in healthy subjects.

Exposure Response Relationship

In clinical studies of immunocompromised patients, a wide range of plasma exposures to posaconazole was noted. A pharmacokinetic-pharmacodynamic analysis of patient data revealed an apparent association between average posaconazole concentrations (C_{av}) and prophylactic efficacy. A lower C_{av} may be associated with an increased risk of treatment failure [defined in the study as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or invasive fungal infections (IFI)].

To enhance the oral absorption of posaconazole and optimize plasma concentrations:

- Each dose of NOXAFIL Oral Suspension should be administered with a full meal or liquid nutritional supplement. For patients who can not eat a full meal or tolerate an oral nutritional supplement, alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.
- Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.
- Co-administration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections. (See **CLINICAL PHARMACOLOGY, Drug Interactions.**)

Pharmacokinetics in Special Populations

Gender

The pharmacokinetics of posaconazole are comparable in men and women. No adjustment in the dosage of NOXAFIL is necessary based on gender.

Race

The pharmacokinetic profile of posaconazole is not significantly affected by race. No adjustment in the dosage of NOXAFIL is necessary based on race.

Geriatric

The pharmacokinetics of posaconazole are comparable in young and elderly subjects (≥65 years of age). No adjustment in the dosage of NOXAFIL is necessary in elderly patients (≥65 years of age) based on age.

Pediatric

In the prophylaxis studies, the mean steady-state posaconazole average concentration (Cav) was similar among ten adolescents (13-17 years of age) and adults (≥ 18 years of age). This is consistent with pharmacokinetic data from another study in which mean steady-state posaconazole Cav from 12 adolescent patients (8-17 years of age) was similar to that in the adults (≥ 18 years of age).

Hepatic Insufficiency

The pharmacokinetic data in subjects with hepatic impairment was not sufficient to determine if dose adjustment is necessary in patients with hepatic dysfunction. It is recommended that posaconazole be used with caution in patients with hepatic impairment. (See **WARNINGS** and **DOSAGE AND ADMINISTRATION**.)

Renal Insufficiency

Following single-dose administration of 400 mg of the oral suspension, there was no significant effect of mild (CLcr: 50-80 mL/min/1.73m², n=6) and moderate (CLcr: 20-49 mL/min/1.73m², n=6) renal insufficiency on posaconazole pharmacokinetics; therefore, no dose adjustment is required in patients with mild to moderate renal impairment. In subjects with severe renal insufficiency (CLcr: <20 mL/min/1.73m²), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (CLcr: >80 mL/min/1.73m²); however, the range of the AUC estimates was highly variable (CV=96%) in these subjects with severe renal insufficiency as compared to that in the other renal impairment groups (CV<40%). Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections. (See **DOSAGE AND ADMINISTRATION**.)

Electrocardiogram Evaluation

Multiple, time-matched ECGs collected over a 12-hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18-85 years of age) administered posaconazole 400 mg BID with a high fat meal. In this pooled analysis, the mean QTc (Fridericia) interval change from baseline was -5 msec following administration of the recommended clinical dose. A decrease in the QTc(F) interval (-3 msec) was also observed in a small number of subjects (n=16) administered placebo. The placebo-adjusted mean maximum QTc(F) interval change from baseline was <0 msec (-8 msec). No healthy subject administered posaconazole had a QTc(F) interval ≥ 500 msec or an increase ≥ 60 msec in their QTc(F) interval from baseline. (See **PRECAUTIONS**.)

Drug Interactions

Effect of Other Drugs on Posaconazole

Posaconazole is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. A summary of drugs studied clinically, which affect posaconazole concentrations, is provided in **TABLE 3**. (See **PRECAUTIONS, Drug Interactions**.)

TABLE 3. Summary of the Effect of Co-administered Drugs on Posaconazole in Healthy Volunteers

Co-administered Drug (Postulated Mechanism of Interaction)	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Posaconazole		Recommendations
			Change in Mean C_{max} (ratio estimate* ; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate* ; 90% CI of the ratio estimate)	
Rifabutin (UDP-G Induction)	300 mg QD x 17 days	200 mg (tablets) QD x 10 days	↓ 43% (0.57; 0.43-0.75)	↓ 49% (0.51; 0.37-0.71)	Avoid concomitant use unless the benefit outweighs the risks.
Phenytoin (UDP-G Induction)	200 mg QD x 10 days	200 mg (tablets) QD x 10 days	↓ 41% (0.59; 0.44-0.79)	↓ 50% (0.50; 0.36-0.71)	Avoid concomitant use unless the benefit outweighs the risks.
Cimetidine (Alteration of Gastric pH)	400 mg BID x 10 days	200 mg (tablets) QD x 10 days	↓ 39% (0.61; 0.53-0.70)	↓ 39% (0.61; 0.54-0.69)	Avoid concomitant use unless the benefit outweighs the risks.

* Ratio Estimate is the ratio of co-administered drug plus posaconazole to posaconazole alone for C_{max} or AUC.

Co-administration of these drugs listed in **TABLE 3** with posaconazole may result in lower plasma concentrations of posaconazole.

No clinically relevant effect on posaconazole bioavailability and/or plasma concentrations was observed when administered with an antacid, glipizide, ritonavir, H2 receptor antagonists other than cimetidine, or proton pump inhibitors; therefore, no posaconazole dose adjustments are required when used concomitantly with these products.

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Effect of Posaconazole on Other Drugs

In vitro studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole. A summary of the drugs studied clinically, for which plasma concentrations were affected by posaconazole, is provided in **TABLE 4**. (See **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS**, **Drug Interactions**)

TABLE 4. Summary of the Effect of Posaconazole on Co-administered Drugs in Healthy Volunteers and Patients

Co-administered Drug (Postulated Mechanism of Interaction)	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Co-administered Drugs		Recommendations
			Change in Mean C_{max} (ratio estimate* ; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate* ; 90% CI of the ratio estimate)	
Cyclosporine (Inhibition of CYP3A4 by posaconazole)	Stable maintenance dose in heart transplant recipients	200 mg (tablets) QD x 10 days	↑ cyclosporine whole blood trough concentrations Cyclosporine dose reductions of up to 29% were required		At initiation of posaconazole treatment, reduce the cyclosporine dose to approximately three-fourths of the original dose. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly.

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Co-administered Drug (Postulated Mechanism of Interaction)	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Co-administered Drugs		Recommendations
			Change in Mean C_{max} (ratio estimate* ; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate* ; 90% CI of the ratio estimate)	
Tacrolimus (Inhibition of CYP3A4 by posaconazole)	0.05 mg/kg single oral dose	400 mg (oral suspension) BID × 7 days	↑121% (2.21; 2.01-2.42)	↑ 358% (4.58; 4.03-5.19)	At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly.
Rifabutin (Inhibition of CYP3A4 by posaconazole)	300 mg QD x 17 days	200 mg (tablets) QD × 10 days	↑ 31% (1.31; 1.10-1.57)	↑ 72% (1.72; 1.51-1.95)	Avoid concomitant use unless the benefit outweighs the risks. If the drugs are co-administered, frequent monitoring of rifabutin adverse effects (eg, uveitis, leukopenia) should be performed.
Midazolam (Inhibition of CYP3A4 by posaconazole)	Single 30 min IV infusion of 0.05 mg/kg	200 mg (tablets) QD x 10 days	NA**	↑ 83% (1.83; 1.57-2.14)	Frequent monitoring of adverse effects of benzodiazepines metabolized by CYP3A4 should be performed and dose reduction of these benzodiazepines should be considered during co-administration with posaconazole.
Phenytoin (Inhibition of CYP3A4 by posaconazole)	200 mg QD PO x 10 days	200 mg (tablets) QD x 10 days	↑ 16% (1.16; 0.85-1.57)	↑ 16% (1.16; 0.84-1.59)	Frequent monitoring of phenytoin concentrations should be performed while co-administered with posaconazole and dose reduction of phenytoin should be considered.
*Ratio Estimate is the ratio of co-administered drug plus posaconazole to co-administered drug alone for C_{max} or AUC. **NA: Not applicable if administered as an IV					

Additional clinical studies demonstrated that no clinically significant effects on zidovudine, lamivudine, ritonavir, indinavir, or caffeine were observed when administered with posaconazole; therefore, no dose adjustments are required for these co-administered drugs.

Posaconazole administration with glipizide does not require a dose adjustment in either drug; however, glucose concentrations decreased in some healthy volunteers administered the combination. Therefore, glucose concentrations should be monitored in accordance with the current standard of care for patients with diabetes when posaconazole is co-administered with glipizide.

MICROBIOLOGY

Mechanism of Action

As a triazole antifungal agent, posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of the enzyme lanosterol 14 α -demethylase and accumulation of methylated sterol precursors.

Activity *in vitro* and *in vivo*

Posaconazole has shown *in vitro* activity against *Aspergillus fumigatus* and *Candida albicans*, including *Candida albicans* isolates from patients refractory to itraconazole or fluconazole or both drugs (See **CLINICAL STUDIES** and **INDICATIONS AND USAGE**.)

In vitro susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) methods (M27-A2, M27-A, M38-A, M38-P). However, correlation between the results of susceptibility studies and clinical outcome has not been established. Posaconazole interpretive criteria/breakpoints have not been established for any fungi.

In immunocompetent and/or immunocompromised mice and rabbits with pulmonary or disseminated infection with *A. fumigatus*, posaconazole administered prophylactically was effective in prolonging survival and reducing mycological burden. Prophylactic posaconazole also prolonged survival of immunocompetent mice challenged with *C. albicans* or *A. flavus*. (See **CLINICAL STUDIES**.)

Drug Resistance

Clinical isolates of *Candida albicans* and *Candida glabrata* with decreases in posaconazole susceptibility were observed in oral swish samples taken during prophylaxis with posaconazole and fluconazole, suggesting a potential for development of resistance. These isolates also showed reduced susceptibility to other azoles, suggesting cross-resistance between azoles. The clinical significance of this finding is not known.

CLINICAL STUDIES

Prophylaxis of *Aspergillus* and *Candida* Infections

Two randomized, controlled studies were conducted using posaconazole as prophylaxis for the prevention of invasive fungal infections (IFIs) among patients at high risk due to severely compromised immune systems.

The first study (Study 1) was a randomized, double-blind trial that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD). Efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy. (Patients may have met more than one of these criteria.) Study 1 assessed all patients while on study therapy plus 7 days and at 16 weeks post-randomization. The mean duration of therapy was comparable between the two treatment groups (80 days, posaconazole; 77 days, fluconazole). **TABLE 5** contains the results from Study 1.

TABLE 5. Results From Blinded Clinical Study 1 in Prophylaxis of IFI in All Randomized Patients with Hematopoietic Stem Cell Transplant (HSCT) and Graft-Vs-Host Disease (GVHD)

	Posaconazole n = 301	Fluconazole n = 299
On therapy plus 7 days		
Clinical Failure ^a	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
(<i>Aspergillus</i>)	3 (1%)	17 (6%)
(<i>Candida</i>)	1 (<1%)	3 (1%)
(Other)	3 (1%)	2 (1%)
All Deaths	22 (7%)	24 (8%)
Proven / probable fungal infection prior to death	2 (<1%)	6 (2%)
SAF ^b	27 (9%)	25 (8%)
Through 16 weeks		

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Clinical Failure ^{a,c}	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(<i>Aspergillus</i>)	7 (2%)	21 (7%)
(<i>Candida</i>)	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths	58 (19%)	59 (20%)
Proven/probable fungal infection prior to death	10 (3%)	16 (5%)
SAF ^b	26 (9%)	30 (10%)
Event free lost to follow-up ^d	24 (8%)	30 (10%)
^a : Patients may have met more than one criterion defining failure. ^b : SAF – systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >4 consecutive days). ^c : 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%) ^d : Patients who are lost to follow-up (not observed for 112 days), and who did not meet another clinical failure endpoint. These patients were considered failures.		

The second study (Study 2) was a randomized, open-label study that compared posaconazole oral suspension (200 mg three times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes. As in Study 1, efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy. (Patients might have met more than one of these criteria.) Study 2 assessed patients while on treatment plus 7 days and 100 days post-randomization. The mean duration of therapy was comparable between the two treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole). **TABLE 6** contains the results from Study 2.

TABLE 6. Results from Open Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and Prolonged Neutropenia

	Posaconazole n = 304	Fluconazole/Itraconazole n = 298
On therapy plus 7 days		
Clinical Failure ^{a,b}	82 (27%)	126 (42%)
Failure due to:		
Proven/Probable IFI	7 (2%)	25 (8%)
(<i>Aspergillus</i>)	2 (1%)	20 (7%)
(<i>Candida</i>)	3 (1%)	2 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	17 (6%)	25 (8%)
Proven/probable fungal infection prior to death	1 (<1%)	2 (1%)
SAF ^c	67 (22%)	98 (33%)
Through 100 days post-randomization		
Clinical Failure ^b	158 (52%)	191 (64%)

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Failure due to:		
Proven/probable IFI	14 (5%)	33 (11%)
(<i>Aspergillus</i>)	2 (1%)	26 (9%)
(<i>Candida</i>)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	44 (14%)	64 (21%)
Proven / probable fungal infection prior to death	2 (1%)	16 (5%)
SAF ^c	98 (32%)	125 (42%)
Event free lost to follow-up ^d	34 (11%)	24 (8%)
^a : 95% confidence interval (posaconazole-fluconazole/itraconazole) = (-22.9%, -7.8%). ^b : Patients may have met more than one criterion defining failure. ^c : Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >3 consecutive days). ^d : Patients who are lost to follow-up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.		

In summary, two clinical studies of prophylaxis were conducted. As seen in the accompanying tables (**TABLES 5** and **6**), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Study 1 (**TABLE 5**), the clinical failure rate of posaconazole (33%) was similar to fluconazole (37%), (95% CI for the difference posaconazole-comparator -11.5% to 3.7%) while in Study 2 (**TABLE 6**) clinical failure was lower for patients treated with posaconazole (27%) when compared to patients treated with fluconazole or itraconazole (42%), (95% CI for the difference posaconazole-comparator -22.9% to -7.8%).

All cause mortality was similar at 16 weeks for both treatment arms in Study 1 [POS 58/301 (19%) vs FLU 59/299 (20%)]; all cause mortality was lower at 100 days for posaconazole-treated patients in Study 2 [POS 44/304 (14%) vs FLU/ITZ 64/298 (21%)]. Both studies demonstrated substantially fewer breakthrough infections caused by *Aspergillus* species in patients receiving posaconazole prophylaxis when compared to patients receiving fluconazole or itraconazole.

For information on a pharmacokinetic/pharmacodynamic analysis of patient data see **CLINICAL PHARMACOLOGY, Exposure Response Relationship**.

Treatment of Oropharyngeal Candidiasis (OPC)

Study 3 was a randomized, controlled, evaluator-blinded study in HIV-infected patients with oropharyngeal candidiasis. Patients were treated with posaconazole or fluconazole oral suspension (both posaconazole and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

Clinical and mycological outcomes were assessed after 14 days of treatment and at 4 weeks after the end of treatment. Patients who received at least one dose of study medication and had a positive oral swish culture of *Candida* species at baseline were included in the analyses (**TABLE 7**). The majority of the subjects had *C. albicans* as the baseline pathogen.

Clinical success at Day 14 (complete or partial resolution of all ulcers and/or plaques and symptoms) and clinical relapse rates (recurrence of signs or symptoms after initial cure or improvement) 4 weeks after the end of treatment were similar between the treatment arms (**TABLE 7**).

Mycologic eradication rates (absence of colony forming units in quantitative culture at the end of therapy, day 14), as well as mycologic relapse rates (4 weeks after the end of treatment) were also similar between the treatment arms (see **TABLE 7**).

TABLE 7. Clinical Success, Mycological Eradication and Relapse Rates in Oropharyngeal Candidiasis

	Posaconazole	Fluconazole
Clinical Success at End of Therapy (Day 14)	155/169 (91.7%)	148/160 (92.5%)
Clinical Relapse (4 Weeks after End of Therapy)	45/155 (29.0%)	52/148 (35.1%)
Mycological Eradication (absence of CFU) at End of Therapy (Day 14)	88/169 (52.1%)	80/160 (50.0%)
Mycological Relapse (4 Weeks after End of Treatment)	49/88 (55.6%)	51/80 (63.7%)

Mycologic response rates, using a criterion for success as a post-treatment quantitative culture with ≤ 20 colony forming units (CFU/mL) were also similar between the two groups (posaconazole 68.0%, fluconazole 68.1%). The clinical significance of this finding is unknown.

Treatment of Oropharyngeal Candidiasis Refractory to Treatment with Fluconazole or Itraconazole

Study 4 was a non-comparative study of posaconazole oral suspension in HIV-infected subjects with OPC that was refractory to treatment with fluconazole or itraconazole. An episode of OPC was considered refractory if there was failure to improve or worsening of OPC after a standard course of therapy with fluconazole ≥ 100 mg/day for at least 10 consecutive days or itraconazole 200

mg/day for at least 10 consecutive days and treatment with either fluconazole or itraconazole had not been discontinued for more than 14 days prior to treatment with posaconazole. Of the 199 subjects enrolled in this study, eighty-nine subjects met these strict criteria for refractory infection.

Forty-five subjects with refractory OPC were treated with posaconazole 400 mg BID for three days, followed by 400 mg QD for 25 days with an option for further treatment during a 3-month maintenance period. Following a dosing amendment, a further 44 subjects were treated with posaconazole 400 mg BID for twenty-eight days. The efficacy of posaconazole was assessed by the clinical success (cure or improvement) rate after 4 weeks of treatment. The clinical success rate was 74.2% (66/89). The clinical success rates for both the original and the amended dosing regimens were similar (73.3% and 75.0%, respectively).

For information on a pharmacokinetic / pharmacodynamic analysis of patient data see **CLINICAL PHARMACOLOGY, Exposure Response Relationship**.

INDICATIONS AND USAGE

NOXAFIL (posaconazole) is indicated 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. (See **MICROBIOLOGY** and **CLINICAL STUDIES**.)

NOXAFIL (posaconazole) is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole (See **MICROBIOLOGY** and **CLINICAL STUDIES**).

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Co-administration with ergot alkaloids. (See **PRECAUTIONS, Drug Interactions**.)

Co-administration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine, or quinidine since this may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes. (See **CLINICAL**

PHARMACOLOGY, Drug Interactions and PRECAUTIONS, Drug Interactions.)

WARNINGS

Hypersensitivity There is no information regarding cross-sensitivity between NOXAFIL and other azole antifungal agents. Caution should be used when prescribing NOXAFIL to patients with hypersensitivity to other azoles.

Hepatic Toxicity In clinical trials, there were infrequent cases of hepatic reactions (eg, mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis). The elevations in liver function tests were generally reversible on discontinuation of therapy, and in some instances these tests normalized without drug interruption and rarely required drug discontinuation. Rarely, more severe hepatic reactions including cholestasis or hepatic failure including fatalities were reported in patients with serious underlying medical conditions (eg, hematologic malignancy) during treatment with posaconazole. These severe hepatic events were seen primarily in subjects receiving the 800 mg daily (400 mg BID or 200 mg QID) in another indication.

Monitoring of hepatic function Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during posaconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of posaconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to posaconazole.

Cyclosporine drug interaction Cases of elevated cyclosporine levels resulting in rare serious adverse events, including nephrotoxicity and leukoencephalopathy, and death were reported in clinical efficacy studies. Dose reduction and more frequent clinical monitoring of cyclosporine, tacrolimus, and sirolimus should be performed when posaconazole therapy is initiated. (See **PRECAUTIONS, Drug Interactions.**)

PRECAUTIONS

Arrhythmias and QT prolongation Some azoles, including posaconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval. During clinical development there was one case of torsades de pointes in a patient taking posaconazole. This patient was seriously ill with multiple confounding risk factors including a history

of cardiotoxic chemotherapy, hypokalemia, and concomitant medications that may have been contributory.

Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions and should not be administered with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4. (See **CLINICAL PHARMACOLOGY, Electrocardiogram Evaluation; CONTRAINDICATIONS**; and **PRECAUTIONS, Drug Interactions**.) Rigorous attempts to correct potassium, magnesium, and calcium should be made before starting posaconazole.

Information for Patients

Patients should be advised to:

- Take each dose of NOXAFIL Oral Suspension with a full meal or liquid nutritional supplement in order to enhance absorption.
- Inform their physician if they develop severe diarrhea or vomiting as these conditions may change blood levels of posaconazole.
- Inform their physician if they are taking other drugs or before they begin taking other drugs as certain drugs can change blood levels. (See **CLINICAL PHARMACOLOGY, Drug Interactions**.)

Drug Interactions

A summary of significant drug interactions with posaconazole that have been studied clinically are provided in **TABLES 8** and **9**. Appropriate precautions for the co-administration of these drugs with posaconazole are provided. (See **CLINICAL PHARMACOLOGY, Drug Interactions** and **WARNINGS**.)

TABLE 8. Summary of the Effect of Co-administered Drugs on Posaconazole

Co-administered Drug	Recommendations
Cimetidine	Avoid concomitant use unless the benefit outweighs the risks.
Rifabutin	Avoid concomitant use unless the benefit outweighs the risks.
Phenytoin	Avoid concomitant use unless the benefit outweighs the risks.

Co-administration of these drugs listed in **TABLE 8** with posaconazole may result in lower plasma concentrations of posaconazole.

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TABLE 9. Summary of the Effect of Posaconazole on Co-administered Drugs

Co-administered Drug	Recommendations
Cyclosporine	Increased cyclosporine concentrations resulted in cyclosporine dose reductions in heart transplant patients co-administered posaconazole. At initiation of posaconazole treatment, reduce the cyclosporine dose to approximately three fourths of the original dose. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly.
Tacrolimus	Posaconazole has been shown to increase C _{max} and AUC of tacrolimus significantly. At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly.
Rifabutin	Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. However, if concomitant administration is required frequent monitoring of full blood counts and adverse events due to increased rifabutin levels (eg, uveitis) is recommended.
Midazolam	Frequent monitoring of adverse effects of benzodiazepines metabolized by CYP3A4 should be performed and dose reduction of these benzodiazepines should be considered during co-administration with posaconazole.
Phenytoin	Frequent monitoring of phenytoin concentrations should be performed while co-administered with posaconazole and dose reduction of phenytoin should be considered.

Although not studied *in vitro* or *in vivo*, posaconazole may affect the plasma concentrations of the drugs or drug classes described in **TABLE 10**. Appropriate precautions for the co-administration of these drugs with posaconazole are provided. (See **CONTRAINDICATIONS**.)

TABLE 10. Drugs Not Studied in vitro or in vivo but Likely to Result in Significant Drug Interactions

Drug or Drug Class (CYP3A4 Substrates)	Recommendations
Terfenadine, Astemizole, Pimozide, Cisapride, Quinidine	Increased plasma concentrations of these drugs can lead to QT prolongation with rare occurrences of torsade de pointes. Co-administration with posaconazole is contraindicated. (See CONTRAINDICATIONS .)
Ergot Alkaloids	Posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism. Co-administration of posaconazole with ergot alkaloids is contraindicated. (See CONTRAINDICATIONS .)
Vinca Alkaloids	Posaconazole may increase the plasma concentrations of vinca alkaloids (eg, vincristine and vinblastine) which may lead to neurotoxicity. Therefore, it is recommended that the dose adjustment of the vinca alkaloid be considered.
Sirolimus	Frequent monitoring of sirolimus whole blood trough concentrations should be performed upon initiation, during co-administration, and at discontinuation of posaconazole treatment, with sirolimus doses reduced accordingly.
HMG-CoA reductase inhibitors (statins) metabolized through CYP3A4	It is recommended that dose reduction of statins be considered during co-administration. Increased statin concentrations in plasma can be associated with rhabdomyolysis.
Calcium Channel Blockers metabolized through CYP3A4	Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during co-administration. Dose reduction of calcium channel blockers may be needed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No drug-related neoplasms were recorded in rats or mice treated with posaconazole for two years at doses below the maximum tolerated dose. In a two-year carcinogenicity study, rats were given posaconazole orally at doses up to 20 mg/kg (females), or 30 mg/kg (males). These doses are equivalent to 3.9 or 3.5 times the exposure achieved with a 400 mg BID regimen, respectively, based on steady-state AUC in healthy volunteers administered a high fat meal (400 mg BID regimen). In the mouse study, mice were treated at oral doses up to 60 mg/kg/day or 4.8 times the exposure achieved with a 400 mg BID regimen.

Posaconazole was not genotoxic or clastogenic when evaluated in bacterial mutagenicity (Ames), a chromosome aberration study in human peripheral blood lymphocytes, a Chinese hamster ovary cell mutagenicity study, and a mouse bone marrow micronucleus study.

Posaconazole had no effect on fertility of male rats at a dose up to 180 mg/kg (1.7 x the 400 mg BID regimen based on steady-state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 x the 400 mg BID regimen).

Pregnancy

Pregnancy Category C Posaconazole has been shown to cause skeletal malformations (cranial malformations and missing ribs) in rats when given in doses ≥ 27 mg/kg (≥ 1.4 times the 400 mg BID regimen based on steady-state plasma concentrations of drug in healthy volunteers). The no-effect dose for malformations in rats was 9 mg/kg, which is 0.7 times the exposure achieved with the 400 mg BID regimen. No malformations were seen in rabbits at doses up to 80 mg/kg. In the rabbit, the no-effect dose was 20 mg/kg, while high doses of 40 mg/kg and 80 mg/kg, 2.9 or 5.2 times the exposure achieved with the 400 mg BID regimen, caused an increase in resorptions. In rabbits dosed at 80 mg/kg, a reduction in body weight gain of females and a reduction in litter size was seen. There are no adequate and well-controlled studies in pregnant women. Posaconazole should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Posaconazole is excreted in milk of lactating rats. The excretion of posaconazole in human breast milk has not been investigated. NOXAFIL should not be used by nursing mothers unless the benefit to the mother clearly outweighs the potential risk to the infant.

Pediatric Use

A total of 12 patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) for prophylaxis of invasive fungal infections. The safety profile in these patients <18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these pediatric patients, the mean steady-state average posaconazole concentration (C_{av}) was similar between these patients and adults (≥ 18 years of age).

A total of 16 patients 8 to 17 years of age were treated with 800 mg/day (400 mg twice a day or 200 mg four times a day) in a study for another indication. Based on pharmacokinetic data in 12 of these pediatric patients, the mean steady-state average posaconazole concentration (C_{av}) was similar between these patients and adults (≥ 18 years of age). (See **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations, Pediatric.**)

Safety and effectiveness of posaconazole in pediatric patients below the age of 13 years have not been established.

Geriatric Use

Of the 605 patients randomized to posaconazole in the prophylaxis clinical trials, 63 (10%) were ≥ 65 years of age. In addition, 48 patients treated with ≥ 800 mg/day posaconazole in another indication were ≥ 65 years of age. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations, Geriatric.**)

ADVERSE REACTIONS

The safety of posaconazole therapy has been assessed in 1844 patients. This includes 605 patients in the prophylaxis studies, 796 in OPC/rOPC studies and over 400 patients treated for other indications. Posaconazole therapy was given to 171 patients for ≥ 6 months, with 58 patients receiving posaconazole therapy for ≥ 12 months.

Prophylaxis of *Aspergillus* and *Candida*

TABLE 11 presents treatment-emergent adverse events observed at an incidence >10% in posaconazole prophylaxis studies.

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TABLE 11. Study 1 and Study 2. Number (%) of Randomized Subjects Reporting Treatment-Emergent Adverse Events: Frequency of at Least 10% in the POS or FLU Treatment Groups (Pooled Prophylaxis Safety Analysis)

	Posaconazole (n=605)		Fluconazole (n=539)		Itraconazole (n=58)	
Subjects Reporting any Adverse Event	595	(98)	531	(99)	58	(100)
Body as a Whole - General Disorders						
Fever	274	(45)	254	(47)	32	(55)
Headache	171	(28)	141	(26)	23	(40)
Rigors	122	(20)	87	(16)	17	(29)
Fatigue	101	(17)	98	(18)	5	(9)
Edema Legs	93	(15)	67	(12)	11	(19)
Anorexia	92	(15)	94	(17)	16	(28)
Dizziness	64	(11)	56	(10)	5	(9)
Edema	54	(9)	68	(13)	8	(14)
Weakness	51	(8)	52	(10)	2	(3)
Cardiovascular Disorders, General						
Hypertension	106	(18)	88	(16)	3	(5)
Hypotension	83	(14)	79	(15)	10	(17)
Disorders of Blood and Lymphatic System						
Anemia	149	(25)	124	(23)	16	(28)
Neutropenia	141	(23)	122	(23)	23	(40)
Febrile Neutropenia	118	(20)	85	(16)	23	(40)
Disorders of the Reproductive System and Breast						
Vaginal Hemorrhage ^a	24	(10)	20	(9)	3	(12)
Gastrointestinal System Disorders						
Diarrhea	256	(42)	212	(39)	35	(60)
Nausea	232	(38)	198	(37)	30	(52)
Vomiting	174	(29)	173	(32)	24	(41)
Abdominal Pain	161	(27)	147	(27)	21	(36)
Constipation	126	(21)	94	(17)	10	(17)
Mucositis NOS	105	(17)	68	(13)	15	(26)
Dyspepsia	61	(10)	50	(9)	6	(10)
Heart Rate and Rhythm Disorders						
Tachycardia	72	(12)	75	(14)	3	(5)
Infection and Infestations						
Bacteremia	107	(18)	98	(18)	16	(28)
Herpes Simplex	88	(15)	61	(11)	10	(17)
Cytomegalovirus Infection	82	(14)	69	(13)	0	
Pharyngitis	71	(12)	60	(11)	12	(21)
Upper Respiratory Tract Infection	44	(7)	54	(10)	5	(9)
Liver and Biliary System Disorders						
Bilirubinemia	59	(10)	51	(9)	11	(19)
Metabolic and Nutritional Disorders						
Hypokalemia	181	(30)	142	(26)	30	(52)
Hypomagnesemia	110	(18)	84	(16)	11	(19)
Hyperglycemia	68	(11)	76	(14)	2	(3)

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	Posaconazole (n=605)	Fluconazole (n=539)	Itraconazole (n=58)
Hypocalcemia	56 (9)	55 (10)	5 (9)
Musculoskeletal System Disorders			
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 and Clotting Disorders			
Thrombocytopenia	175 (29)	146 (27)	20 (34)
Petechiae	64 (11)	54 (10)	9 (16)
Psychiatric Disorders			
Insomnia	103 (17)	92 (17)	11 (19)
Anxiety	52 (9)	61 (11)	9 (16)
Respiratory System Disorders			
Coughing	146 (24)	130 (24)	14 (24)
Dyspnea	121 (20)	116 (22)	15 (26)
Epistaxis	82 (14)	73 (14)	12 (21)
Skin and Subcutaneous Tissue Disorders			
Rash	113 (19)	96 (18)	25 (43)
Pruritus	69 (11)	62 (12)	11 (19)

^a Percentages of sex-specific adverse events are based on the number of males/females.
NOS = not otherwise specified.

TABLES 12 and 13 present treatment-related adverse events observed at an incidence $\geq 2\%$ in the posaconazole prophylaxis studies.

TABLE 12. Study 1. Treatment-Related Adverse Events, Occurring in Greater Than or Equal to 2% of Patients in Posaconazole or Fluconazole Treatment Group

Body System/Preferred Term	Posaconazole N=301	Fluconazole N=299
	n (%)	n (%)
Subjects Reporting Any Adverse Event	107 (36)	115 (38)
Body as a Whole – General Disorders		
Drug Level Altered	5 (2)	2 (1)
Dizziness	4 (1)	5 (2)
Fatigue	4 (1)	6 (2)
Anorexia	3 (1)	7 (2)
Headache	3 (1)	8 (3)
Weakness	3 (1)	5 (2)
Cardiovascular Disorders, General		
Hypertension	2 (1)	5 (2)
Central and Peripheral Nervous System Disorders		
Tremor	4 (1)	6 (2)
Disorders of the Eye		
Vision Blurred	3 (1)	5 (2)
Gastrointestinal System Disorders		

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	Posaconazole N=301	Fluconazole N=299
	n (%)	n (%)
Nausea	22 (7)	28 (9)
Vomiting	13 (4)	15 (5)
Diarrhea	8 (3)	12 (4)
Abdominal Pain	4 (1)	7 (2)
Dyspepsia	3 (1)	6 (2)
Constipation	1 (<1)	5 (2)
Liver and Biliary System Disorders		
SGPT Increased	9 (3)	4 (1)
GGT Increased	9 (3)	7 (2)
Bilirubinemia	8 (3)	5 (2)
Hepatic Enzymes Increased	8 (3)	7 (2)
SGOT Increased	8 (3)	3 (1)
Metabolic and Nutritional Disorders		
Phosphatase Alkaline Increased	5 (2)	5 (2)
Renal and Urinary System Disorders		
Blood Creatinine Increased	6 (2)	5 (2)
Special Senses, Other Disorders		
Taste Perversion	3 (1)	5 (2)

GGT = gamma-glutamyl transpeptidase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

TABLE 13. Study 2. Treatment-Related Adverse Events, Occurring in Greater Than or Equal to 2% of Patients in Posaconazole or Fluconazole/Itraconazole Treatment Group

	Number (%) of Patients			
	Posaconazole (n=304)	Fluconazole/ Itraconazole (n=298)	Fluconazole (n=240)	Itraconazole (n=58)
Body System/Preferred Term				
Subjects Reporting Any Adverse Event	102 (34)	101 (34)	71 (30)	30 (52)
Body as a Whole - General Disorders				
Headache	5 (2)	1 (<1)	0	1 (2)
Gastrointestinal System Disorders				
Nausea	22 (7)	25 (8)	17 (7)	8 (14)
Diarrhea	20 (7)	21 (7)	12 (5)	9 (16)
Vomiting	14 (5)	20 (7)	14 (6)	6 (10)
Abdominal Pain	9 (3)	9 (3)	8 (3)	1 (2)
Mucositis NOS	7 (2)	0	0	0
Dyspepsia	5 (2)	3 (1)	3 (1)	0
Constipation	3 (1)	7 (2)	7 (3)	0
Heart Rate and Rhythm Disorders				
QT/QTc Prolongation	12 (4)	9 (3)	5 (2)	4 (7)
Liver and Biliary System				

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Body System/Preferred Term	Number (%) of Patients			
	Posaconazole (n=304)	Fluconazole/ Itraconazole (n=298)	Fluconazole (n=240)	Itraconazole (n=58)
Disorders				
Bilirubinemia	7 (2)	8 (3)	5 (2)	3 (5)
Hepatic Enzymes Increased	7 (2)	3 (1)	3 (1)	0
SGPT Increased	7 (2)	5 (2)	4 (2)	1 (2)
SGOT Increased	6 (2)	5 (2)	4 (2)	1 (2)
GGT Increased	5 (2)	2 (1)	1 (<1)	1 (2)
Metabolic and Nutritional Disorders				
Hypokalemia	9 (3)	6 (2)	5 (2)	1 (2)
Skin and Subcutaneous Tissue Disorders				
Rash	9 (3)	11 (4)	10 (4)	1 (2)

GGT = gamma-glutamyl transpeptidase; NOS = not otherwise specified; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

The most common treatment-related serious adverse events (1% each) in the combined prophylaxis studies were bilirubinemia, increased hepatic enzymes, hepatocellular damage, nausea, and vomiting.

Overview of Adverse Events in HIV infected subjects with OPC

In two randomized comparative studies in OPC, the safety of posaconazole at a dose of ≤ 400 mg QD in 557 HIV infected patients was compared to the safety of fluconazole in 262 HIV infected patients at a dose of 100 mg QD.

An additional 239 HIV infected patients with refractory OPC received posaconazole in 2 non-comparative trials for refractory OPC (rOPC). 149 of these subjects received the 800 mg/day dose and the remainder received the ≤ 400 QD dose.

TABLE 14 presents Treatment-Emergent Adverse Events of Clinical Significance in the comparative and non-comparative studies of OPC.

TABLE 14. Treatment-Emergent Adverse Events of Clinical Significance in OPC studies

	Number (%) of Subjects		Refractory OPC Pool
	Controlled OPC Pool		
	POS n=557	FLZ n=262	POS n=239
Subjects Reporting any Adverse Event^a	356 (64)	175 (67)	221 (92)
Body as a Whole - General Disorders			
Fever	34 (6)	22 (8)	82 (34)
Headache	44 (8)	23 (9)	47 (20)

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	Number (%) of Subjects		
	Controlled OPC Pool		Refractory OPC Pool
Anorexia	10 (2)	4 (2)	46 (19)
Fatigue	18 (3)	12 (5)	31 (13)
Asthenia	9 (2)	5 (2)	31 (13)
Rigors	2 (<1)	4 (2)	29 (12)
Pain	4 (1)	2 (1)	27 (11)
Disorders of Blood and Lymphatic System			
Neutropenia	21 (4)	8 (3)	39 (16)
Anemia	11 (2)	5 (2)	34 (14)
Neutropenia Aggravated	0	0	5 (2)
Gastro-Intestinal System Disorders			
Diarrhea	58 (10)	34 (13)	70 (29)
Nausea	48 (9)	30 (11)	70 (29)
Vomiting	37 (7)	18 (7)	67 (28)
Abdominal Pain	27 (5)	17 (6)	43 (18)
Infection and Infestations			
Candidiasis, Oral	3 (1)	1 (<1)	28 (12)
Herpes Simplex	16 (3)	8 (3)	26 (11)
Pneumonia	17 (3)	6 (2)	25 (10)
Liver and Biliary System Disorders			
Bilirubinemia	6 (1)	2 (1)	6 (3)
Hepatic Enzymes Increased	1 (<1)	1 (<1)	8 (3)
Hepatic Function Abnormal	8 (1)	4 (2)	0
Hepatitis	3 (1)	0	5 (2)
Hepatomegaly	0	0	8 (3)
Jaundice	0	0	4 (2)
SGOT Increased	8 (1)	5 (2)	6 (3)
SGPT Increased	6 (1)	5 (2)	6 (3)
Metabolic and Nutritional Disorders			
Weight Decrease	4 (1)	2 (1)	33 (14)
Dehydration	4 (1)	7 (3)	27 (11)
Hypokalemia	6 (1)	3 (1)	15 (6)
Platelet, Bleeding and Clotting Disorders			
Thrombocytopenia	4 (1)	1 (<1)	12 (5)
Psychiatric Disorders			
Insomnia	8 (1)	3 (1)	39 (16)
Renal & Urinary System Disorders			
Renal Failure Acute	0	0	7 (3)
Respiratory System Disorders			
Coughing	18 (3)	11 (4)	60 (25)
Dyspnea	8 (1)	8 (3)	28 (12)
Skin and Subcutaneous Tissue Disorders			
Rash	15 (3)	10 (4)	36 (15)
Sweating Increased	13 (2)	5 (2)	23 (10)
OPC=oropharyngeal candidiasis; POS=posaconazole; FLZ=fluconazole; SGOT=serum glutamic oxaloacetic transaminase (same as AST); SGPT=serum glutamic pyruvic transaminase (same as ALT).			
^a : Number of subjects reporting treatment-emergent adverse events at least once during the study, without regard to relationship to treatment. Subjects may have reported more than one event.			

Treatment-related, treatment-emergent events observed in patients with OPC at an incidence of $\geq 2\%$ are shown in **TABLE 15**.

TABLE 15. Treatment-Related, Adverse Events (Any Grade) $\geq 2\%$

	Number (%) of Subjects		
	Controlled OPC Pool		Refractory OPC Pool
	POS	FLZ	POS

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Adverse Event	Number (%) of Subjects		Refractory OPC Pool n=239
	Controlled OPC Pool n=557	n=262	
Subjects Reporting any Adverse Event^a	150 (27)	70 (27)	135 (56)
Body As A Whole - General Disorders			
Headache	16 (3)	5 (2)	18 (8)
Anorexia	6 (1)	1 (<1)	7 (3)
Asthenia	4 (1)	2 (1)	6 (3)
Dizziness	9 (2)	5 (2)	8 (3)
Fatigue	8 (1)	5 (2)	7 (3)
Fever	10 (2)	1 (<1)	6 (3)
Central and Periph Nerv System			
Somnolence	4 (1)	5 (2)	3 (1)
Disorders of Blood and Lymphatic System			
Neutropenia	10 (2)	4 (2)	20 (8)
Anemia	2 (<1)	0	6 (3)
Gastro-Intestinal System Disorders			
Diarrhea	19 (3)	13 (5)	26 (11)
Nausea	27 (5)	18 (7)	20 (8)
Vomiting	20 (4)	4 (2)	16 (7)
Abdominal Pain	10 (2)	8 (3)	12 (5)
Flatulence	6 (1)	0	11 (5)
Mouth Dry	7 (1)	6 (2)	5 (2)
Liver and Biliary System Disorders			
Hepatic Enzymes Increased	1 (<1)	0	5 (2)
Hepatic Function Abnormal	3 (1)	4 (2)	0
Metabolic and Nutritional Disorders			
Phosphatase Alkaline Increased	3 (1)	3 (1)	5 (2)
Musculo-Skeletal System Disorders			
Myalgia	1 (<1)	0	4 (2)
Platelet, Bleeding and Clotting Disorders			
Thrombocytopenia	3 (1)	0	4 (2)
Psychiatric Disorders			
Insomnia	3 (1)	0	6 (3)
Skin and Subcutaneous Tissue Disorders			
Rash	8 (1)	4 (2)	10 (4)
Pruritus	6 (1)	2 (1)	5 (2)
OPC=oropharyngeal candidiasis; POS=posaconazole; FLZ=fluconazole; SGOT=serum glutamic oxaloacetic transaminase (same as AST); SGPT=serum glutamic pyruvic transaminase (same as ALT).			
a: Number of subjects reporting treatment-related adverse events at least once during the study, without regard to relationship to treatment. Subjects may have reported more than one event.			

Adverse events were reported more frequently in the pool of patients with refractory OPC. Among these highly immunocompromised patients with advanced HIV disease, serious adverse events (SAEs) were reported in 55% (132/239). The most commonly reported SAEs were fever (13%) and neutropenia (10%).

Treatment-related SAEs were reported for 14% (34/239) of these patients and included neutropenia (5%) and abdominal pain (2%). Posaconazole was discontinued in two patients who developed neutropenia that was considered serious and treatment-related. All other reported treatment-related SAEs occurred in ≤ 1% of subjects on posaconazole.

Uncommon and rare treatment-related serious or medically significant adverse events reported during clinical trials in prophylaxis, OPC/rOPC or other indications with posaconazole have included adrenal insufficiency, allergic and/or hypersensitivity reactions.

Rare cases of hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and pulmonary embolus have been reported primarily among patients who had been receiving concomitant cyclosporine or tacrolimus for management of transplant rejection or graft-vs-host disease.

During clinical development there was a single case of torsade de pointes in a patient taking posaconazole. This report involved a seriously ill patient with multiple confounding, potentially contributory risk factors, such as a history of palpitations, recent cardiotoxic chemotherapy, hypokalemia, and hypomagnesemia.

Additionally, in another indication, 428 patients were treated with ≥ 800 mg/day with a similar AE profile.

Clinical Laboratory Values

In healthy volunteers and patients, elevation of liver function test values did not appear to be associated with higher plasma concentrations of posaconazole. The majority of abnormal liver function tests were minor, transient, and did not lead to discontinuation of therapy.

For the prophylaxis studies, the number of patients with changes in liver function tests from Common Toxicity Criteria (CTC) Grade 0, 1, or 2 at baseline to Grade 3 or 4 during the study is presented in **TABLE 16**.

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TABLE 16. Study 1 and Study 2. Changes in Liver Function Test Results from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4

Laboratory Parameter	Number (%) of Patients With Change ^a	
	Study 1	
	Posaconazole N=301	Fluconazole N=299
AST	11/266 (4)	13/266 (5)
ALT	47/271 (17)	39/272 (14)
Bilirubin	24/271 (9)	20/275 (7)
Alkaline Phosphatase	9/271 (3)	8/271 (3)
Laboratory Parameter	Study 2	
	Posaconazole (n=304)	Fluconazole/Itraconazole (n=298)
AST	9/286 (3)	5/280 (2)
ALT	18/289 (6)	13/284 (5)
Bilirubin	20/290 (7)	25/285 (9)
Alkaline Phosphatase	4/281 (1)	1/276 (<1)

^a Change from Grade 0 to 2 at Baseline to Grade 3 or 4 during the study. These data are presented in the form X/Y, where X represents the number of patients who met the criterion as indicated, and Y represents the number of patients who had a baseline observation and at least one post-baseline observation.

CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase.

The number of patients treated for OPC with clinically significant liver function test (LFT) abnormalities at any time during the studies is provided in **TABLE 17** (LFT abnormalities were present in some of these patients prior to initiation of the study drug).

TABLE 17. Clinically Significant Laboratory Test Abnormalities Without Regard to Baseline Value

Laboratory Test	Controlled		Refractory
	POS	FLZ	POS
	N = 557	N = 262	N = 239
ALT > 3.0 x ULN	16/537(3)	13/254(5)	25/226(11)
AST > 3.0 x ULN	33/537(6)	26/254(10)	39/223(17)
Total Bilirubin > 1.5 x ULN	15/536(3)	5/254(2)	9/197(5)
Alkaline Phosphatase > 3.0 x ULN	17/535(3)	15/253(6)	24/190(13)

ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase

OVERDOSAGE

During the clinical trials, some patients received posaconazole up to 1600 mg/day with no adverse events noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg BID for 3 days. No related adverse events were noted by the investigator. Posaconazole is not removed by hemodialysis.

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DOSAGE AND ADMINISTRATION

Indication	Dose and Duration of therapy
Prophylaxis of Invasive Fungal Infections	200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.
Oropharyngeal Candidiasis	Loading dose of 100 mg (2.5 mL) twice a day on the first day, then 100 mg (2.5 mL) once a day for 13 days.
Oropharyngeal Candidiasis Refractory to itraconazole and/or fluconazole	400 mg (10 mL) twice a day. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response.

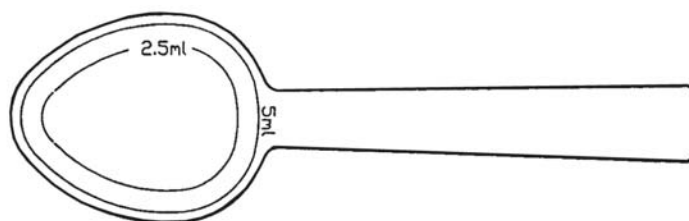
Each dose of NOXAFIL should be administered with a full meal or with a liquid nutritional supplement in patients who can not eat a full meal. (See **CLINICAL PHARMACOLOGY**)

To enhance the oral absorption of posaconazole and optimize plasma concentrations:

- Each dose of NOXAFIL Oral Suspension should be administered with a full meal or liquid nutritional supplement. For patients who can not eat a full meal or tolerate an oral nutritional supplement, alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.
- Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.
- Co-administration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections. (See **CLINICAL PHARMACOLOGY, Drug Interactions.**)

Shake NOXAFIL Oral Suspension well before use.

A measured dosing spoon is provided, marked for doses of 2.5 mL and 5 mL.



It is recommended that the spoon is rinsed with water after each administration and before storage.

Renal Insufficiency

No dose adjustment is recommended for patients with renal dysfunction. However, the range of the posaconazole AUC estimates was highly variable (CV=96%) in subjects with severe renal insufficiency as compared to that in the other renal impairment groups (CV<40%). Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough IFIs. (See **CLINICAL PHARMACOLOGY**.)

Hepatic Insufficiency

The pharmacokinetic data in subjects with hepatic impairment was not sufficient to determine if dose adjustment is necessary in patients with hepatic dysfunction. It is recommended that posaconazole be used with caution in patients with hepatic impairment. (See **CLINICAL PHARMACOLOGY** and **WARNINGS**.)

HOW SUPPLIED

NOXAFIL (posaconazole) Oral Suspension is available in 4-ounce (123 mL) amber glass bottles with child-resistant closures (NDC 0085-1328-01) containing 105 mL of suspension (40 mg of posaconazole per mL).

Supplied with each bottle is a plastic dosing spoon calibrated for measuring 2.5-mL and 5-mL doses.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. DO NOT FREEZE.

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MODULE 1

Schering Corporation
Kenilworth, NJ 07033 USA

U.S. Patents 5,703,079, 5,661,151, 6,713,481 and 5,703,236.
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PATIENT INFORMATION

NOXAFIL[®]

(posaconazole) Oral Suspension

Read the Patient Information that comes with NOXAFIL before you start taking it and each time you get a refill. There may be new information. This information does not replace talking with your doctor about your condition or treatment. Only your doctor can prescribe NOXAFIL and determine if it is right for you.

What is NOXAFIL?

- NOXAFIL[®] is a prescription medicine that is used to prevent invasive fungal infections (infections that can spread throughout the body) caused by *Aspergillus* or *Candida* in patients with weak immune systems because of medicines or diseases [such as stem cell transplantation with graft versus host disease or chemotherapy for hematologic malignancy (blood cancers)].
- NOXAFIL is also used to treat fungal infections in the mouth or throat area (known as “thrush”) caused by fungi called *Candida*. NOXAFIL can be used as initial treatment or as a treatment after itraconazole and/or fluconazole have failed.

NOXAFIL is for adults and children over 13 years of age.

What should I tell my doctor before taking NOXAFIL?

Tell your doctor about all your health conditions, including if you:

- are taking certain drugs that suppress your immune system like **cyclosporine (Neoral[®])**, **tacrolimus (Prograf[®])**, or **sirolimus (Rapamune[®])**. Serious and rare fatal toxicity from cyclosporine has occurred when taken in combination with posaconazole and therefore reduction of the dose of drugs like **cyclosporine, tacrolimus, or sirolimus** and frequent monitoring of drug levels of these medicines is necessary when taking them in combination with posaconazole.
- have ever had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole, or voriconazole.
- are taking any other medicines, including prescription and non-prescription medicines, vitamins, and herbal supplements.
- have, or have had liver problems. Your doctor may do blood tests to make sure you should take NOXAFIL[®].
- have, or have had an abnormal heart rate or rhythm.
- are, or think you are pregnant. Do not use NOXAFIL during pregnancy unless specifically advised by your doctor. You should use effective birth control while you are taking NOXAFIL if you are a woman who could become pregnant.

Contact your doctor immediately if you become pregnant while being treated with NOXAFIL.

Do not breast-feed while being treated with NOXAFIL, unless specifically advised by your doctor.

Who should not take NOXAFIL?

- Do NOT take NOXAFIL[®] if you are taking any of the medicines listed below. If any of these medicines are taken together with NOXAFIL, serious or life-threatening side effects from these medicines, or a decrease in the effect of NOXAFIL can occur. Tell your doctor right away if you are taking any of these medicines:
 - ergot alkaloids [ergotamine, dihydroergotamine, methylsergide, methylergonovine, ergonovine or bromocriptine]
 - terfenadine
 - astemizole
 - cisapride
 - pimozone
 - halofantrine
 - quinidine
 - rifabutin
 - phenytoin
 - cimetidine
- If you have questions or are uncertain about your medicines, talk with your doctor or pharmacist.
- Do not take NOXAFIL if you are allergic to anything in it. There is a list of what is in NOXAFIL at the end of this leaflet.

Can I take other medicines with NOXAFIL?

NOXAFIL[®] and many medicines can interact with each other and some must not be taken together (see “**Who should not take NOXAFIL?**”). The dose of other medicines may need to be adjusted when taken with NOXAFIL [for example, **cyclosporine (Neoral[®])**, **tacrolimus (Prograf[®])**, or **sirolimus (Rapamune[®])**]. (See “**What should I tell my doctor before taking NOXAFIL?**”).

Knowing the medicines that you are taking is important. **Tell your doctor** about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. Keep a list of them with you to show your doctor or pharmacist. Do not take any new medicine without talking to your doctor.

What are possible side effects of NOXAFIL?

The most commonly reported side effects related to NOXAFIL[®] use were nausea, diarrhea, vomiting, headache, stomach pain, bloating, liver problems, low blood potassium, and decrease in neutrophils (certain type of white blood cells that fight infection).

Rarely, NOXAFIL may cause serious or life-threatening side effects. It may also cause severe drug interactions as discussed above. Call your doctor right away if you have any of the symptoms listed below.

Changes in heart rate or rhythm. People who have certain heart conditions or who take certain other medicines have a higher chance for this problem.

Rarely, very serious liver problems were reported in patients with serious underlying medical conditions. Your doctor may test your liver function while you are taking NOXAFIL. Call your doctor if you have any of these symptoms, as these may be signs of liver problems: you have itching, your eyes or skin turn yellow, you feel more tired than usual or feel like you have the flu, or you have nausea or vomiting.

Rarely, an increase in blood clots may occur in patients with blood cancers or post stem cell transplantation. These events may or may not be further increased in patients also on posaconazole and primarily occurred in patients also receiving cyclosporine or tacrolimus. If you notice swelling of one leg or shortness of breath, notify your doctor immediately.

These are not all the side effects associated with NOXAFIL. For more information, ask your doctor or pharmacist. If you experience any unusual effects while taking NOXAFIL, contact your doctor immediately.

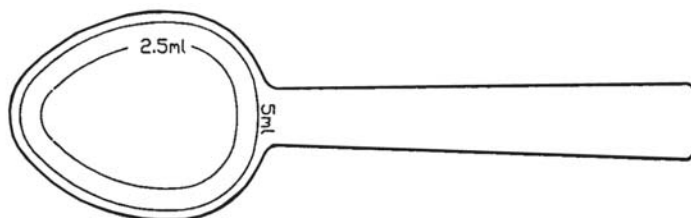
How do I take NOXAFIL?

- NOXAFIL[®] comes in cherry-flavored liquid form. Shake NOXAFIL Oral Suspension well before use.
- Take NOXAFIL for as long as your doctor tells you. Take each dose of NOXAFIL with a full meal, or with a liquid nutritional supplement if you are unable to eat a full meal.
- Follow your doctor's instructions on when and how much of NOXAFIL you should take.

If you miss a dose of NOXAFIL, take it as soon as you remember.

- If you take too much NOXAFIL, call your doctor or poison control center immediately.
- Tell your doctor right away if you develop severe diarrhea or vomiting.

A measured dosing spoon is provided, marked for doses of 2.5 mL and 5 mL.



It is recommended that the spoon is rinsed with water after each administration and before storage.

How do I store NOXAFIL?

- Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. DO NOT FREEZE. Keep all containers tightly closed.
- **Keep NOXAFIL[®], as well as other medicines, out of the reach of children.**

General information about NOXAFIL

Doctors can prescribe medicines for conditions that are not in this leaflet. Use NOXAFIL[®] only as directed by your doctor. Do not give it to other people, even if they have the same symptoms as you. It may harm them.

This leaflet gives the most important information about NOXAFIL. For more information, talk to your doctor. You can ask your doctor or pharmacist for information about NOXAFIL that is written for health professionals.

What is in NOXAFIL?

Active ingredient: posaconazole

Inactive ingredients: polysorbate 80, simethicone, sodium benzoate, sodium citrate dihydrate, citric acid monohydrate, glycerin, xanthan gum, liquid glucose, titanium dioxide, artificial cherry flavor, and purified water.

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Rx only