

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205053Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Noxafil® (posaconazole) delayed-release tablets, 100 mg and Noxafil® (posaconazole) oral suspension 40 mg/mL
Initial U.S. Approval: 2006 (oral suspension)

RECENT MAJOR CHANGES

Indications and Usage (1) 11/2013
Dosage and Administration (2) 11/2013
Warnings and Precautions (5.1) 11/2013

INDICATIONS AND USAGE

Noxafil is an azole antifungal agent indicated for:

Delayed-release tablets and oral suspension

- 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)

Oral suspension

- 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 <i>Aspergillus</i> and <i>Candida</i> infections	Delayed-Release Tablets: <u>Loading dose:</u> 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. <u>Maintenance dose:</u> 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.1) Oral Suspension: 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.2)
Oropharyngeal Candidiasis (OPC)	Oral Suspension: <u>Loading dose:</u> 100 mg (2.5 mL) twice a day on the first day. <u>Maintenance dose:</u> 100 mg (2.5 mL) once a day for 13 days. (2.2)
OPC Refractory (rOPC) to Itraconazole and/or Fluconazole	Oral Suspension: 400 mg (10 mL) twice a day. Duration of therapy is based on the severity of the patient's underlying disease and clinical response. (2.2)

DOSAGE FORMS AND STRENGTHS

- Noxafil delayed-release tablet 100 mg (3)
- 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:
 - Sirolimus: can result in sirolimus toxicity (4.2, 7.1)
 - CYP3A4 substrates (pimozide, quinidine): can result in QTc interval prolongation and cases of TdP (4.3, 7.2)
 - HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4: can lead to rhabdomyolysis (4.4, 7.3)
 - 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 cases 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 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 (>25%) in prophylaxis studies with posaconazole are fever, diarrhea, and nausea. (6.2)
- Common treatment-emergent adverse reactions (>5%) in controlled OPC pool with posaconazole oral suspension are diarrhea, nausea, headache, vomiting, and fever. Common adverse reactions (>20%) in the refractory OPC pool are fever, diarrhea, nausea, vomiting, and coughing. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Interaction Drug	Interaction
Rifabutin, phenytoin, efavirenz, cimetidine, esomeprazole*	Avoid coadministration unless the benefit outweighs the risks (7.6, 7.7, 7.8, 7.9)
Other drugs metabolized by CYP3A4	Consider dosage adjustment and monitor for adverse effects and toxicity (7.1, 7.10, 7.11)
Digoxin	Monitor digoxin plasma concentrations (7.12)
Fosamprenavir, metoclopramide*	Monitor for breakthrough fungal infections (7.6, 7.13)
*The drug interactions with esomeprazole and metoclopramide do not apply to posaconazole tablets.	

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 and FDA-approved patient labeling.

Revised: 11/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Noxafil® delayed-release tablets and oral suspension are 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 oral suspension is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole.

2 DOSAGE AND ADMINISTRATION

General

The prescriber should follow the specific dosing instructions for each formulation. The delayed-release tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation.

Noxafil delayed-release tablets should be swallowed whole, and not be divided, crushed, or chewed. Noxafil delayed-release tablets should be taken with food [see *Dosage and Administration* (2.3)].

Noxafil oral suspension 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.

Coadministration 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)].

Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.

2.1 Instructions for use with Noxafil Delayed-Release Tablets

Table 1: Dosing for Noxafil Delayed-Release Tablets

Indication	Dose and Duration of Therapy
Prophylaxis of invasive <i>Aspergillus</i> and <i>Candida</i> infections	<p><u>Loading dose:</u> 300 mg (three 100 mg delayed-release tablets) twice a day on the first day.</p> <p><u>Maintenance dose:</u> 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.</p>

2.2 Instructions for use with Noxafil Oral Suspension

Table 2: Dosing for Noxafil Oral Suspension

Indication	Dose and Duration of Therapy
Prophylaxis of invasive <i>Aspergillus</i> and <i>Candida</i> infections	200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.
Oropharyngeal Candidiasis	<p><u>Loading dose:</u> 100 mg (2.5 mL) twice a day on the first day.</p> <p><u>Maintenance dose:</u> 100 mg (2.5 mL) once a day for 13 days.</p>
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.

Administration Instructions for Noxafil oral suspension
Shake Noxafil oral suspension well before use.

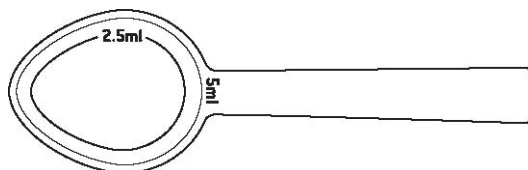


Figure 1: A measured dosing spoon is provided, marked for doses of 2.5 mL and 5 mL.

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

2.3 Administration Information

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

- Noxafil delayed-release tablets should be administered with food.
- Each dose of Noxafil oral suspension should be administered during or immediately (i.e., within 20 minutes) following a full meal.
- For patients who cannot eat a full meal, Noxafil delayed-release tablets should be used instead of Noxafil oral suspension. Noxafil delayed-release tablets should be used only for the prophylaxis indication. Noxafil delayed-release tablets provide higher plasma drug exposures than Noxafil oral suspension under fasted conditions.
- In patients who cannot eat a full meal and for whom Noxafil delayed-release tablets are not an option, each dose of Noxafil oral suspension 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 and who do not have the option of taking Noxafil delayed-release tablets, an alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.

3 DOSAGE FORMS AND STRENGTHS

Noxafil 100 mg delayed-release tablets are available as yellow, coated, oblong tablets, debossed with "100" on one side.

Noxafil oral suspension is available in 4-ounce (123 mL) amber glass bottles with child-resistant closures 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 cases of torsades de pointes [see *Warnings and Precautions* (5.2) and *Drug Interactions* (7.2)].

4.4 HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 (e.g., atorvastatin, lovastatin, and simvastatin) is contraindicated since increased plasma

concentration of these drugs can lead to 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 deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine or tacrolimus 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, 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 oral suspension 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. 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 posaconazole oral suspension 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. In clinical trials, the type of adverse reactions reported for posaconazole delayed-release tablets were generally similar to that reported in trials of posaconazole oral suspension.

Clinical Trial Experience with Posaconazole Delayed-Release Tablets

The safety of posaconazole delayed-release tablets has been assessed in 230 patients in clinical trials. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole delayed-release tablets when given as antifungal prophylaxis (Delayed-Release Tablet Study 1). Patients were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 62% male, had a mean age of 51 years (range 19-78 years, 17% of patients were ≥65 years of age), and were 93% white and 16% Hispanic. Posaconazole therapy was given for a median duration of 28 days. Twenty patients received 200 mg daily dose and 210 patients received 300 mg daily dose (following BID dosing on Day 1 in each cohort). Table 3 presents treatment-emergent adverse reactions observed in patients treated with 300 mg daily dose at an incidence of ≥10% in posaconazole delayed-release tablet study.

Table 3: Posaconazole Delayed-Release Tablet Study 1: Number (%) of Subjects Treated with 300 mg Daily Dose Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10%

Body System Preferred Term	Posaconazole delayed-release tablet (300 mg) (n=210)	
Subjects Reporting any Adverse Reaction	201	(99)
<i>Blood and Lymphatic System Disorder</i>		
Anemia	22	(10)
Thrombocytopenia	29	(14)
<i>Gastrointestinal Disorder</i>		
Abdominal Pain	23	(11)
Constipation	20	(10)
Diarrhea	61	(29)
Nausea	56	(27)
Vomiting	28	(13)
<i>General Disorders and Administration Site Conditions</i>		
Asthenia	20	(10)
Chills	22	(10)
Mucosal Inflammation	29	(14)

Edema Peripheral	33	(16)
Pyrexia	59	(28)
<i>Metabolism and Nutrition Disorders</i>		
Hypokalemia	46	(22)
Hypomagnesemia	20	(10)
<i>Nervous System Disorders</i>		
Headache	30	(14)
<i>Respiratory, Thoracic and Mediastinal Disorders</i>		
Cough	35	(17)
Epistaxis	30	(14)
<i>Skin and Subcutaneous Tissue Disorders</i>		
Rash	34	(16)
<i>Vascular Disorders</i>		
Hypertension	23	(11)

The most frequently reported adverse reactions (>25%) with posaconazole delayed-release tablets 300 mg once daily were diarrhea, pyrexia, and nausea.

The most common adverse reaction leading to discontinuation of posaconazole delayed-release tablets 300 mg once daily was nausea (2%).

Clinical Trial Safety Experience with Posaconazole Oral Suspension

The safety of posaconazole oral suspension has been assessed in 1844 patients. 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, GVHD post HSCT, 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 4** presents treatment-emergent adverse reactions observed at an incidence of >10% in posaconazole prophylaxis studies. **Table 5** 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 (Oral Suspension Studies 1 and 2), the safety of posaconazole oral suspension 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 4: Posaconazole Oral Suspension Study 1 and Study 2. Number (%) of Randomized Subjects Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10% in the Posaconazole Oral Suspension 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)
<i>Body as a Whole - General Disorders</i>						
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)
<i>Cardiovascular Disorders, General</i>						
Hypertension	106	(18)	88	(16)	3	(5)
Hypotension	83	(14)	79	(15)	10	(17)
<i>Disorders of Blood and Lymphatic System</i>						
Anemia	149	(25)	124	(23)	16	(28)
Neutropenia	141	(23)	122	(23)	23	(40)
<i>Disorders of the Reproductive System and Breast</i>						
Vaginal Hemorrhage*	24	(10)	20	(9)	3	(12)
<i>Gastrointestinal System Disorders</i>						
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)
Dyspepsia	61	(10)	50	(9)	6	(10)
<i>Heart Rate and Rhythm Disorders</i>						
Tachycardia	72	(12)	75	(14)	3	(5)
<i>Infection and Infestations</i>						
Pharyngitis	71	(12)	60	(11)	12	(21)
<i>Liver and Biliary System Disorders</i>						
Bilirubinemia	59	(10)	51	(9)	11	(19)
<i>Metabolic and Nutritional Disorders</i>						

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)
<i>Musculoskeletal System Disorders</i>						
Musculoskeletal Pain	95	(16)	82	(15)	9	(16)
Arthralgia	69	(11)	67	(12)	5	(9)
Back Pain	63	(10)	66	(12)	4	(7)
<i>Platelet, Bleeding and Clotting Disorders</i>						
Thrombocytopenia	175	(29)	146	(27)	20	(34)
Petechiae	64	(11)	54	(10)	9	(16)
<i>Psychiatric Disorders</i>						
Insomnia	103	(17)	92	(17)	11	(19)
<i>Respiratory System Disorders</i>						
Coughing	146	(24)	130	(24)	14	(24)
Dyspnea	121	(20)	116	(22)	15	(26)
Epistaxis	82	(14)	73	(14)	12	(21)
<i>Skin and Subcutaneous Tissue Disorders</i>						
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.						

HIV Infected Subjects with OPC: In 2 randomized comparative studies in OPC, the safety of posaconazole oral suspension at a dose of less than or equal to 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 oral suspension in 2 non-comparative trials for refractory OPC (rOPC). Of these subjects, 149 received the 800-mg/day dose and the remainder received the less than or equal to 400-mg QD dose.

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

The most common adverse reactions that led to treatment discontinuation of posaconazole in the Controlled OPC Pool included respiratory impairment (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 impairment (3%).

Table 5: Treatment-Emergent Adverse Reactions with Frequency of at Least 10% in OPC Studies with Posaconazole Oral Suspension (Treated Population)

Body System Preferred Term	Number (%) of Subjects		
	Controlled OPC Pool		Refractory OPC Pool
	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 *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, AST Increased, ALT 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.

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 6**.

Table 6: Posaconazole Oral Suspension 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*		
Oral Suspension 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)
Oral Suspension 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)
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 7** (LFT abnormalities were present in some of these patients prior to initiation of the study drug).

Table 7: Posaconazole Oral Suspension Studies: Clinically Significant Laboratory Test Abnormalities without Regard to Baseline Value

Laboratory Test	Controlled		Refractory
	Posaconazole	Fluconazole	Posaconazole
	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. Coadministration 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.

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 cases 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) Primarily 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 inhibitors primarily metabolized through CYP3A4 [see *Contraindications* (4.4) and *Clinical Pharmacology* (12.3)].

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 of ritonavir and atazanavir should be performed during coadministration with posaconazole.

Fosamprenavir: Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended [see *Clinical Pharmacology* (12.3)].

7.7 Rifabutin

Rifabutin induces UDP-glucuronidase and decreases posaconazole plasma concentrations. Rifabutin is also metabolized by CYP3A4. Therefore, coadministration 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 for 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, coadministration 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 for breakthrough fungal infections is recommended and frequent monitoring of phenytoin concentrations should be performed while coadministered with posaconazole and dose reduction of phenytoin should be *considered*.

7.9 Gastric Acid Suppressors/Neutralizers

Posaconazole Delayed-Release Tablet:

No clinically relevant effects on the pharmacokinetics of posaconazole were observed when posaconazole delayed-release tablets are concomitantly used with antacids, H₂-receptor antagonists and proton pump inhibitors [see *Clinical Pharmacology* (12.3)]. No dosage adjustment of posaconazole delayed-release tablets is required when posaconazole delayed-release tablets are concomitantly used with antacids, H₂-receptor antagonists and proton pump inhibitors.

Posaconazole Oral Suspension:

Cimetidine (an H₂-receptor antagonist) and esomeprazole (a proton pump inhibitor) when given with posaconazole oral suspension results in decreased posaconazole plasma concentrations [see *Clinical Pharmacology* (12.3)]. It is recommended to avoid concomitant use of cimetidine and esomeprazole with posaconazole oral suspension unless the benefit outweighs the risks. However, if concomitant administration is required, close monitoring for breakthrough fungal infections is recommended.

No clinically relevant effects were observed when posaconazole oral suspension is concomitantly used with antacids and H₂-receptor antagonists other than cimetidine. No dosage adjustment of posaconazole oral suspension is required when posaconazole oral suspension is concomitantly used with antacids and H₂-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 coadministration. 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 coadministration.

7.13 Gastrointestinal Motility Agents

Posaconazole Delayed-Release Tablet:

Concomitant administration of metoclopramide with posaconazole delayed-release tablets did not affect the pharmacokinetics of posaconazole [see *Clinical Pharmacology* (12.3)]. No dosage adjustment of posaconazole delayed-release tablets is required when given concomitantly with metoclopramide.

Posaconazole Oral Suspension:

Metoclopramide, when given with posaconazole oral suspension, decreases posaconazole plasma concentrations [see *Clinical Pharmacology* (12.3)]. If metoclopramide is concomitantly administered with posaconazole oral suspension, 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 oral suspension 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 oral suspension 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 oral suspension 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 oral suspension and posaconazole delayed-release tablets have been established in the age groups 13 to 17 years of age. Use of posaconazole in these age groups is supported by evidence from adequate and well-controlled studies of posaconazole in adults. The safety and effectiveness of posaconazole in pediatric patients below the age of 13 years have not been established.

A total of 12 patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) of posaconazole oral suspension 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) of posaconazole oral suspension 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 230 patients treated with posaconazole delayed-release tablets, 38 (17%) were greater than 65 years of age. The pharmacokinetics of posaconazole delayed-release tablets are comparable in young

and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Of the 605 patients randomized to posaconazole oral suspension in the prophylaxis clinical trials, 63 (10%) were ≥ 65 years of age. In addition, 48 patients treated with greater than or equal to 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 oral suspension 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 Impairment

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) or moderate (CLcr: 20-49 mL/min/1.73m², n=6) renal impairment on posaconazole pharmacokinetics; therefore, no dose adjustment is required in patients with mild to moderate renal impairment. In subjects with severe renal impairment (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 impairment 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)]. Similar recommendations apply to posaconazole delayed-release tablets; however, a specific study has not been conducted with the delayed-release tablets.

8.7 Hepatic Impairment

After a single oral dose of posaconazole oral suspension 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), or severe (Child-Pugh Class C, N=6) hepatic impairment, 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, or severe hepatic impairment, respectively. The mean apparent oral clearance (CL/F) was reduced by 18%, 36%, and 28% in subjects with mild, moderate, or severe hepatic impairment, respectively, compared to subjects with normal hepatic function. The elimination half-life (t_{1/2}) was 27 hours, 39 hours, 27 hours, and 43 hours in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment, respectively.

It is recommended that no dose adjustment of Noxafil is needed in patients with mild to severe hepatic impairment (Child-Pugh Class A, B, or C) [see *Dosage and Administration* (2) and *Warnings and Precautions* (5)]. Similar recommendations apply to posaconazole delayed-release tablets; however, a specific study has not been conducted with the delayed-release tablets.

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.

8.10 Weight

Pharmacokinetic modeling suggests that patients weighing greater than 120 kg may have lower posaconazole plasma drug exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections.

10 OVERDOSAGE

There is no experience with overdosage of posaconazole delayed-release tablets.

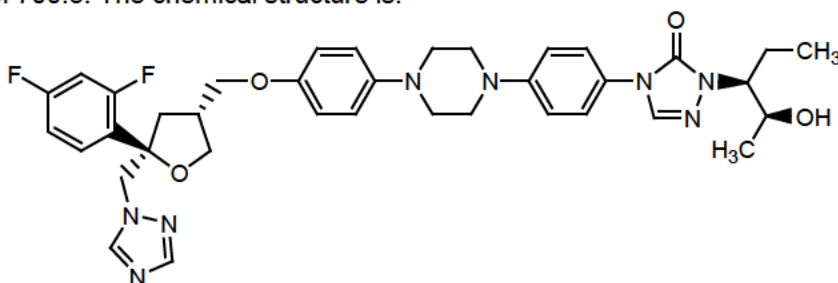
During the clinical trials, some patients received posaconazole oral suspension up to 1600 mg/day with no adverse reactions noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg BID posaconazole oral suspension for 3 days. No related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

Posaconazole is not removed by hemodialysis.

11 DESCRIPTION

Noxafil is an azole antifungal agent available as a delayed-release tablet or suspension for oral administration.

Posaconazole is designated chemically as 4-[4-[4-[4-[(3R,5R)-5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one 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 with a low aqueous solubility.

Noxafil delayed-release tablet is a yellow, coated, oblong tablet containing 100 mg of posaconazole. Each delayed-release tablet contains the inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, hydroxypropylcellulose, silicon dioxide, croscarmellose sodium, magnesium stearate, and Opadry® II Yellow (consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350, titanium dioxide, talc, and iron oxide yellow).

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 an azole antifungal agent [see *Clinical Pharmacology* (12.4)].

12.2 Pharmacodynamics

Exposure Response Relationship: In clinical studies of neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) or hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD), 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 (Table 8). A lower C_{av} may be associated with an increased risk of treatment failure, defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive fungal infections.

Table 8: Noxafil Oral Suspension Exposure Analysis (C_{av}) in Prophylaxis Trials

	Prophylaxis in AML/MDS ^a		Prophylaxis in GVHD ^b	
	C_{av} Range (ng/mL)	Treatment Failure ^c (%)	C_{av} Range (ng/mL)	Treatment Failure ^c (%)
Quartile 1	90-322	54.7	22-557	44.4
Quartile 2	322-490	37.0	557-915	20.6
Quartile 3	490-734	46.8	915-1563	17.5
Quartile 4	734-2200	27.8	1563-3650	17.5

Cav = the average posaconazole concentration when measured at steady state
 * Neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS
 † HSCT recipients with GVHD
 ‡ Defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive fungal infections

12.3 Pharmacokinetics

General Pharmacokinetic Characteristics

Noxafil delayed-release tablets exhibit dose proportional pharmacokinetics after single and multiple dosing up to 300 mg. The mean pharmacokinetic parameters of posaconazole at steady state following administration of Noxafil delayed-release tablets 300 mg twice daily (BID) on Day 1, then 300 mg once daily (QD) thereafter in healthy volunteers and in neutropenic patients who are receiving cytotoxic chemotherapy for AML or MDS or HSCT recipients with GVHD are shown in **Table 9**.

Table 9: Arithmetic Mean (%CV) of Steady State PK Parameters in Healthy Volunteers and Patients Following Administration of Posaconazole Delayed-Release Tablets (300 mg)*

	N	AUC _{0-24 hr} (ng·hr/mL)	Cav [†] (ng/mL)	C _{max} (ng/mL)	C _{min} (ng/mL)	T _{max} [‡] (h)	t _{1/2} (h)	CL/F (L/h)
Healthy Volunteers	12	51618 (25)	2151 (25)	2764 (21)	1785 (29)	4 (3-6)	31 (40)	7.5 (26)
Patients	50	37900 (42)	1580 (42)	2090 (38)	1310 (50)	4 (1.3-8.3)	-	9.39 (45)

CV = coefficient of variation expressed as a percentage (%CV); AUC_{0-24 hr} = Area under the plasma concentration-time curve from time zero to 24 hr; C_{max} = maximum observed concentration; C_{min} = minimum observed plasma concentration; T_{max} = time of maximum observed concentration; t_{1/2} = terminal phase half-life; CL/F = Apparent total body clearance
 *300 mg BID on Day 1, then 300 mg QD thereafter
 † Cav = time-averaged concentrations (i.e., AUC_{0-24 hr}/24hr)
 ‡ Median (minimum-maximum)

Dose-proportional increases in plasma exposure (AUC) to posaconazole oral suspension 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 in healthy volunteers. No further increases in exposure were observed when the dose of the oral suspension increased from 400 mg BID to 600 mg BID in febrile neutropenic patients or those with refractory invasive fungal infections.

The mean (%CV) [min-max] posaconazole oral suspension 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 Oral Suspension 200 mg TID and 400 mg BID

Dose*	Cav (ng/mL)	AUC [†] (ng·hr/mL)	CL/F (L/hr)	V/F (L)	t _{1/2} (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

† AUC_(0-24 hr) for 200 mg TID and AUC_(0-12 hr) for 400 mg BID
‡ HSCT recipients with GVHD
§ Not done
¶ 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
The variability in average plasma posaconazole concentrations in patients was relatively higher than that in healthy subjects.

Absorption: When given orally in healthy volunteers, posaconazole delayed-release tablets are absorbed with a median T_{max} of 4 to 5 hours. Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (QD after BID loading dose at Day 1). The absolute bioavailability of the oral delayed-release tablet is approximately 54%. The effect of food intake on the oral bioavailability of posaconazole following administration of posaconazole delayed-release tablets is not known. However, since the oral bioavailability of posaconazole is significantly increased when the oral suspension is administered with food or a nutritional supplement (see below), it is also recommended that posaconazole delayed-release tablets be taken with food.

Concomitant administration of posaconazole delayed-release tablets with drugs affecting gastric pH or gastric motility did not demonstrate any significant effects on posaconazole pharmacokinetic exposure (see **Table 11**).

Table 11: The Effect of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Posaconazole Delayed-Release Tablets in Healthy Volunteers

Coadministered Drug	Administration Arms	Change in C_{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in AUC_{0-last} (ratio estimate*; 90% CI of the ratio estimate)
Mylanta® Ultimate strength liquid (Increase in gastric pH)	25.4 meq/5 mL, 20 mL	↑6% (1.06; 0.90 -1.26)†	↑4% (1.04; 0.90 -1.20)
Ranitidine (Zantac®) (Alteration in gastric pH)	150 mg (morning dose of 150 mg Ranitidine BID)	↑4% (1.04; 0.88 -1.23)†	↓3% (0.97; 0.84 -1.12)
Esomeprazole (Nexium®) (Increase in gastric pH)	40 mg (QAM 5 days, day -4 to 1)	↑2% (1.02; 0.88-1.17)†	↑5% (1.05; 0.89 -1.24)
Metoclopramide (Reglan®) (Increase in gastric motility)	15 mg four times daily during 2 days (Day -1 and 1)	↓14% (0.86, 0.73,1.02)	↓7% (0.93, 0.803,1.07)

* Ratio Estimate is the ratio of coadministered drug plus posaconazole to posaconazole alone for C_{max} or AUC_{0-last} .

Posaconazole oral suspension is absorbed with a median T_{max} of ~3 to 5 hours. 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 the oral suspension is 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 posaconazole oral suspension 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 12**). In addition, the effects of varying gastric administration conditions on the C_{max} and AUC of posaconazole oral suspension in healthy volunteers have been investigated and are shown in **Table 13**.

In order to assure attainment of adequate plasma concentrations, it is recommended to administer Noxafil oral suspension during or immediately following a full meal. In patients who cannot eat a full meal,

Noxafil oral suspension should be taken with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale).

Table 12: The Mean (%CV) [min-max] Posaconazole Pharmacokinetic Parameters Following Single-Dose Oral Suspension Administration of 200 mg and 400 mg Under Fed and Fasted Conditions

Dose (mg)	C _{max} (ng/mL)	T _{max} * (hr)	AUC (l) (ng-hr/mL)	CL/F (L/hr)	t _{1/2} (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]. [†] n=15 for AUC (l), CL/F, and t _{1/2} [‡] 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=10 for AUC (l), CL/F, and t _{1/2}					

Table 13: The Effect of Varying Gastric Administration Conditions on the C_{max} and AUC of Posaconazole Oral Suspension in Healthy Volunteers

Study Description	Administration Arms	Change in C _{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in AUC (ratio estimate*; 90% CI of the 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 an 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)
<p>*Ratio Estimate is the ratio of coadministered drug plus posaconazole to coadministered drug alone for C_{max} or AUC.</p> <p>†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 increased risk of treatment failure.</p>			

Concomitant administration of posaconazole oral suspension with drugs affecting gastric pH or gastric motility results in lower posaconazole exposure. (See **Table 14**).

Table 14: The Effect of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Posaconazole Oral Suspension in Healthy Volunteers

Coadministered Drug (Postulated Mechanism of Interaction)	Coadministered 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)
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)
Esomeprazole (Increase in gastric pH)‡	40 mg QAM x 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 x 2 days	400 mg (oral suspension) single dose	↓ 21% (0.79; 0.72-0.87)	↓ 19% (0.81; 0.72-0.91)
<p>* Ratio Estimate is the ratio of coadministered drug plus posaconazole to coadministered drug alone for C_{max} or AUC.</p> <p>† The tablet refers to a non-commercial tablet formulation without polymer.</p> <p>‡ The drug interactions associated with the oral suspension are also relevant for the delayed-release tablet with the exception of Esomeprazole and Metoclopramide.</p>				

Distribution: Posaconazole has a mean (CV%) volume of distribution of 287 L (24%) in healthy volunteers. Posaconazole is highly bound to human plasma proteins (>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 15**.

Table 15: Summary of the Effect of Coadministered Drugs on Posaconazole in Healthy Volunteers

Coadministered Drug (Postulated Mechanism of Interaction)	Coadministered 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 x 10 and 20 days	400 mg (oral suspension) BID x 10 and 20 days	↓45% (0.55; 0.47-0.66)	↓50% (0.50; 0.43-0.60)
Fosamprenavir (unknown mechanism)	700 mg BID x 10 days	200 mg QD on the 1 st day, 200 mg BID on the 2 nd day, then 400 mg BID x 8 Days	↓21% 0.79 (0.71-0.89)	↓23% 0.77 (0.68-0.87)
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)
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)

* Ratio Estimate is the ratio of coadministered drug plus posaconazole to posaconazole alone for C_{max} or AUC.
[†] The tablet refers to a non-commercial tablet formulation without polymer.

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 16** [see *Contraindications* (4) and *Drug Interactions* (7.1) including recommendations].

Table 16: Summary of the Effect of Posaconazole on Coadministered Drugs in Healthy Volunteers and Patients

Coadministered Drug (Postulated Mechanism of Interaction is Inhibition of CYP3A4 by posaconazole)	Coadministered Drug Dose/Schedule	Posaconazole Dose/ Schedule	Effect on Bioavailability of Coadministered 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)
Cyclosporine	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 x 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 x 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 coadministered drug plus posaconazole to coadministered drug alone for C _{max} or AUC. [†] The tablet refers to a non-commercial tablet formulation without polymer. [‡] The mean terminal half-life of midazolam was increased from 3 hours to 7 to 11 hours during coadministration 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 coadministered drugs when coadministered with posaconazole 200 mg QD.

Excretion: 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).

Posaconazole delayed-release tablet is eliminated with a mean half-life (t_{1/2}) ranging between 26 to 31 hours.

Posaconazole oral suspension is eliminated with a mean half-life (t_{1/2}) of 35 hours (range: 20-66 hours).

12.4 Microbiology

Mechanism of Action:

Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14 α -demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation

of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane. This may be responsible for the antifungal activity of posaconazole.

Activity in vitro:

Posaconazole has *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 and Usage* (1) and *Dosage and Administration* (2)]. However, correlation between the results of susceptibility tests and clinical outcome has not been established. Posaconazole interpretive criteria (breakpoints) have not been established for any fungus.

Drug Resistance:

Clinical isolates of *Candida albicans* and *Candida glabrata* with decreased susceptibility to posaconazole 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 oral suspension regimen, respectively, based on steady-state AUC in healthy volunteers administered a high-fat meal (400-mg BID oral suspension 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 oral suspension 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 oral suspension 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 oral suspension regimen).

14 CLINICAL STUDIES

14.1 Prophylaxis of *Aspergillus* and *Candida* Infections with Posaconazole Oral Suspension

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 (Oral Suspension 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). This 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 17** contains the results from Oral Suspension Study 1.

Table 17: Results from Blinded Clinical Study in Prophylaxis of IFI in All Randomized Patients with Hematopoietic Stem Cell Transplant (HSCT) and Graft-vs.-Host Disease (GVHD):

Oral Suspension Study 1		
	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%)
(<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 [†]	27 (9%)	25 (8%)
Through 16 weeks		
Clinical Failure*[‡]	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 [†]	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 (Oral Suspension Study 2) was a randomized, open-label study that compared posaconazole oral suspension (200 mg 3 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 AML or MDS. As in Oral Suspension 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). This study assessed patients while on treatment plus 7 days and 100 days postrandomization. The mean duration of therapy was comparable between the 2 treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole). **Table 18** contains the results from Oral Suspension Study 2.

Table 18: Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and Prolonged Neutropenia:
Oral Suspension Study 2

	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%)
(<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 [‡]	67 (22%)	98 (33%)
Through 100 days postrandomization		
Clinical Failure[†]	158 (52%)	191 (64%)
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 [‡]	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 with the posaconazole oral suspension. As seen in the accompanying tables (**Tables 17 and 18**), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Oral Suspension Study 1 (**Table 17**), 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 Oral Suspension Study 2 (**Table 18**) 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 Oral Suspension Study 1 [POS 58/301 (19%) vs. FLU 59/299 (20%)] all-cause mortality was lower at 100 days for posaconazole-treated patients in Oral Suspension 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 with Posaconazole Oral Suspension

Posaconazole Oral Suspension 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 (see **Table 19**). 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 (see **Table 19**).

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 19**).

Table 19: Posaconazole Oral Suspension 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 posttreatment 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 Posaconazole Oral Suspension Treatment of Oropharyngeal Candidiasis Refractory to Treatment with Fluconazole or Itraconazole

Posaconazole Oral Suspension 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 greater than or equal to 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 oral suspension 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

Delayed-Release Tablets

Noxafil 100 mg delayed-release tablets; yellow, coated, oblong, debossed with "100" on one side. Bottles with child-resistant closures of 60 delayed-release tablets (NDC 0085-4324-02). Store at 20-25 °C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Oral Suspension

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).

Supplied with each oral suspension 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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

17.1 Administration

Noxafil Delayed-Release Tablets

Advise patients to take Noxafil delayed-release tablets with food.

Physicians should instruct their patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is within 12 hours of the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Noxafil Oral Suspension

Advise patients to 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 oral suspension 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 they notice swelling in an arm or 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 develop itching, nausea or vomiting, their eyes or skin turn yellow, they feel more tired than usual or feel like they have the flu.
- have ever had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole, or voriconazole.

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 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

Delayed-Release Tablets: Manuf. by: N. V. Organon, Kloosterstraat 6, 5349 AB Oss, Netherlands

Oral Suspension: Manuf. by: Patheon Inc., Whitby, Ontario, Canada L1N 5Z5

For patent information: www.merck.com/product/patent/home.html

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Patient Information

Noxafil® (**NOX**-a-fil)
(posaconazole)
delayed-release tablets

Noxafil® (**NOX**-a-fil)
(posaconazole)
oral suspension

What is Noxafil?

Noxafil delayed-release tablets and Noxafil oral suspension are prescription medicines used to help prevent fungal infections that can spread throughout your body (invasive fungal infections). These infections are caused by fungi called *Aspergillus* or *Candida*. Noxafil is used in people who have an increased chance of getting these infections due to a weak immune system. These include people who have:

- had a hematopoietic stem cell transplantation (bone marrow transplant) with graft versus host disease
- a low white blood cell count due to chemotherapy for blood cancers (hematologic malignancy)

Noxafil oral suspension is also used to treat a fungal infection called “thrush” caused by *Candida* in your mouth or throat area. Noxafil oral suspension can be used as the first treatment for thrush, or as another treatment for thrush after itraconazole or fluconazole treatment has not worked.

It is not known if Noxafil is safe and effective in children under 13 years of age.

Who should not take Noxafil?

Do not take Noxafil if you:

- are allergic to posaconazole, any of the ingredients in Noxafil, or other azole antifungal medicines. See the end of this leaflet for a complete list of ingredients in Noxafil.
- are taking any of the following medicines:
 - sirolimus
 - pimozide
 - quinidine
 - certain statin medicines that lower cholesterol (atorvastatin, lovastatin, simvastatin)
 - ergot alkaloids (ergotamine, dihydroergotamine)

Ask your healthcare provider or pharmacist if you are not sure if you are taking any of these medicines.

Do not start taking a new medicine without talking to your healthcare provider or pharmacist.

What should I tell my healthcare provider before taking Noxafil?

Before you take Noxafil, tell your healthcare provider if you:

- are taking certain medicines that lower your immune system like cyclosporine or tacrolimus.
- are taking certain drugs for HIV infection, such as ritonavir, atazanavir, efavirenz, or fosamprenavir. Efavirenz and fosamprenavir can cause a decrease in the Noxafil levels in your body. Efavirenz and fosamprenavir should not be taken with Noxafil.
- are taking midazolam, a hypnotic and sedative medicine.
- have or had liver problems.
- have or had kidney problems.
- have or had an abnormal heart rate or rhythm, heart problems, or blood circulation problems.
- are pregnant or plan to become pregnant. It is not known if Noxafil will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Noxafil passes into your breast milk. You and your healthcare provider should decide if you will take Noxafil or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take:

- rifabutin or phenytoin. If you are taking these medicines, you should not take Noxafil delayed-release tablets or Noxafil oral suspension.
- cimetidine or esomeprazole. If you are taking these medicines, you should not take Noxafil oral suspension.

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them with you to show your healthcare provider or pharmacist when you get a new medicine.

How should I take Noxafil?

- Take Noxafil exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much Noxafil to take and when to take it.
- Take Noxafil for as long as your healthcare provider tells you to take it.
- If you take too much Noxafil, call your healthcare provider or go to the nearest hospital emergency room right away.
- **Noxafil Delayed-Release Tablets:**
 - Take Noxafil delayed-release tablets with food.
 - Take Noxafil delayed-release tablets whole. Do not break, crush, dissolve or chew Noxafil delayed-release tablets before swallowing. If you cannot swallow Noxafil delayed-release tablets whole, tell your healthcare provider. You may need a different medicine.

- If you miss a dose, take it as soon as you remember and then take your next scheduled dose at its regular time. If, however, it is within 12 hours of your next dose, do not take the missed dose. Skip the missed dose and go back to your regular schedule. Do not double your next dose or take more than your prescribed dose.
- **Noxafil Oral Suspension:**
 - Shake Noxafil oral suspension well before use.
 - Take each dose of Noxafil oral suspension during or within 20 minutes after a full meal. If you cannot eat a full meal, take each dose of Noxafil oral suspension with a liquid nutritional supplement or an acidic carbonated beverage, like ginger ale.
 - A measured dosing spoon comes with your Noxafil oral suspension and is marked for doses of **2.5 mL** and **5 mL**. See Figure A.

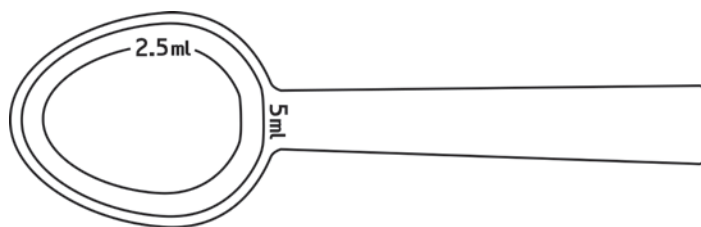


Figure A

- Rinse the spoon with water after each dose of Noxafil oral suspension and before you store it away.

Follow your doctor's instructions on how much Noxafil you should take and when.

What are the possible side effects of Noxafil?

Noxafil may cause serious side effects, including:

- **drug interactions with cyclosporine or tacrolimus.** If you take Noxafil with cyclosporine or tacrolimus, your blood levels of cyclosporine or tacrolimus may increase. Serious side effects can happen in your kidney or brain if you have high levels of cyclosporine or tacrolimus in your blood. Your healthcare provider should do blood tests to check your levels of cyclosporine or tacrolimus if you are taking these medicines while taking Noxafil. Tell your healthcare provider right away if you have swelling in your arm or leg or shortness of breath.
- **problems with the electrical system of your heart (arrhythmias and QTc prolongation).** Certain medicines used to treat fungus called azoles, including posaconazole, the active ingredient in Noxafil, may cause heart rhythm problems. People who have certain heart problems or who take certain medicines have a higher chance for this problem. Tell your healthcare provider right away if your heartbeat becomes fast or irregular.
- **liver problems.** Some people who also have other serious medical problems may have severe liver problems that may lead to death, especially if you take certain doses of Noxafil. Your healthcare provider should do blood tests to check your liver while you are taking Noxafil. Call your healthcare provider right away if you have any of the following symptoms of liver problems:

- itchy skin
- nausea or vomiting
- yellowing of your eyes
- feeling very tired
- flu-like symptoms
- **increased amounts of midazolam in your blood.** If you take Noxafil with midazolam, Noxafil increases the amount of midazolam in your blood. This can make your sleepiness last longer. Your healthcare provider should check you closely for side effects if you take midazolam with Noxafil.

The most common side effects of Noxafil Delayed-Release Tablets include:

- diarrhea
- fever
- nausea

The most common side effects of Noxafil Oral Suspension include:

- diarrhea
- nausea
- headache
- vomiting
- fever

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Noxafil. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Noxafil?

- Store Noxafil at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep Noxafil delayed-release tablets in a tightly closed container.
- **Do not** freeze Noxafil oral suspension.
- Safely throw away medicine that is out of date or no longer needed.

Keep Noxafil and all medicines out of the reach of children.

General information about the safe and effective use of Noxafil.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Noxafil for a condition for which it was not prescribed. Do not give Noxafil to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about Noxafil. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about Noxafil that is written for health care professionals.

For more information, go to www.noxafil.com or call 1-800-672-6372.

What are the ingredients in Noxafil?

Active ingredient: posaconazole


- **Noxafil Delayed-Release Tablets:**

Inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, hydroxypropylcellulose, silicon dioxide, croscarmellose sodium, magnesium stearate, and Opadry® II Yellow (consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350, titanium dioxide, talc, and iron oxide yellow)

- **Noxafil Oral Suspension:**

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

This Patient Information has been approved by the U.S. Food and Drug Administration.

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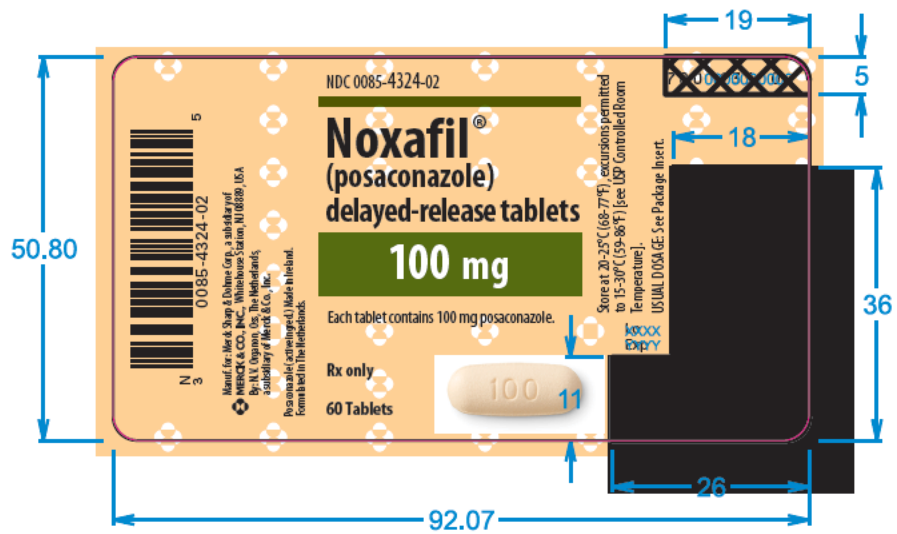
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/s/

KATHERINE A LAESSIG
11/25/2013