F-XXXXXXXX

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NOXAFIL ORAL SUSPENSION safely and effectively. See full prescribing information for NOXAFIL ORAL SUSPENSION.

NOXAFIL® (Posaconazole) ORAL SUSPENSION 40 mg/mL

Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Contraindications, Hypersensitivity (4.1)	[9/10]
Contraindications, Use with Simvastatin (4.4)	[9/10]
Warnings and Precautions, Use with Midazolam (5.4)	[9/10]

----------INDICATIONS AND USAGE----------

NOXAFIL is a triazole antifungal agent 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 HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy. (1.1)
- the treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole. (1.2)

----------DOSAGE AND ADMINISTRATION----------

Indication	Dose and Duration of therapy
Prophylaxis of Invasive Fungal Infections	200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.1)
Oropharyngeal Candidiasis (OPC)	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. (2.1)
OPC Refractory (rOPC) 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. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

NOXAFIL Oral Suspension 40 mg per mL (3)

----------CONTRAINDICATIONS----------

• Do not administer to persons with known hypersensitivity to posaconazole, any component of NOXAFIL, or other azole antifungal agents (4.1)

• Do not coadminister NOXAFIL with the following drugs; NOXAFIL increases concentrations of:

o Sirolimus: can result in sirolimus toxicity (4.2, 7.1)

o CYP3A4 substrates (pimozide, quinidine): can result in QTc interval prolongation and rare occurrences of TdP (4.3, 7.2)

o Simvastatin: can result in rhabdomyolysis (4.4, 7.3)

o Ergot alkaloids: can result in ergotism (4.5, 7.4)

----------WARNINGS AND PRECAUTIONS----------

- Calcineurin Inhibitor Toxicity: NOXAFIL increases concentrations of cyclosporine or tacrolimus; reduce dose of cyclosporine and tacrolimus and monitor concentrations frequently. (5.1)
- Arrhythmias and QTc Prolongation: NOXAFIL has been shown to prolong the QTc interval and cause rare occurrences of TdP. Administer with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs known to prolong QTc interval and metabolized through CYP3A4. Correct K^+, Mg^{++}, and Ca^{++} before starting NOXAFIL. (5.2)
- Hepatic Toxicity: elevations in LFTs (generally reversible on discontinuation) may occur. Discontinuation should be considered in patients who develop abnormal LFTs or monitor LFTs during treatment. (5.3)
- Midazolam: NOXAFIL can prolong hypnotic/sedative effects. Monitor patients and benzodiazepine receptor antagonists should be available. (5.4, 7.5)

----------ADVERSE REACTIONS----------

- Common treatment-emergent adverse reactions (>30%) in prophylaxis studies are fever, diarrhea and nausea.(6.2)
- Common treatment-emergent adverse reactions (>5%) in controlled OPC pool are diarrhea, nausea, headache, and vomiting. Common adverse reactions (>20%) in the refractory OPC pool are fever, diarrhea, nausea, and vomiting (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Schering Corporation, a subsidiary of Merck & Co., Inc., at 800-526-4099 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

Interaction Drug	Interaction
Rifabutin, phenytoin, efavirenz, cimetidine, esomeprazole	Avoid co-administration unless the benefit outweighs the risks (7.6, 7.7, 7.8, 7.9)
Other drugs metabolized by CYP3A (tacrolimus, cyclosporine, vinca alkaloids, calcium channel blockers)	Consider dosage adjustment and monitor for adverse effects and toxicity (7.1,7.10, 7.11)
Digoxin	Monitor digoxin plasma concentrations (7.12)
Metoclopramide	Monitor for breakthrough fungal infections (7.13)

----------USE IN SPECIFIC POPULATIONS----------

• Pregnancy: Based on animal data, may cause fetal harm. (8.1)

• Nursing Mothers: Discontinue drug or nursing, taking in to consideration the importance of drug to the mother. (8.3)

• Severe renal impairment: Monitor closely for breakthrough fungal Infections. (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/20XX

FULL PRESCRIBING INFORMATION: CONTENTS*

***** Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

NOXAFIL Oral Suspension 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.

1.2 Treatment of Oropharyngeal Candidiasis Including Oropharyngeal Candidiasis Refractory to Itraconazole and/or Fluconazole

NOXAFIL is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.

2. DOSAGE AND ADMINISTRATION

2.1 Dosage

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.

2.2 Administration Instructions

Shake NOXAFIL Oral Suspension well before use.

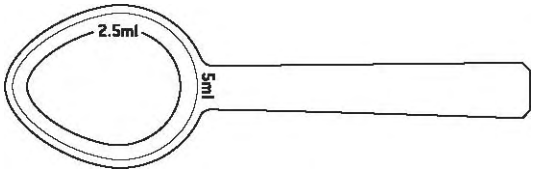


Figure 1: A measured dosing spoon is provided, marked for doses of 2.5 mL and 5 mL.

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

Each dose of NOXAFIL should be administered with a full meal or with a liquid nutritional supplement or an acidic carbonated beverage (e.g. ginger ale) in patients who cannot eat a full meal.

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

- Each dose of NOXAFIL should be administered during or immediately (i.e. within 20 minutes) following a full meal. In patients who cannot eat a full meal, each dose of NOXAFIL should be administered with a liquid nutritional supplement or an acidic carbonated beverage. For patients who cannot eat a full meal or tolerate an oral nutritional supplement or an acidic carbonated beverage, 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 Drug Interactions (*7.6, 7.7, 7.8, 7.9, 7.13*)*].

3. DOSAGE FORMS AND STRENGTHS

NOXAFIL 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).

4. CONTRAINDICATIONS

4.1 Hypersensitivity

NOXAFIL is contraindicated in persons with known hypersensitivity to posaconazole, any component of NOXAFIL, or other azole antifungal agents.

4.2 Use With Sirolimus

NOXAFIL is contraindicated with sirolimus. Concomitant administration of NOXAFIL with sirolimus increases the sirolimus blood concentrations by approximately 9 fold and can result in sirolimus toxicity *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

4.3 QT Prolongation With Concomitant Use With CYP3A4 Substrates

NOXAFIL is contraindicated with CYP3A4 substrates that prolong the QT interval. Concomitant administration of NOXAFIL with the CYP3A4 substrates, pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to QTc prolongation and rare occurrences of torsades de pointes *[see Warnings and Precautions (5.2) and Drug Interactions (7.2)]*.

4.4 Use With Simvastatin

Concomitant administration of NOXAFIL with simvastatin increases the simvastatin plasma concentrations by approximately 10 fold. Increased plasma statin concentrations can be associated with rhabdomyolysis *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

4.5 Use With Ergot Alkaloids

Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism [*see Drug Interactions (7.4)*].

5. WARNINGS AND PRECAUTIONS

5.1 Calcineurin-Inhibitor Drug Interactions

Concomitant administration of NOXAFIL with cyclosporine or tacrolimus increases the whole blood trough concentrations of these calcineurin-inhibitors [*see Drug Interactions (7.1) and Clinical Pharmacology (12.3)*]. Nephrotoxicity and leukoencephalopathy (including isolated deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine concentrations. Frequent monitoring of tacrolimus or cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus or cyclosporine dose adjusted accordingly.

5.2 Arrhythmias and QT Prolongation

Some azoles, including posaconazole, have been associated with prolongation of the QT interval on the electrocardiogram. In addition, rare cases of torsades de pointes have been reported in patients taking posaconazole.

Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval. 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.

Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4 *[see Contraindications (4.3) and Drug Interactions (7.2)]*. Rigorous attempts to correct potassium, magnesium, and calcium should be made before starting posaconazole.

5.3 Hepatic Toxicity

Hepatic reactions (e.g., mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and/or clinical hepatitis) have been reported in clinical trials. 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. Isolated cases of more severe hepatic reactions including cholestasis or hepatic failure including deaths have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with posaconazole. These severe hepatic reactions were seen primarily in subjects receiving the 800 mg daily (400 mg BID or 200 mg QID) in clinical trials.

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.

5.4 Use with Midazolam

Concomitant administration of NOXAFIL with midazolam increases the midazolam plasma concentrations by approximately 5 fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Patients must be monitored closely for adverse effects associated with high plasma concentrations of midazolam and benzodiazepine receptor antagonists must be available to reverse these effects *[see Drug Interactions (7.5) and Clinical Pharmacology (12.3)]*.

6. ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions

The following serious and otherwise important adverse reactions are discussed in detail in another section of the labeling:

- Hypersensitivity *[see Contraindications (4.1)]*
- Arrhythmias and QT Prolongation *[see Warnings and Precautions (5.2)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.3)]*

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of NOXAFIL cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of posaconazole therapy has been assessed in 1844 patients in clinical trials. This includes 605 patients in the active-controlled prophylaxis studies, 557 patients in the active-controlled OPC studies, 239 patients in refractory OPC studies, and 443 patients from other indications. This represents a heterogeneous population, including immunocompromised patients, e.g., patients with hematological malignancy, neutropenia post-chemotherapy, graft vs. host disease post hematopoietic stem cell transplant, and HIV infection, as well as non-neutropenic patients. This patient population was 71% male, had a mean age of 42 years (range 8-84 years, 6% of patients were ≥65 years of age and 1% was <18 years of age), and were 64% white, 16% Hispanic, and 36% non-white (including 14% black). Posaconazole therapy was given to 171 patients for ≥6 months, with 58 patients receiving posaconazole therapy for ≥12 months. **Table 1** presents treatment-emergent adverse reactions observed at an incidence of >10% in posaconazole prophylaxis studies. **Table 2** presents treatment-emergent adverse reactions observed at an incidence of at least 10% in the OPC/rOPC studies.

Prophylaxis of Aspergillus and Candida: In the 2 randomized, comparative prophylaxis studies, the safety of posaconazole 200 mg three times a day was compared to fluconazole 400 mg once daily or itraconazole 200 mg twice a day in severely immunocompromised patients.

The most frequently reported adverse reactions (>30%) in the prophylaxis clinical trials were fever, diarrhea and nausea.

The most common adverse reactions leading to discontinuation of posaconazole in the prophylaxis studies were associated with GI disorders, specifically, nausea (2%), vomiting (2%), and hepatic enzymes increased (2%).

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

Body System Preferred Term	Posaconazole (n=605)		Fluconazole (n=539)		Itraconazole (n=58)	
Subjects Reporting any Adverse Reaction	**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*	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)
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)

[*] Percentages of sex-specific adverse reactions are based on the number of males/females.
NOS = not otherwise specified.

HIV Infected Subjects With OPC: In 2 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).
Of these subjects, 149 received the 800-mg/day dose and the remainder received the ≤400-mg QD dose.

In the OPC/rOPC studies, the most common adverse reactions were fever, diarrhea, nausea, headache, and vomiting.

The most common adverse reactions that led to treatment discontinuation of posaconazole in the Controlled OPC Pool included respiratory insufficiency (1%) and pneumonia (1%). In the refractory OPC pool, the most common adverse reactions that led to treatment discontinuation of posaconazole were AIDS (7%) and respiratory insufficiency (3%).

TABLE 2: Treatment-Emergent Adverse Reactions With Frequency of at Least 10% in OPC Studies (Treated Population)

	Number (%) of Subjects		
	Controlled OPC Pool		**Refractory OPC Pool**
Body System **Preferred Term**	**Posaconazole n=557**	**Fluconazole n=262**	**Posaconazole n=239**
Subjects Reporting any Adverse Reaction[*]	**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)
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)
Gastrointestinal 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)
Metabolic and Nutritional Disorders			
Weight Decrease	4 (1)	2 (1)	33 (14)
Dehydration	4 (1)	7 (3)	27 (11)
Psychiatric Disorders			
Insomnia	8 (1)	3 (1)	39 (16)
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; SGOT=serum glutamic oxaloacetic transaminase (same as AST); SGPT=serum glutamic pyruvic transaminase (same as ALT).

* Number of subjects reporting treatment-emergent adverse reactions at least once during the study, without regard to relationship to treatment. Subjects may have reported more than 1 event.

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

Less Common Adverse Reactions: Clinically significant adverse reactions reported during clinical trials in prophylaxis, OPC/rOPC or other trials with posaconazole which occurred in less than 5% of patients are listed below:

- **Blood and lymphatic system disorders:** hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, neutropenia aggravated
- **Endocrine disorders:** adrenal insufficiency
- **Nervous system disorders:** paresthesia
- **Immune system disorders:** allergic reaction [*see Contraindications (4.1)]*
- **Cardiac disorders:** Torsades de pointes *[see Warnings and Precautions (5.2)]*
- **Vascular disorders:** pulmonary embolism
- **Liver and Biliary System Disorders**: bilirubinemia, hepatic enzymes increased, hepatic function abnormal, hepatitis, hepatomegaly, jaundice, SGOT Increased, SGPT Increased
- **Metabolic and Nutritional Disorders:** Hypokalemia
- **Platelet, Bleeding, and Clotting Disorders:** Thrombocytopenia
- **Renal & Urinary System Disorders:** Renal Failure Acute

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 3.**

TABLE 3: 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

Number (%) of Patients With Change*		
Study 1		
Laboratory Parameter	**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)
Study 2		
Laboratory Parameter	**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)

	Number (%) of Patients With Change*	
Alkaline Phosphatase	4/281 (1)	1/276 (<1)

* 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 4**. (LFT abnormalities were present in some of these patients prior to initiation of the study drug).

TABLE 4: Clinically Significant Laboratory Test Abnormalities Without Regard to Baseline Value

	Controlled		Refractory
	Posaconazole	Fluconazole	Posaconazole
Laboratory Test	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.

6.3 Postmarketing Experience
No clinically significant postmarketing adverse reactions were identified that have not previously been reported during clinical trials experience.

7. DRUG INTERACTIONS

Posaconazole is primarily metabolized via UDP glucuronidation and is a substrate of p-glycoprotein efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. Posaconazole is also a strong inhibitor of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole *[see Clinical Pharmacology (12.3)]*.

7.1 Immunosuppressants Metabolized by CYP3A4
Sirolimus: Concomitant administration of posaconazole with sirolimus increases the sirolimus blood concentrations by approximately 9 fold and can result in sirolimus toxicity. Therefore, posaconazole is contraindicated with sirolimus *[see Contraindications (4.2) and Clinical Pharmacology (12.3)]*.

Tacrolimus: Posaconazole has been shown to significantly increase the C_{max} and AUC of tacrolimus. 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 *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Cyclosporine: Posaconazole has been shown to increase cyclosporine whole blood concentrations in heart transplant patients upon initiation of posaconazole treatment. It is recommended to reduce cyclosporine dose to approximately three-fourths of the original dose upon initiation of posaconazole treatment. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

7.2 CYP3A4 Substrates
Concomitant administration of posaconazole with CYP3A4 substrates such as pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to QTc prolongation and rare occurrences of torsades de pointes. Therefore, posaconazole is contraindicated with these drugs. *[see Contraindications (4.3), and Warnings and Precautions (5.2)]*.

7.3 HMG-CoA reductase Inhibitors (Statins) Metabolized Through CYP3A4
Concomitant administration of posaconazole with simvastatin increases the simvastatin plasma concentrations by approximately 10 fold. Therefore, posaconazole is contraindicated with HMG-CoA reductase inhibitor simvastatin [*see Contraindications (4.4) and Clinical Pharmacology (12.3)*].
Although not studied clinically with statins other than simvastatin, posaconazole may increase the plasma concentrations of statins that are metabolized by CYP3A4. Increased plasma statin concentrations can be associated with rhabdomyolysis. It is recommended that patients be monitored for adverse events and dose reduction of the statin be considered during co-administration with posaconazole.

7.4 Ergot Alkaloids
Most of the ergot alkaloids are substrates of CYP3A4. Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism. Therefore, posaconazole is contraindicated with ergot alkaloids *[see Contraindications (4.5)]*.

7.5 Benzodiazepines Metabolized by CYP3A4
Concomitant administration of posaconazole with midazolam increases the midazolam plasma concentrations by approximately 5 fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant use of posaconazole and other

benzodiazepines metabolized by CYP3A4 (e.g., alprazolam, triazolam) could result in increased plasma concentrations of these benzodiazepines. Patients must be monitored closely for adverse effects associated with high plasma concentrations of benzodiazepines metabolized by CYP3A4 and benzodiazepine receptor antagonists must be available to reverse these effects. *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)].*

7.6 Anti-HIV Drugs

Efavirenz: Efavirenz induces UDP-glucuronidase and significantly decreases posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)]*. It is recommended to avoid concomitant use of efavirenz with posaconazole unless the benefit outweighs the risks.

Ritonavir and Atazanavir: Ritonavir and atazanavir are metabolized by CYP3A4 and posaconazole increases plasma concentrations of these drugs *[see Clinical Pharmacology (12.3)]*. Frequent monitoring of adverse effects and toxicity and dosage adjustments of ritonavir and atazanavir should be performed during co-administration with posaconazole.

7.7 Rifabutin

Rifabutin induces UDP-glucuronidase and decreases posaconazole plasma concentrations. Rifabutin is also metabolized by CYP3A4. Therefore, Co-administration of rifabutin with posaconazole increases rifabutin plasma concentrations [*see Clinical Pharmacology (12.3)]*. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. However, if concomitant administration is required, close monitoring of breakthrough fungal infections as well as frequent monitoring of full blood counts and adverse reactions due to increased rifabutin plasma concentrations (e.g., uveitis, leukopenia) are recommended.

7.8 Phenytoin

Phenytoin induces UDP-glucuronidase and decreases posaconazole plasma concentrations. Phenytoin is also metabolized by CYP3A4. Therefore, co-administration of phenytoin with posaconazole increases phenytoin plasma concentrations *[see Clinical Pharmacology (12.3)]*. Concomitant use of posaconazole and phenytoin should be avoided unless the benefit to the patient outweighs the risk. However, if concomitant administration is required, close monitoring of breakthrough fungal infections is recommended and frequent monitoring of phenytoin concentrations should be performed while co-administered with posaconazole and dose reduction of phenytoin should be considered.

7.9 Gastric Acid Suppressors/Neutralizers

Cimetidine (an H_2-recpetor antagonist) and esomeprazole (a proton pump inhibitor) decrease posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)]*. It is recommended to avoid concomitant use of cimetidine and esomeprazole with posaconazole unless the benefit outweighs the risks. However, if concomitant administration is required, close monitoring of breakthrough fungal infections is recommended.
No clinically relevant effects were observed when posaconazole is concomitantly used with antiacids and H_2-receptor antagonists other than cimetidine. No dosage adjustment of posaconazole is required when posaconazole is concomitantly used with antacids and H_2-receptor antagonists other than cimetidine.

7.10 Vinca Alkaloids

Most of the vinca alkaloids are substrates of CYP3A4. Posaconazole may increase the plasma concentrations of vinca alkaloids (e.g., vincristine and vinblastine) which may lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered.

7.11 Calcium Channel Blockers Metabolized by CYP3A4

Posaconazole may increase the plasma concentrations of calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, diltiazem, nifedipine, nicardipine, felodipine). Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers is recommended during co-administration. Dose reduction of calcium channel blockers may be needed.

7.12 Digoxin

Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and posaconazole. Therefore, monitoring of digoxin plasma concentrations is recommended during co-administration.

7.13 Gastrointestinal Motility Agents

Metoclopramide decreases posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)].* If metoclopramide is concomitantly administered, it is recommended to closely monitor for breakthrough fungal infections.

Loperamide does not affect posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)].* No dosage adjustment of posaconazole is required when loperamide and posaconazole are used concomitantly.

7.14 Glipizide

Although no dosage adjustment of glipizide is required, it is recommended to monitor glucose concentrations when posaconazole and glipizide are concomitantly used.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. NOXAFIL should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus.

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 were seen.

8.3 Nursing Mothers

Posaconazole is excreted in milk of lactating rats. It is not known whether NOXAFIL is excreted in human milk. Because of the potential for serious adverse reactions from NOXAFIL in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of posaconazole have been established in the age groups 13 to 17 years of age. The safety and effectiveness of posaconazole in pediatric patients below the age of 13 years have not been established. Use of posaconazole in these age groups is supported by evidence from adequate and well-controlled studies of posaconazole in adults with additional data.

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 (Cav) 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 (Cav) was similar between these patients and adults (≥18 years of age).

In the prophylaxis studies, the mean steady-state posaconazole average concentration (Cav) was similar among ten adolescents (13 to 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).

8.5 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.

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.

No overall differences in the pharmacokinetics and safety were observed between elderly and young subjects during clinical trials, but greater sensitivity of some older individuals cannot be ruled out.

8.6 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/1.73m^2, n=6) and moderate (CLcr: 20-49 mL/min/1.73m^2, 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/1.73m^2), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (CLcr: >80 mL/min/1.73m^2); 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 (2)]*.

8.7 Hepatic Insufficiency

After a single oral dose of posaconazole 400 mg, the mean AUC was 43%, 27%, and 21% higher in subjects with mild (Child-Pugh Class A, N=6), moderate (Child-Pugh Class B, N=6), and severe (Child-Pugh Class C, N=6) hepatic insufficiency, respectively, compared to subjects with normal hepatic function (N=18). Compared to subjects with normal hepatic function, the mean C_{max} was 1% higher, 40% higher, and 34% lower in subjects with mild, moderate, and severe hepatic insufficiency, respectively. The mean apparent oral clearance (CL/F) was reduced by 18%, 36%, and 28% in subjects with mild, moderate, and severe hepatic insufficiency, respectively, compared to subjects with normal hepatic function. The elimination half-life (t½) was 27 hours, 39 hours, 27 hours, and 43 hours in subjects with normal hepatic function and mild, moderate, and severe hepatic insufficiency, respectively.

It is recommended that no dose adjustment of NOXAFIL is needed in patients with mild to severe hepatic insufficiency (Child-Pugh Class A, B, and C) *[see Dosage and Administration (2)*, and *Warnings and Precautions (5)]*.

8.8 Gender

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

8.9 Race

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

10. OVERDOSAGE

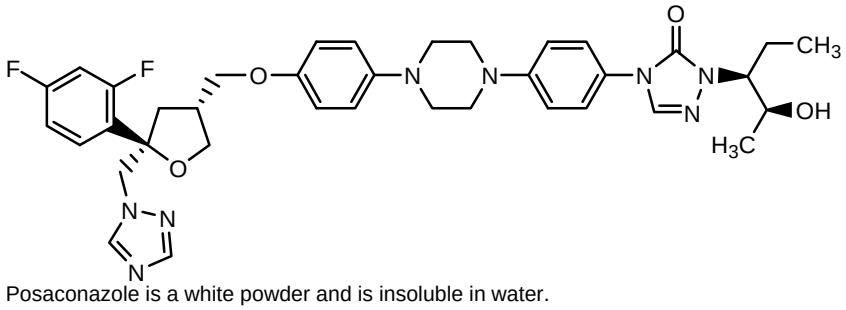
During the clinical trials, some patients received posaconazole up to 1600 mg/day with no adverse reactions noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg BID for 3 days. No related adverse reactions were noted by the investigator.

Posaconazole is not removed by hemodialysis.

11. DESCRIPTION

NOXAFIL 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 $C_{37}H_{42}F_2N_8O_4$ and a molecular weight of 700.8. The chemical structure 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.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Posaconazole is a triazole antifungal agent *[see Clinical pharmacology (12.4)]*.

12.2 Pharmacodynamics

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 (Cav) and prophylactic efficacy. A lower Cav 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 should be administered during or immediately (i.e. within 20 minutes) following a full meal. In patients who cannot eat a full meal, each dose of NOXAFIL should be administered with a liquid nutritional supplement or an acidic carbonated beverage. For patients who cannot eat a full meal or tolerate an oral nutritional supplement or an acidic carbonated beverage, 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 Drug Interactions (7.2)]*.

12.3 Pharmacokinetics

Absorption: 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 (Cav) and prophylactic efficacy. A lower Cav 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)].

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 8**). In order to assure attainment of adequate plasma concentrations, it is recommended to administer posaconazole with food or a nutritional supplement.

TABLE 8: 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}* (hr)	AUC (I) (ng·hr/mL)	CL/F (L/hr)	t½ (hr)
200 mg fasted (n=20) ‡	132 (50) [45-267]	3.50 [1.5-36†]	4179 (31) [2705-7269]	51 (25) [28-74]	23.5 (25) [15.3-33.7]
200 mg nonfat (n=20) ‡	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) ‡	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) §	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) §	355 (43) [145-720]	5 [4-8]	11,295 (40) [3865-20,592]	43 (56) [19-103]	26.0 (19) [18.2-35.0]

* Median [min-max]
† 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).
‡ n=15 for AUC (I), CL/F, and t ½
§ n=10 for AUC (I), CL/F, and t ½

Table 9: The Effect of Varying Gastric Administration Conditions on the C_{max} and AUC of Posaconazole in Healthy Volunteers

Study Description	Administration Arms	Change in C_{max}(ratio estimate**; 90% CI of the	Change in AUC(ratio estimate**; 90% CI of the

		ratio estimate)	ratio estimate)
400-mg single dose with a high-fat meal relative to fasted state (n=12)	5 minutes before high-fat meal	↑96% (1.96; 1.48-2.59)	↑111% (2.11; 1.60-2.78)
	During high-fat meal	↑339% (4.39; 3.32-5.80)	↑382% (4.82; 3.66-6.35)
	20 minutes after high-fat meal	↑333% (4.33; 3.28-5.73)	↑387% (4.87; 3.70-6.42)
400 mg BID and 200 mg QID for 7 days in fasted state and with liquid nutritional supplement (BOOST®)(n=12)	400 mg BID with BOOST	↑65% (1.65; 1.29-2.11)	↑66% (1.66; 1.30-2.13)
	200 mg QID with BOOST	No Effect	No Effect
Divided daily dose from 400 mg BID to 200 mg QID for 7 days regardless of fasted conditions or with BOOST (n=12)	Fasted state	↑136% (2.36; 1.84-3.02)	↑161% (2.61; 2.04-3.35)
	With BOOST	↑137% (2.37; 1.86-3.04)	↑157% (2.57; 2.00-3.30)
400-mg single dose with carbonated acidic beverage (ginger ale) and/or proton pump inhibitor (esomeprazole) (n=12)	Ginger ale	↑92% (1.92; 1.51-2.44)	↑70% (1.70; 1.43-2.03)
	Esomeprazole	↓32% (0.68; 0.53-0.86)	↓30% (0.70; 0.59-0.83)
400-mg single dose with a prokinetic agent (metoclopramide 10 mg TID for 2 days) + BOOST or a antikinetic agent (loperamide 4- mg single dose) + BOOST (n=12)	With metoclopramide + BOOST	↓21% (0.79; 0.72-0.87)	↓19% (0.81; 0.72-0.91)
	With loperamide + BOOST	↓3% (0.97; 0.88-1.07)	↑11% (1.11; 0.99-1.25)
400-mg single dose either orally with BOOST or via an NG tube with BOOST (n=16)	Via NG tube*	↓19% (0.81; 0.71-0.91)	↓23% (0.77; 0.69-0.86)
*In 5 subjects, the C_{max} and AUC decreased substantially (range: -27% to -53% and -33% to -51%, respectively) when NOXAFIL was administered via an NG tube compared to when NOXAFIL was administered orally. It is recommended to closely monitor patients for breakthrough fungal infections when NOXAFIL is administered via an NG tube because a lower plasma exposure may be associated with an increase risk of treatment failure. **Ratio Estimate is the ratio of co-administered drug plus posaconazole to co-administered drug alone for C_{max} or AUC.			

The mean (%CV) [min-max] posaconazole average steady-state plasma concentrations (Cav) 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 10.**

TABLE 10: 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*	Cav (ng/mL)	AUC‖ (ng·hr/mL)	CL/F (L/hr)	V/F (L)	t½ (hr)
200 mg TID† (n=252)	1103 (67) [21.5– 3650]	ND¶	ND¶	ND¶	ND¶
200 mg TID‡ (n=215)	583 (65) [89.7-2200]	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§ (n=23)	723 (86) [6.70-2256]	9093 (80) [1564-26,794]	76.1 (78) [14.9-256]	3088 (84) [407-13,140]	31.7 (42) [12.4-67.3]

Note: Cav based on observed data; other pharmacokinetic parameters based on estimates from population pharmacokinetic analyses
* Oral suspension administration
† Allogeneic hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease
‡ Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes
§ Febrile neutropenic patients or patients with refractory invasive fungal infections, Cav n=24
‖ AUC $_{(0\text{-}24\ hr)}$ for 200 mg TID and AUC $_{(0\text{-}12\ hr)}$ for 400 mg BID
¶ Not done
The variability in average plasma posaconazole concentrations in patients was relatively higher than that in healthy subjects.

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.

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 11.**

TABLE 11: 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	
			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)
Efavirenz (UDP-G Induction)	400 mg QD × 10 and 20 days	400 mg (oral suspension) BID × 10 and 20 days	↓45% (0.55; 0.47-0.66)	↓ 50% (0.50; 0.43-0.60)
Rifabutin (UDP-G Induction)	300 mg QD x 17 days	200 mg (tablets) QD × 10 days	↓ 43% (0.57; 0.43-0.75)	↓ 49% (0.51; 0.37-0.71)
Phenytoin (UDP-G Induction)	200 mg QD x 10 days	200 mg (tablets) QD × 10 days	↓ 41% (0.59; 0.44-0.79)	↓ 50% (0.50; 0.36-0.71)
Cimetidine (Alteration of Gastric pH)	400 mg BID × 10 days	200 mg (tablets) QD × 10 days	↓ 39% (0.61; 0.53-0.70)	↓ 39% (0.61; 0.54-0.69)
Esomeprazole (Increase in gastric pH)	40 mg QAM × 3 days	400 mg (oral suspension) single dose	↓ 46% (0.54; 0.43-0.69)	↓ 32% (0.68; 0.57-0.81)
Metoclopramide (Increase in gastric motility)	10 mg TID × 2 days	400 mg (oral suspension) single dose	↓ 21% (0.79; 0.72-0.87)	↓ 19% (0.81; 0.72-0.91)

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

In vitro studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4. A clinical study in healthy volunteers also indicates that posaconazole is a strong CYP3A4 inhibitor as evidenced by a >5-fold increase in midazolam AUC. 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 12** [*see Contraindications (4),* and *Drug Interactions (7.1)* including recommendations].

TABLE 12: Summary of the Effect of Posaconazole on Co-administered Drugs in Healthy Volunteers and Patients

Coadministered Drug *(Postulated Mechanism of*	Coadministered Drug Dose/Schedule	Posaconazole Dose/ Schedule	Effect on Bioavailability of Co-administered Drugs

			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)
Sirolimus	2-mg single oral dose	400 mg (oral suspension) BID x 16 days	↑ 572% (6.72; 5.62-8.03)	↑ 788% (8.88; 7.26-10.9)
Cyclosporin	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	
Tacrolimus	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)
Simvastatin	40-mg single oral dose	100 mg (oral suspension) QD x 13 days	Simvastatin ↑ 841% (9.41, 7.13 - 12.44) Simvastatin Acid ↑ 817% (9.17, 7.36 - 11.43)	Simvastatin ↑ 931% (10.31, 8.40 - 12.67) Simvastatin Acid ↑634% (7.34, 5.82 - 9.25)
		200 mg (oral suspension) QD x 13 days	Simvastatin ↑ 1041% (11.41, 7.99 - 16.29) Simvastatin Acid ↑851% (9.51, 8.15 - 11.10)	Simvastatin ↑ 960% (10.60, 8.63 - 13.02) Simvastatin Acid ↑748% (8.48, 7.04 - 10.23)
Midazolam	0.4-mg single IV dose†	200 mg (oral suspension) BID x 7 days	↑ 30% (1.3; 1.13-1.48)	↑ 362% (4.62; 4.02-5.3)
	0.4-mg single IV dose†	400 mg (oral suspension) BID x 7 days	↑62% (1.62; 1.41-1.86)	↑524% (6.24; 5.43-7.16)
	2-mg single oral dose†	200 mg (oral suspension) QD x 7 days	↑ 169% (2.69; 2.46-2.93)	↑ 470% (5.70; 4.82-6.74)
	2-mg single oral dose†	400 mg (oral suspension) BID x 7 days	↑ 138% (2.38; 2.13-2.66)	↑ 397% (4.97; 4.46-5.54)
Rifabutin	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)
Phenytoin	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)
Ritonavir	100 mg QD x 14 days	400 mg (oral suspension) BID x 7 days	↑ 49% (1.49; 1.04-2.15)	↑ 80% (1.8;1.39-2.31)
Atazanavir	300 mg QD x 14 days	400 mg (oral suspension) BID x 7 days	↑ 155% (2.55; 1.89-3.45)	↑ 268% (3.68; 2.89-4.70)
Atazanavir/ ritonavir boosted regimen	300 mg/100 mg QD x 14 days	400 mg (oral suspension) BID x 7 days	↑ 53% (1.53; 1.13-2.07)	↑ 146% (2.46; 1.93-3.13)

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

† The mean terminal half-life of midazolam was increased from 3 hours to 7 to 11 hours during co-administration with posaconazole.

Additional clinical studies demonstrated that no clinically significant effects on zidovudine, lamivudine, indinavir, or caffeine were observed when administered with posaconazole 200 mg QD; therefore, no dose adjustments are required for these co-administered drugs when co-administered with posaconazole 200 mg QD.

Excretion: Posaconazole is eliminated with a mean half-life (t½) of 35 hours (range: 20-66 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).

12.4 Microbiology

Mechanism of Action: Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of the enzyme lanosterol 14α-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* (14), *Indications* (1), and *Dosage and Administration (2)]*.

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*.

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.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No drug-related neoplasms were recorded in rats or mice treated with posaconazole for 2 years at doses higher than the clinical dose. In a 2-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).

13.2 Animal Toxicology and/or Pharmacology

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 (14)]*.

14. CLINICAL STUDIES

14.1 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 2 treatment groups (80 days, posaconazole; 77 days, fluconazole). **Table 13** contains the results from Study 1.

TABLE 13: 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*	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
(*Aspergillus*)	3 (1%)	17 (6%)
(*Candida*)	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†	27 (9%)	25 (8%)
Through 16 weeks		
Clinical Failure*,‡	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(*Aspergillus*)	7 (2%)	21 (7%)
(*Candida*)	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†	26 (9%)	30 (10%)
Event free lost to follow-up§	24 (8%)	30 (10%)

* Patients may have met more than one criterion defining failure.
† Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage > 4 consecutive days).
‡ 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%).
§ 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 14** contains the results from Study 2.

TABLE 14: 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*,†	82 (27%)	126 (42%)
Failure due to:		
Proven/Probable IFI	7 (2%)	25 (8%)
(*Aspergillus*)	2 (1%)	20 (7%)
(*Candida*)	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‡	67 (22%)	98 (33%)
Through 100 days post-randomization		
Clinical Failure†	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(*Aspergillus*)	2 (1%)	26 (9%)
(*Candida*)	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‡	98 (32%)	125 (42%)
Event free lost to follow-up§	34 (11%)	24 (8%)

* 95% confidence interval (posaconazole-fluconazole/itraconazole) = (-22.9%, -7.8%).
† Patients may have met more than one criterion defining failure.
‡ Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage > 3 consecutive days).
§ 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, 2 clinical studies of prophylaxis were conducted. As seen in the accompanying tables (**Tables 14** and **15)**, clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Study 1 (**Table 14**), 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 15**) 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.

14.2 Treatment of Oropharyngeal Candidiasis

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 1 dose of study medication and had a positive oral swish culture of *Candida* species at baseline were included in the analyses (**Table 16**). 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 16**).

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 16**).

TABLE 16: 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.

14.3 Treatment of Oropharyngeal Candidiasis Refractory to Treatment With Fluconazole or Itraconazole

Study 4 was a noncomparative 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, 89 subjects met these strict criteria for refractory infection.

Forty-five subjects with refractory OPC were treated with posaconazole 400 mg BID for 3 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 28 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).

16. HOW SUPPLIED/STORAGE AND HANDLING

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). DO NOT FREEZE.

17. PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling. (17.4)

17.1 Administration with Food

Take each dose of NOXAFIL Oral Suspension during or immediately (i.e. within 20 minutes) following a full meal. In patients who cannot eat a full meal each dose of NOXAFIL should be administered with a liquid nutritional supplement or an acidic carbonated beverage (e.g. ginger ale) in order to enhance absorption.

17.2 Drug Interactions

Patients should be advised to inform their physician immediately if they:

- develop severe diarrhea or vomiting.
- are currently taking drugs that are known to prolong the QTc interval and are metabolized through CYP3A4.
- are currently taking a cyclosporine or tacrolimus, or if you notice swelling of one leg or shortness of breath.
- are taking other drugs or before they begin taking other drugs as certain drugs can decrease or increase the plasma concentrations of posaconazole.

17.3 Serious and Potentially Serious Adverse Reactions

Patients should be advised to inform their physician immediately if they:

- notice a change in heart rate or heart rhythm, or have a heart condition or circulatory disease. Posaconazole can be administered with caution to patients with potentially proarrhythmic conditions are pregnant, plan to become pregnant, or are nursing.
- have liver disease or you develop itching, your eyes or skin turn yellow, you feel more tired than usual or feel like you have the flu.
- have ever had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole, or voriconazole.

17.4 See Accompanying FDA-Approved Patient Labeling

Schering Plough
Kenilworth, NJ 07033 USA

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Rev. xx/2010

F-XXXXXXXX **PATIENT INFORMATION**

NOXAFIL®
(posaconazole) ORAL SUSPENSION

Read the Patient Information that comes with NOXAFIL® Oral Suspension 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-vs.-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®),** or **tacrolimus (Prograf®).** 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** or **tacrolimus** and frequent monitoring of drug levels of these medicines is necessary when taking them in combination with NOXAFIL.
- are taking certain drugs for HIV infection, such as **ritonavir**, **atazanavir,** or **efavirenz**. Frequent monitoring of drug levels of ritonavir and/or atazanavir is necessary when taking them in combination with NOXAFIL. Efavirenz can cause a decrease in NOXAFIL levels in the body, and, therefore, it is recommended that efavirenz should not be administered with NOXAFIL.
- are taking **midazolam**, a hypnotic and sedative medication. NOXAFIL in combination with midazolam increases the midazolam plasma concentrations, which could increase and prolong sleepiness.
- 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 nonprescription 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 breastfeed 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:
  - sirolimus
  - ergot alkaloids (ergotamine, dihydroergotamine, methylsergide, methylergonovine, ergonovine, or bromocriptine)
  - pimozide
  - quinidine
  - simvastatin
  - 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®), ritonavir, or atazanavir**] (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 nonprescription 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 were fever, nausea, diarrhea, vomiting, and headache.

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.

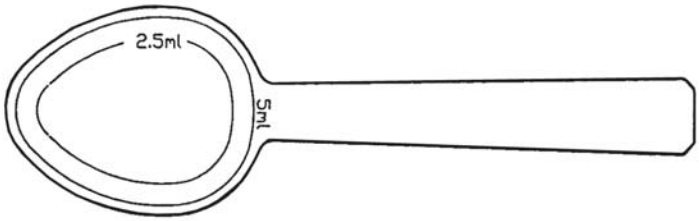
How do I take NOXAFIL®?

- 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 during or immediately (i.e., within 20 minutes) following a full meal. In patients who cannot eat a full meal, each dose of NOXAFIL should be administered with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale).
- Follow your doctor's instructions on how much NOXAFIL you should take and when.

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 care 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.

Schering Corporation
Kenilworth, NJ 07033 USA

Rx only

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