These highlights do not include all the information needed to use POSACONAZOLE safely and effectively. See full prescribing information for POSACONAZOLE. Posaconazole delaved-release tablets, for oral use

Posaconazole delayed-release tablet: 100 mg (3)

Posaconazole oral suspension: 40 mg per mL (3

increases concentrations and toxicities of:

7/2021

Sirolimus (4.2, 5.1, 7.1)

Ergot alkaloids (4.5, 7.4)

Known hypersensitivity to posaconazole or other azole antifungal agents. (4.1)
Coadministration of posaconazole with the following drugs is contraindicated: posaconazol

....WARNINGS AND PRECAUTIONS...

<u>Calcineurin-Inhibitor Toxicity:</u> Posaconazole increases concentrations of cyclosporine or tacrolimus; reduce dose of cyclosporine and tacrolimus and monitor concentrations frequently. (5.1)

Arrhythmias and OTC Prolongation: Posaconazole has been shown to prolong the OTc 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. (5.2) <u>Electrolyte Disturbances:</u> Monitor and correct, especially those involving potassium (K+), magnesium (Mg++), and calcium (Ca++), before and during posaconazole therapy. (5.3)

Hepatic Toxicity: Elevations in liver tests may occur. Discontinuation should be considered in patients who develop abnormal liver tests or monitor liver tests during treatment. (5.4)

<u>Concomitant Use with Midazolam:</u> Posaconazole can prolong hypnotic/sedative effects. Monitor patients and benzodiazepine receptor antagonists should be available. (5.6, 7.5)

vith vincristine has been associated with neurotoxicity and other serious adverse reactions

vincristine, who have no alternative antifungal treatment options. (5.7,7.10)

<u>Breakthrough Fungal Infections</u>: Monitor patients with severe diarrhea or vomiting when receiving

<u>Venetoclax Toxicity:</u> Concomitant administration of posaconazole with venetoclax may increase venetoclax toxicities, including the risk of tumor lysis syndrome, neutropenia, and serious infections;

Common adverse reactions in studies with posaconazole are diarrhea, nausea, fever, vomiting,

----ADVERSE REACTIONS-

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 --

* The drug interactions with esomeprazole and metoclopramide do not apply to Posaconazole tablets.

14.1 Treatment of Invasive Aspergillosis with Noxafil Injection and Noxafil Delayed-Release Tablets

14.3 Treatment of Oropharyngeal Candidiasis with Noxafil Oral Suspension
14.4 Noxafil Oral Suspension Treatment of Oropharyngeal Candidiasis Refractory to Treatment

Concomitant administration of posaconazole 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

requent monitoring of tacrolimus or cyclosporine whole blood trough concentrations should be performed

uring and at discontinuation of posaconazole treatment and the tacrolimus or cyclosporine dose adjus

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

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

Noxafil oral suspension 400 mg twice daily 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 (in-16) administered placebo. The placebo-adjusted mean maximum QTc(F) interval change from baseline was <0 msec (–8 msec). No healthy subject administered Noxafil had a QTc(F) interval ≥500 msec or an

Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increas

Posaconazole should be administered with caution to patients with potentially proarrhythmic ions. Do not administer with drugs that are known to prolong the QTc interval and are metabolized

Electrolyte Disturbances
Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels,

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 reporte in clinical trials. The elevations in liver 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

Liver tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver 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 tests and bilirubin). Discontinuation of posaconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable

14.2 Prophylaxis of Asperaillus and Candida Infections with Noxafil Oral Suspension

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

---- USE IN SPECIFIC POPULATIONS -

Severe Renal Impairment: Monitor closely for breakthrough fungal infections. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Avoid coadministration unless the benefit

dverse effects and toxicity (7.1, 7.10, 7.11)

Monitor for breakthrough fungal infections (7.6,

utweighs the risks (7.6, 7.7, 7.8, 7.9)

Posaconazole delayed-release tablets and Posaconazole oral suspension. (5.8)

monitor for toxicity and reduce venetoclax dose. (4.6, 5.9, 7.15)

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

headache, coughing, and hypokalemia. (6.1)

Rifabutin, phenytoin, efavirenz, cimetidine,

ther drugs metabolized by CYP3A4

7.6 Anti-HIV Drugs

7.10 Vinca Alkaloids

8 USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment 8.7 Hepatic Impairment

CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

13.2 Animal Toxicology and/or Pharmacology

16 HOW SUPPLIED/STORAGE AND HANDLING

PATIENT COUNSELING INFORMATION

WARNINGS AND PRECAUTIONS

increase ≥60 msec in their QTc(F) interval from baseline.

Hepatic Toxicity

through CYP3A4 [see Contraindications (4.3) and Drug Interactions (7.2)].

should be monitored and corrected as necessary before and during posaconazole therapy

suspension 800 mg daily (400 mg twice daily or 200 mg four times a day) in clinical trials.

Calcineurin-Inhibitor Toxicity

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

16.1 How Supplied

Pregnancy

8.4 Pediatric Use

8.5 Geriatric Use

7.9 Gastric Acid Suppressors/Neutralizers

7.13 Gastrointestinal Motility Agents

7.11 Calcium Channel Blockers Metabolized by CYP3A4

7.8 Phenytoir

7.12 Digoxin

8.2 Lactation

8.8 Gender

8.10 Weight

OVERDOSAGE

DESCRIPTION

14 CLINICAL STUDIES

reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including

Vincristine Toxicity: Concomitant administration of azole antifungals, including posaconazol

CYP3A4 substrates (pimozide, quinidine): can result in QTc interval prolongation and

Venetoclax: In patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) at initiation and during the ramp-up phase (4.6, 5.9, 7.15)

cases of torsades de pointes (TdP) (4.3, 5.2, 7.2) HMG-CoA Reductase Inhibitors Primarily Metabolized through CYP3A4 (4.4, 7.3)

Posaconazole oral suspensio Initial U.S. Approval: 2006 RECENT MAJOR CHANGES

Indications and Usage (1) Dosage and Administration (2) Contraindications (4) 1/2022 -- INDICATIONS AND USAGE Posaconazole is an azole antifungal indicated as follow Posaconazole delayed-release tablets are indicated for the treatment of invasive aspergillosis in

adults and pediatric patients 13 years of age and older. (1.1) **Posaconazole** is indicated for the prophylaxis of invasive *Aspergillus* and *Candida* infections in pa 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 as follows: (1.2)

Posaconazole delayed-release tablets: adults and pediatric patients 2 years of age and older

 Posaconazole oral suspension: adults and pediatric patients 13 years of age and older
 Posaconazole oral suspension is indicated for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole in adult and pediatric patients aged 13 years and older. (1.3)

Posaconazole oral suspension is not substitutable with Posaconazole delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension due to the differences in the dosing Therefore, follow the specific dosage recommendations for each of the formulations. (2.1, 2.2, 2.3) ole delayed-release tablets with or without food. (2.1)

osage Form, Dose, and Duration of Therapy Aspergillosis <u>Loading dose:</u> 300 mg (three 100 mg delayed-release tablets) twice a day Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day nereafter. Recommended total duration of therapy is 6 to 12 weeks. (2.2) witching between the intravenous and delayed-release tablets is acceptabloading dose is not required when switching between formulations. (2.2) conazole Delayed-Release Tablets: Aspergillus and Candida Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Duration of therapy is based on recover from neutropenia or immunosuppression. (2.2, 2.3) Posaconazole Oral Suspension: 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppr pharyngeal Candidiasis | Posaconazole Oral Suspension Loading dose: 100 mg (2.5 mL) twice a day on the first day Maintenance dose: 100 mg (2.5 mL) once a day for 13 days. (2.2, 2.3) Posaconazole Oral Suspension: 400 mg (10 mL) twice a day. Duration of erapy is based on the severity of the patient's underlying disease and

For pediatric patients, see the Full Prescribing Information for dosing recommendations for Posaconazole delayed-release tablets and Posaconazole oral suspension based on the age and indication associated with the dosage form. (1.1, 1.2, 1.3, 2.1, 2.3) **FULL PRESCRIBING INFORMATION: CONTENTS*** 1 INDICATIONS AND USAGE

clinical response. (2.2, 2.3)

Fluconazole

Administer Posaconazole oral suspension with a full meal. (2.1)

Treatment of Invasive Aspergillosis Prophylaxis of Invasive *Aspergillus* and *Candida* Infections 1.3 Treatment of Oropharyngeal Candidiasis Including Oropharyngeal Candidiasis Refractory to 2 DOSAGE AND ADMINISTRATION Important Administration Instructions Dosing Regimen in Adult Patients

 Non-substitutability between Posaconazole Oral Suspension and Other Formulations
 Dosage Adjustments in Patients with Renal Impairment DOSAGE FORMS AND STRENGTHS CONTRAINDICATIONS 4.1 Hypersensitivity 4.2 Use with Sirolimus

2.5 Administration Instructions for Posaconazole Oral Suspension

2.3 Dosing Regimen in Pediatric Patients (ages 2 to less than 18 years of age)
2.4 Administration Instructions for Posaconazole Delayed-Release Tablets

4.3 QT Prolongation with Concomitant Use with CYP3A4 Substrates 4.4 HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4 Use with Ergot Alkaloids 4.6 Use with Venetoclax WARNINGS AND PRECAUTIONS Calcineurin-Inhibitor Toxicity

5.2 Arrhythmias and QT Prolongation 5.3 Electrolyte Disturbances 5.4 Hepatic Toxicity 5.5 Renal Impairment 5.6 Midazolam Toxicity 5.7 Vincristine Toxicity

5.8 Breakthrough Fungal Infections ADVERSE REACTIONS Clinical Trials Experience 6.2 Postmarketing Experience DRUG INTERACTIONS 7.2 CYP3A4 Substrates

HMG-CoA Reductase Inhibitors (Statins) Primarily Metabolized Through CYP3A4 7.4 Ergot Alkaloids 7.5 Benzodiazepines Metabolized by CYP3A4 FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE Treatment of Invasive Aspergillosis

onazole delayed-release tablets are indicated for the treatment of invasive aspergillosis in adults and pediatric patients 13 years of age and older. Prophylaxis of Invasive Aspergillus and Candida Infections

Posaconazole is indicated for the prophylaxis of invasive Asperaillus and Candida infections in

tients 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 Isee Clinical Studies (14.1)] as follows Posaconazole delayed-release tablets: adults and pediatric patients 2 years of age and older who weigh greater than 40 kg Posaconazole oral suspension: adults and pediatric patients 13 years of age and older

Treatment of Oropharyngeal Candidiasis Including Oropharyngeal Candidiasis Refractory to Posaconazole oral suspension is indicated for the treatment of oronbaryogeal candidiasis luding oropharyngeal candidiasis refractory to itraconazole and/or fluconazole in adults and pediatric patients 13 years of age and older. DOSAGE AND ADMINISTRATION

Important Administration Instructions Posaconazole oral suspension is not substitutable with Posaconazole delayed-release tablets

r Noxafil PowderMix for delayed-release oral suspension due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations [see Dosage and Administration (2.2, 2.3)]. Posaconazole delayed-release tablets Swallow tablets whole. Do not divide crush or chew

Administer with or without food [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]. For patients who cannot eat a full meal, Posaconazole delayed-release tablets should be used instead of Posaconazole oral suspension for the prophylaxis indication. Posaconazole delayed-release tablets generally provide higher plasma drug exposures than Posaconazole oral suspension under both fed and fasted conditions [see Dosage and Administration (2.5)]. Administer 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 [see Dosage and Administration (2.5)].

Co-administration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections [see Drug Interactions (7.6, 7.7, 7.8, 7.9, 7.13)]. **Dosing Regimen in Adult Patients** Table 1: Dosing Regimens in Adult Patients

Table 1. Dosing negimens in Addit Patients				
Indication	Dose and Frequency	Duration of Therapy		
Treatment of invasive Aspergillosis	Posaconazole Delayed-Release Tablets: Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day.	Loading dose: 1 day Maintenance dose: Recommended total duration of therapy is 6 to 12 weeks.		
	Switching between the intravenous and delayed-release tablets is acceptable. A loading dose is not required when switching between formulations.			
Prophylaxis of invasive Aspergillus and Candida infections	Posaconazole Delayed-Release Tablets: Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on	Loading dose: 1 day		
	the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. Posaconazole Oral Suspension: 200 mg (5 mL) three times a day.	Maintenance dose: Duration of therapy is based on recovery from neutropenia or immunosuppression.		
Oropharyngeal Candidiasis (OPC)	Posaconazole Oral Suspension: Loading dose: 100 mg (2.5 mL) twice a day on the first day. Maintenance dose: 100 mg (2.5 mL) once a day thereafter.	Loading dose: 1 day Maintenance dose: 13 days		
OPC Refractory (rOPC) to Itraconazole and/or Fluconazole	Posaconazole 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.		

Dosing Regimen in Pediatric Patients (ages 2 to less than 18 years of age) ne recommended dosing regimen of posaconazole for pediatric patients 2 to less than 18 years of age is shown in Tables 2 and 3 [see Dosage and Administration (2.4, 2.5) and Clinical Pharmacology (12.3)].

Table 2: Posaconazole Delayed-Release Tablet Dosing Regimens for Pediatric Patients

lable 2. Fusa		ess than 18 years of age)	attic rationts
Recommended Pediatric Dosage and Formulatio			
Indication	Weight/Age	Delayed-Release Tablet	Duration of therapy
Prophylaxis of invasive Aspergillus and Candida	Less than or equal to 40 kg (2 to less than 18 years of age)	Not Applicable	Duration of therapy is based on recovery from
infections	Greater than 40 kg (2 to less than	Loading dose: 300 mg twice daily on the first day	neutropenia or immunosuppression.
	18 years of age)	Maintenance dose: 300 mg once daily	
Treatment of invasive Aspergillosis	13 to less than 18 years of age regardless of weight.	Loading dose: 300 mg (three 100 mg delayed-release tablets)	<u>Loading dose:</u> 1 day
		twice a day on the first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day.	Maintenance dose: Recommended total duration of therapy is 6 to 12 weeks.
		Switching between the intravenous and delayed-release tablets is acceptable. A loading dose is	

Table 3: Posaconazole Oral Suspension Dosing Regimens for Pediatric Patients (ages 13 to less than 18 years of age) Indication **Loading Dose** Maintenance Dose | Duration of therapy frequency requency 200 mg (5 mL) Aspergillus and Candida three times a day three times a day recovery from neutropenia or Oropharyngeal Candidiasis 100 mg (2.5 mL) 100 mg (2.5 mL) 13 days first dav

400 mg (10 mL) 400 mg (10 mL) Duration of therapy is based on the to Itraconazole and/or twice daily twice daily severity of the natient's underlying disease and clinical response. Administration Instructions for Posaconazole Delayed-Release Tablets Swallow tablets whole. Do not divide, crush, or chew. Administer Posaconazole delayed-release tablets with or without food [see Clinical Pharmacology (12.3)]. Administration Instructions for Posaconazole Oral Suspension:

Shake Posaconazole oral suspension well before use. Administer with measured dosing spoon (see Figure 1) provided - 2.5 ml

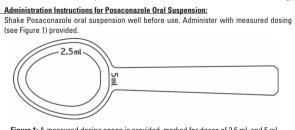


Figure 1: A measured dosing spoon is provided, marked for doses of 2.5 mL and 5 mL. Rinse the spoon with water after each administration and before storage.

Administer each dose of Posaconazole oral suspension during or immediately (i.e., within 20 minutes) following a full meal [see Clinical Pharmacology (12.3)]. For patients who cannot eat a full meal Posaconazole delayed-release tablets should be used instead of Posaconazole oral suspension for the prophylaxis indication. Posaconazo delayed-release tablets provide higher plasma drug exposures than Posaconazole oral ension under fasted conditions [see Dosage and Administration (2.1)]. In patients who cannot eat a full meal and for whom Posaconazole delayed-release tablets or Noxafil injection are not options. administer each dose of Posaconazole oral suspension with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale). 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 Posaconazole delayed-release tablets or Noxafil injection, an alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections

Non-substitutability between Posaconazole Oral Suspension and Other Formulations Posaconazole oral suspension is not substitutable with Posaconazole delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension due to the differences in the dosing of Dosage Adjustments in Patients with Renal Impairment

each formulation. Therefore, follow the specific dosage recommendations for each of the formula [see Dosage and Administration (2.2, 2.3)]. The pharmacokinetics of Posaconazole oral suspension and Posaconazole delayed-release

tablets are not significantly affected by renal impairment. Therefore, no adjustment is necessary for oral dosing in patients with mild to severe renal impairment. 3 DOSAGE FORMS AND STRENGTHS Posaconazole Delayed-Release Tablets Posaconazole delayed-release tablets are available as yellow, coated, oblong tablets, debossed

with "100" on one side containing 100 mg of posaconazole Posaconazole Oral Suspension Posaconazole oral suspension is available as a white, cherry-flavored suspension in 4-ounce (123 mL) amber glass bottles with child-resistant closures containing 105 mL of suspension (40 mg of posaconazole per mL).

CONTRAINDICATIONS

Posaconazole is contraindicated in persons with known hypersensitivity to posaconazole or other azole antifungal agents.

4.2 Use with Sirolimus Posaconazole is contraindicated with sirolimus. Concomitant administration of posaconazole 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

Concomitant administration of posaconazole 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 nistration 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 aconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism [see Drug Interactions (7.4)]. 4.6 Use with Venetoclax

contraindicated in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)

due to the potential for increased risk of tumor lysis syndrome [see Warnings and Precautions (5.9) and

Drug Interactions (7.15)].

Due to the variability in exposure with Posaconazole delayed-release tablets and Posaconazole oral suspension, patients with severe renal impairment should be monitored closely for breakthrough fungal infections [see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]. Midazolam Toxicity 5.7 Vincristine Toxicity

System Organ Class

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. 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)]. Concomitant administration of azole antifungals, including posaconazole, with vincristine has

been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options [see Drug Interactions (7.10)].

Breakthrough Fungal Infections Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections when receiving Posaconazole delayed-release tablets or Posaconazole oral suspension Venetoclax Toxicity infections. In patients with CLI/SLL, administration of posaconazole during initiation and the ramp-up phase of venetoclax is contraindicated [see Contraindications (4.6)]. Refer to the venetoclax labeling for safety monitoring and dose reduction in the steady daily dosing phase in CLL/SLL patients.

Concomitant administration of posaconazole, a strong CYP3A4 inhibitor, with venetoclax may crease venetoclax toxicities, including the risk of tumor lysis syndrome (TLS), neutropenia, and serious For patients with acute myeloid leukemia (AML), dose reduction and safety monitoring are mended across all dosing phases when coadministering posaconazole with venetoclax [see Drug Interactions (7.15)]. Refer to the venetoclax prescribing information for dosing instructions. 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 (5.4)] 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 **Clinical Trial Experience in Adults**

Clinical Trial Experience with Noxafil Injection and Noxafil Delayed-Release Tablets for the Treatment The safety of Noxafil injection and Noxafil delayed-release tablet was assessed in a randomized double-blind, active-controlled clinical study of Noxafil injection and Noxafil delayed-release tablets versus voriconazole for treatment of invasive aspergillosis (Aspergillosis Treatment Study). A total of 575 (288 in Noxafil arm, 287 in voriconazole arm) adult and pediatric patients 13 years of age and older with proven, probable or possible invasive aspergillosis were included. The median duration of treatment was 67 days for Noxafil injection or Noxafil delayed-release tablet and 64 days for voriconazole with 55% to 60% of subjects starting treatment with the IV formulation of either drug. The median duration of the first instance of IV treatment (before switching to oral treatment or discontinuing or completing study

treatment) was 9 days for both groups. **Table 4** presents adverse reactions reported at an incidence of ≥10% in either one of the groups in Aspergillosis Treatment Study. Adverse reactions leading to treatment discontinuation were reported for 33.9% of subjects. The most commonly reported adverse reactions (>2% of subjects) leading to treatment discontinuation were septic shock, respiratory failure, and bronchopulmonary aspergillosis in the Noxafil arm, and septic shock and acute myeloid leukemia in the voriconazole arm. Table 4: Novafil Invasive Aspernillosis Treatment Study: Adverse Reactions in at Least 10% of Subjects

Treated with Noxafil Injection or Noxafil Delayed-Release Tablets

	(N = 288), n (%)	(N = 287), n (%)
Blood and lymphatic system disorders		
Anemia	25 (8.7)	29 (10.1)
Febrile neutropenia	42 (14.6)	38 (13.2)
Gastrointestinal disorders		
Abdominal pain	29 (10.1)	24 (8.4)
Constipation	32 (11.1)	23 (8.0)
Diarrhea	52 (18.1)	52 (18.1)
Nausea	65 (22.6)	51 (17.8)
Vomiting	52 (18.1)	39 (13.6)
General disorders and administration site conditions		
Edema peripheral	32 (11.1)	24 (8.4)
Pyrexia	81 (28.1)	72 (25.1)
nfections and infestations		
Pneumonia	36 (12.5)	26 (9.1)
nvestigations		
Alanine aminotransferase increased	42 (14.6)	37 (12.9)
Aspartate aminotransferase increased	38 (13.2)	36 (12.5)
Blood alkaline phosphatase increased	21 (7.3)	29 (10.1)
Metabolism and nutrition disorders		
Hypokalemia	82 (28.5)	49 (17.1)
Hypomagnesemia	29 (10.1)	18 (6.3)
lervous system disorders		
Headache	35 (12.2)	25 (8.7)
Respiratory, thoracic and mediastinal lisorders		
Cough	30 (10.4)	24 (8.4)
Epistaxis	32 (11.1)	17 (5.9)
The most frequently reported advers pokalemia (28%), and nausea (23%).		
	innion ini i iop	

The safety of Noxafil delayed-release tablets has been assessed in 230 patients in clinical trials Patients were enrolled in a non-comparative pharmacokinetic and safety trial of Noxafil delayed-release tablets when given as antifungal prophylaxis (Noxafil Delayed-Release Tablet Study). 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

osaconazole therapy was given for a median duration of 28 days. Twenty patients received 200 mg daily lose and 210 patients received 300 mg daily dose (following twice daily dosing on Day 1 in each cohort). ≥10% in Noxafil Delayed-Release Tablet Study. Table 5: Noxafil Delayed-Release Tablet Study: Adverse Reactions in at Least 10% of Subjects Treated with 300 mg Daily Dose Rody System Noxafil delayed-release tablet (300 mg) n=210 (%) bjects Reporting any Adverse Reaction (99) ood and Lymphatic System Disorder

Table 5 presents adverse reactions observed in patients treated with 300 mg daily dose at an incidence of minal Pain (29) (27) (13) General Disorders and Administration Site Conditions (10) ucosal Inflammation (14) (16) dema Peripheral (28) /pokalemia (22) (10) vous System Disorder. (14) espiratory, Thoracic and Mediastinal Disorders Skin and Subcutaneous Tissue Disorders Vascular Disorders Hypertension The most frequently reported adverse reactions (>25%) with Noxafil delayed-release tablets 300 mg once daily were diarrhea, pyrexia, and nausea.

The most common adverse reaction leading to discontinuation of Noxafil delayed-release

The safety of Noxafil oral suspension has been assessed in 1844 patients. This includes 605 patients ctive-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

Noxafil therapy for ≥12 months. Table 6 presents adverse reactions observed at an incidence of >10% in

Noxafil prophylaxis studies. Table 7 presents adverse reactions observed at an incidence of at least 10%

cluding 14% black). Noxafil therapy was given to 171 patients for ≥6 months, with 58 patients receiving

s 300 mg once daily was nausea (2%)

Clinical Trial Safety Experience with Noxafil Oral Suspension

Prophylaxis of Aspergillus and Candida: In the 2 randomized, comparative prophylaxis studies (Noxafil Oral Suspension Study 1 and 2), the safety of Noxafil 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 nocompromised nationts The most frequently reported adverse reactions (>30%) in the prophylaxis clinical trials were fever, The most common adverse reactions leading to discontinuation of Noxafil in the prophylaxis

studies were associated with GI disorders, specifically, nausea (2%), vomiting (2%), and hepatic enzymes

Table 6: Noxafil Oral Suspension Study 1 and Study 2. Adverse Reactions in at Least 10% of the

Noxafil Oral Suspension or Fluconazole Treatment Groups (Pooled Prophylaxis Safety Analysis) Body System Noxafil Oral n=539 (%) n=58 (%) n=605 (%) 595 (98) 531 (99) 58 (100) ubjects Reporting any Adverse Reaction Body as a Whole - General Disorders leadache 171 (28) 141 (26) 23 (40) 122 (20) 87 (16) 17 93 (15) 67 (12) 11 (19) dema Legs 64 (11) 56 (10) 5 54 (9) 68 (13) 8 zziness 51 (8) 52 (10) 2 (3) Cardiovascular Disorders, Genera 106 (18) 88 (16) 3 pertension 83 (14) 79 (15) 10 (17) orders of Blood and Lymphatic System 149 (25) 124 (23) 16 (28) 141 (23) 122 (23) 23 (40) sorders of the Reproductive System and Breast 24 (10) 20 (9) 3 (12) aginal Hemorrhage^{*}
 232
 (38)
 198
 (37)
 30
 (52)

 174
 (29)
 173
 (32)
 24
 (41)

 161
 (27)
 147
 (27)
 21
 (36)
 usea 126 (21) 94 (17) 10 (17) 61 (10) 50 (9) 6 (10) leart Rate and Rhythm Disorders 72 (12) 75 (14) 3 (5) chycardia Infection and Infe 71 (12) 60 (11) 12 (21) Liver and Biliary System Disorders 59 (10) 51 (9) 11 (19) Metabolic and Nutritional Disorders ypokalemia 181 (30) 142 (26) 30 (52)
 110
 (18)
 84
 (16)
 11
 (19)

 68
 (11)
 76
 (14)
 2
 (3)
 pomagnesemia perglycemia 56 (9) 55 (10) 5 (9) ocalcemia
 95
 (16)
 82
 (15)
 9
 (16)

 69
 (11)
 67
 (12)
 5
 (9)
 culoskeletal Pain rthralgia Platelet, Bleeding and Clotting Disorde 175 (29) 146 (27) 20 (34) Petechiae 64 (11) 54 (10) 9 (16) Psychiatric Disorders 103 (17) 92 (17) 11 (19) Respiratory System Disorders Coughing 146 (24) 130 (24) 14 (24) yspnea 82 (14) 73 (14) 12 (21) Skin and Subcutaneous Tissue Disorders 69 (11) 62 (12) 11 (19) Pruritus * Percentages of sex-specific adverse reactions are based on the number of males/females

Noxafil oral suspension at a dose of less than or equal to 400 mg once daily in 557 HIV-infected patients was compared to the safety of fluconazole in 282 HIV-infected patients at a dose of 100 mg once daily.

An additional 239 HIV-infected patients with refractory OPC received Noxafil oral suspensi 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 once daily 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 Noxafil 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 Noxafil were AIDS (7%) and respiratory impairment (3%).

HIV Infected Subjects with OPC: In 2 randomized comparative studies in OPC, the safety of

Table 7: Adverse Reactions in at Least 10% of the Treated Population in OPC Studies with

	Number (%) of Subjects			
	Controlled OPC Pool Refractory OPC Pool			
	Noxafil Oral Suspension	Fluconazole	Noxafil Oral Suspension	
Body System	n=557	n=262	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)	
nfection 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)	

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 Other clinically significant adverse reactions reported in less than 5% of patients in clinical trials of Noxafil 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 stinal disorders: pancreatitis Liver and Biliary System Disorders: hepatic enzymes increased, hepatic function abnormal, hepatitis, hepatomegaly, jaundice

Renal & Urinary System Disorders: renal failure acute

Clinical Laboratory Values: In healthy volunteers and patients, elevation of liver 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 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 8. Table 8: Noxafil Oral Suspension Study 1 and Study 2. Changes in Liver Test Results from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4

Number (%) of Patients with Change* Noxafil Oral Suspension Study 1							
	Noxafil Oral Suspension Fluconazole						
Laboratory Parameter	n=301	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)					
	Noxafil Oral Suspension Study 2						
	Noxafil Oral Suspension	Fluconazole/Itraconazole					
Laboratory Parameter	(n=304)	(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)					
the form X/Y, where X represent		ne criterion as indicated, and					

The number of patients treated for OPC with clinically significant liver test abnormalities at any

time during the studies is provided in Table 9 (liver test abnormalities were present in some of these patients prior to initiation of the study drug).

	Controlled		Refractory
	Noxafil Oral Suspension	Fluconazole	Noxafil Oral Suspension
Laboratory Test	n=557 (%)	n=262 (%)	n=239 (%)
T > 3.0 x ULN	16/537 (3)	13/254 (5)	25/226 (11)
Γ > 3.0 x ULN	33/537 (6)	26/254 (10)	39/223 (17)
al Bilirubin > 1.5 x ULN	15/536 (3)	5/254 (2)	9/197 (5)
aline Phosphatase > 3.0 x ULN	17/535 (3)	15/253 (6)	24/190 (13)
= Alanine Aminotransferase; AS	T= Aspartate Aminotra	ansferase.	

	Without Regard to Base	eline value	
	Controlled		Refractory
	Noxafil Oral	Fluconazole	Noxafil Oral
	Suspension		Suspension
Laboratory Test	n=557 (%)	n=262 (%)	n=239 (%)
T > 3.0 x ULN	16/537 (3)	13/254 (5)	25/226 (11)
T > 3.0 x ULN	33/537 (6)	26/254 (10)	39/223 (17)
tal Bilirubin > 1.5 x ULN	15/536 (3)	5/254 (2)	9/197 (5)
caline Phosphatase > 3.0 x ULN	17/535 (3)	15/253 (6)	24/190 (13)
T= Alanine Aminotransferase; AS	ST= Aspartate Aminotra	insferase.	
The number of patients tr normalities at any time during t		nent Study is provide	d in Table 10 . Liver to

> 3.0 X OLIV	10/337 (3)	13/234 (3)	23/220 (11)
> 3.0 x ULN	33/537 (6)	26/254 (10)	39/223 (17)
al Bilirubin > 1.5 x ULN	15/536 (3)	5/254 (2)	9/197 (5)
aline Phosphatase > 3.0 x ULN	17/535 (3)	15/253 (6)	24/190 (13)
= Alanine Aminotransferase; A	ST= Aspartate Aminotra	insferase.	
The number of patients tr ormalities at any time during t ormalities present prior to the ini Table 10: Aspergillosis Treatme	he Aspergillosis Treatm itiation of study drug inc	nent Study is provided luded ALT (22%), AST (1: ver Test Results from CT	in Table 10 . Liver tes 3%), and bilirubin (13%
N	umber (%) of Patients v	vith Change*	
	Noxafil	V	oriconazole/
aboratory Parameter	n/N (%)		n/N (%)

ALT 29/281(10) 23/282 (8) Bilirubir 25/284 (9) 26/280 (9) Alkaline Phosphatase 12/282 (4) 20/284 (7)

Change from Grade 0 to 2 at baseline to Grade 3 or 4 during the study. These data are presented in

the form n N represe observation	Vill, where n represents the number of patients who met the criterion as indicated, and nts the number of patients who met the criterion as indicated, and nts the number of patients who had a baseline observation and at least one post-baseline on. of subjects for a given laboratory test with a baseline value of CTC Grade 0, 1, or 2 and
at least one CTC = Comm	post-baseline value. ion Toxicity Criteria; AST= Aspartate Aminotransferase; e Aminotransferase.
Clinical Trial	Experience in Pediatrics
The prophylaxis of PK and safet Study 1, NC1 pediatric pat and Noxafil to 6 mg/kg (to for at least suspension. (range: 1 to delayed-release Repo	Experience in Pediatric Patients (2 to less than 18 Years of Age) safety of Noxafil injection and Noxafil PowderMix for delayed-release oral suspension for finwasive fungal infections has been assessed in an open label uncontrolled dose-ranging y study (Noxafil injection/ Noxafil PowderMix for delayed-release oral suspension Pediatri 0245034); hereinafter referred to as Noxafil Pediatric Study) in 115 immunocompromise ients 2 to less than 18 years of age with known or expected neutropenia. Noxafil injectic PowderMix for delayed-release oral suspension was administered at daily doses of to vice daily on day 1) in three dose cohorts. All 115 subjects initially received Noxafil injectic of days, and 63 subjects were transitioned to Noxafil PowderMix for delayed-release or The mean overall treatment duration for all treated subjects was 20.6 days with 14.3 day 28 days) on Noxafil injection and 11.6 days (range: 2 to 18 days) on Noxafil PowderMix fasse oral suspension. The dadverse reaction profile of Noxafil in pediatric patients was consistent with the safet affil in adults.
	marketing Experience following adverse reaction has been identified during the post-approval use of posaconazol

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency Endocrine Disorders: Pseudoaldosteronism DRUG INTERACTIONS Posaconazole is primarily metabolized via UDP glucuronosyltransferase and is a substrate

of p-glycoprotein (P-gp) 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)] The following information was derived from data with Noxafil oral suspension, early tablet formulation unless otherwise noted. All drug interactions with Posaconazole oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility), are considered relevant Posaconazole injection, Posaconazole delayed-release tablet, and Posaconazole PowderMix for delayed-release oral suspension as well [see Drug Interactions (7.9) and (7.13)].

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 \mathbf{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 tecrolimus 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 cyclospo

in heart transplant patients upon initiation of posaconazole treatment. It is recommended to reduce relations that the patents and the production of the original dose 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 nings and Precautions (5.1) and Clinical Pharmacology (12.3)]. Concomitant administration of posaconazole with CYP3A4 substrates such as pimozide and

quinidine may result in increased plasma concentrations of these drugs, leading to QTD 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 Frant 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)]. Benzodiazenines 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

netabolized 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 (5.6) and nical 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 creases plasma concentrations of these drugs [see Clinical Pharmacology (12.3)]. Frequent monitoring

Fosamprenavir: Combining fosamprenavir with posaconazole may lead to decreased

of adverse effects and toxicity of ritonavir and atazanavir should be performed during coadministration

posaconazole plasma concentrations. If concomitant administration is required, close monitoring for

eakthrough fungal infections is recommended [see Clinical Pharmacology (12.3)].

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 (e.g., vincristine and vinblastine) are substrates of CYP3A4.

concomitantly used with antacids, H₂-receptor antagonists and proton pump inhibitors.

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

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)].

with posaconazone increases prientytom pashia concentrations see Cannea Frannacology (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

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

concentrations (e.g., uveitis, leukopenia) are recommended.

7.9 Gastric Acid Suppressors/Neutralizers

Posaconazole Oral Suspension:

Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see Warnings and Precautions (5.7)]. Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options. 7.11 Calcium Channel Blockers Metabolized by CYP3A4 saconazole may increase the plasma concentrations of calcium channel blockers metabolized

by CYP3A4 (e.g., verapamil, diltiazem, nifedinine, nicardinine, felodinine). Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers is recommended during coad Dose reduction of calcium channel blockers may be needed.

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 conazole delayed-release tablets is required when given concomitantly with metoclo 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 after Posaconazole oral suspension administration [see Clinical Pharmacology (12.3]]. No dosage adjustment of Posaconazole oral suspension is required when loperamide and Posaconazole oral suspension are used concomitantly

Although no dosage adjustment of glipizide is required, it is recommended to monitor glucose concentrations when posaconazole and glipizide are concomitantly used Concomitant use of venetoclax (a CYP3A4 substrate) with posaconazole increases venetoclax C_{max} and AUC_{0-INF}, which may increase venetoclax toxicities [see Contraindications (4.6), Warnings and

Precautions (5.9)]. Refer to the venetoclax prescribing information for more information on the dosing **USE IN SPECIFIC POPULATIONS**

Risk Summary

Based on findings from animal data, posaconazole may cause fetal harm when administered to pregnant women. Available data for use of Noxafil in pregnant women are insufficient to establish

a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, skeletal malformations (cranial malformations and missing ribs) and maternal toxicity reduced food consumption and reduced body weight gain) were observed when posaconazole was dosed orally to pregnant rats during organogenesis at doses ≥1.4 times the 400 mg twice daily oral suspension regimen based on steady-state plasma concentrations of Noxafil in healthy volunteers. In pregnant rabbits dosed orally during organogenesis, increased resorptions, reduced litter size, and reduced body weight gain of females were seen at doses 5 times the exposure achieved with the 400 mg twice daily oral suspension regimen. Doses of ≥ 3 times the clinical exposure caused an increase in resorptions rabbits (see Data). Based on animal data, advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically ecognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Posaconazole resulted in maternal toxicity (reduced food consumption and reduced body weight gain) and skeletal malformations (cranial malformations and missing ribs) when given orally to pregnant rats during organogenesis (Gestational Days 6 through 15) at doses ≥27 mg/kg (≥1.4 times the 400 mg twice daily oral suspension regimen based on steady-state plasma concentrations of drug in realthy volunteers). The no-effect dose for malformations and maternal toxicity in rats was 9 mg/kg, which s 0.7 times the exposure achieved with the 400 mg twice daily oral suspension regimen. No ma were seen in rabbits dosed during organogenesis (Gestational Days 7 through 19) at doses up to 80 mg/kg (5 times the exposure achieved with the 400 mg twice daily oral suspension regimen). In the rabbit, the o-effect dose was 20 mg/kg, while high doses of 40 mg/kg and 80 mg/kg (3 or 5 times the clinical expo caused an increase in resorptions. In rabbits dosed at 80 mg/kg, a reduction in body weight gain of female and a reduction in litter size were seen. 8.2 Lactation Risk Summary

There are no data on the presence of posaconazole in human milk, the effects on the breastfed infant, or the effects on milk production. Posaconazole is excreted in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for osaconazole and any potential adverse effects on the breastfed child from posaconazole or from the The safety and effectiveness of Posaconazole oral suspension and Posaconazole delayed-releas

tablets for the prophylaxis of invasive Aspergillus and Candida infections have been established in pediatric patients aged 2 and older who are at high risk of developing these infections due to being severely mpromised, such as HSCT recipients with GVHD or those with hematologic malignancies with d neutropenia from chemotherapy. The safety and effectiveness of **Posaconazole injection** and **Posaconazole delayed-release** tablets for the treatment of invasive aspergillosis have been established in pediatric patients aged 13 years and older.

The safety and effectiveness of **Posaconazole oral suspension** have been established for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole in pediatric patients aged 13 years and older.

Use of posaconazole in these age groups is supported by evidence from adequate and well-controlled studies of Noxafil in adult and pediatric patients and additional pharmacokinetic and safety data in pediatric patients 2 years of age and older [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), The safety and effectiveness of posaconazole have not been established in pediatric patients younger than 2 years of age.

8.5 Geriatric Use No overall differences in the safety of Noxafil delayed-release tablets and Noxafil oral suspension were observed between geriatric patients and younger adult patients in the clinical trials; therefore, no dosage adjustment is recommended for any formulation of posaconazole in geriatric patients. No clinically meaningful differences in the pharmacokinetics of Noxafil were observed in geriatric patients compared to younger adult patients during clinical trials [see Clinical Pharmacology (12.3)] Of the 230 patients treated with Noxafil delayed-release tablets, 38 (17%) were greater than Of the 605 patients randomized to **Noxafil oral suspension** in Noxafil Oral Suspension Study 1 and

Study 2, 63 (10%) were ≥65 years of age. In addition, 48 patients treated with greater than or equal to 800-mg/day Noxafil oral suspension in another indication were ≥65 years of age. Of the 288 patients randomized to Noxafil injection/Noxafil delayed-release tablets in the Aspergillosis Treatment Study, 85 (29%) were ≥65 years of 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 Noxafil oral suspension, there was no significant effect of mild (eGFR: 50-80 mL/min/1.73 m², n=6) or moderate (eGFR: 20-49 mL/min/1.73 m², 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 (eGFR: <20 mL/min/1.73 m²), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (eGFR: >80 mL/min/1.73 m²); 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 pply to Posaconazole delayed-release tablets; however, a specific study has not been conducted with the saconazole delayed-release tablets.

Hepatic Impairment After a single oral dose of Noxafil 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 posaconazole 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 (5.4)). Similar recommendations apply to Posaconazole delayed-release tablets; however, a specific study has not been conducted with the Posaconazole delayed-release tablets. 8.8 Gender

The pharmacokinetics of posaconazole are comparable in males and females. No adjustment in the dosage of posaconazole 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 posaconazole 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 particularly when using Posaconazole oral suspension [see Clinical Pharmacology (12.3)]. OVERDOSAGE There is no experience with overdosage of Posaconazole delayed-release tablets During the clinical trials, some patients received Noxafil oral suspension up to 1600 mg/day with no adverse reactions noted that were different from the lower doses. In addition, acci was noted in one patient who took 1200 mg twice daily Noxafil oral suspension for 3 days. No related

adverse reactions were noted by the investigato

Posaconazole is not removed by hemodialysis. DESCRIPTION Posaconazole is an azole antifungal agent available as delayed-release tablet or suspension for

(1H-1,2,4-triazol-1-y|methy|)-3-furany|]methoxy]pheny|]-1-piperaziny|]pheny|]-2-[(1S,2S)-1-ethy|-2-hydroxypropy|]-2,4-dihydro-3<math>H-1,2,4-triazol-3-one with an empirical formula of $C_{37}H_42F_2N_8O_4$ and a molecular weight of 700.8. The chemical structure is:

osaconazole is a white powder with a low aqueous solubility. Posaconazole delayed-release tablet is a yellow, coated, oblong tablet containing 100 mg of posaconazole. Each delayed-release tablet contains the inactive ingredients: croscarmellose sodium, hydroxynronylcellulose hypromellose acetate succinate iron oxide vellow Macrogol/PEG 3350

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

CLINICAL PHARMACOLOGY 12.1 Mechanism of Action Posaconazole is an azole antifungal agent [see Clinical Pharmacology (12.4)].

Exposure Response Relationship Prophylaxis: In clinical studies of neutropenic patients who

omes (MDS) or hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Dis (GVHD), a wide range of plasma exposures to posaconazole was noted following administration of Noxafil oral suspension. A pharmacokinetic-pharmacodynamic analysis of patient data revealed an apparent association between average posaconazole concentrations (Cavg) and prophylactic efficacy (**Table 11**). A lower Cavg may be associated with an increased risk of treatment failure, defined as treatment , use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive Table 11: Noxafil Oral Suspension Exposure Analysis (Cavg) in Prophylaxis Trials

Prophylaxis in AML/MDS* Prophylaxis in GVHD† Cavg Range (ng/mL) | Treatment Failure + (%) | Cavg Range (ng/mL) | Treatment Failure + (%) 11 1 Quartile 2 322-490 37.0 557-915 20.6 Quartile 3 490-734 46.8 915-1563 17.5 734-2200 27.8 Quartile 4 1563-3650 Cavg = the average posaconazole concentration when measured at steady s Neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS HSCT recipients with GVHD fined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrenc of breakthrough invasive fungal infections

 ${\it Exposure Response Relationship Treatment of Invasive Aspergillosis:}$ Across a range of posaconazole plasma minimum concentrations (C_{min}, range: 244 to 5663 ng/mL) following administration of Noxafil injection and Noxafil delayed-release tablets in patients treated fo nvasive aspergillosis in Aspergillosis Treatment Study, there was no association between posaconazole C_{min} and treatment efficacy [see Clinical Pharmacology (12.3) and Clinical Studies (14.1)]. Similarly, across range of population pharmacokinetic model-predicted steady-state plasma average conc (Cavg, range: 589 to 6315 ng/mL), there was no association between posaconazole Cavg and treatment efficacy.

12.3 Pharmacokinetics General Pharmacokinetic Characteristics Posaconazole Delayed-Release Tablets Noxafil delayed-release tablets exhibit dose proportional pharmacokinetics after single and ollowing administration of Noxafil delayed-release tablets 300 mg twice daily on Day 1, then 300 mg once daily thereafter in healthy volunteers and in neutropenic patients who are receiving cytotoxic herapy for AML or MDS or HSCT recipients with GVHD are shown in Table 12.

2151 2764 1785 (25) (21) (29) 51618 (25) 50 37900 1580 2090 1310 4 (1.3-8.3) (42) (42) (38) (50) CV = coefficient of variation expressed as a percentage (%CV); $AUC_{0-T} = Area$ under the plasm 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 time of in-terminal phase half-life; CL/F = Apparent total body clearance 300 mg twice daily on Day 1, then 300 mg once daily thereafter Cav = time-averaged concentrations (i.e., AUC_{0-24 hr}/24hr)

Table 12: Arithmetic Mean (%CV) of Steady State PK Parameters in Healthy Volunteers and Patients

Following Administration of Noxafil Delayed-Release Tablets (300 mg)*

Posaconazole Oral Suspension Dose-proportional increases in plasma exposure (AUC) to Noxafil oral suspension were observed following single oral doses from 50 mg to 800 mg and following multiple-dose administration from 50 mg twice daily to 400 mg twice daily in healthy volunteers. No further increases in exposure were observed when the dose of the oral suspension increased from 400 mg twice daily to 600 mg twice daily in febrile neutropenic patients or those with refractory invasive fungal infections. The mean (%CV) [min-max] Noxafil oral suspension average steady-state plasma concentration (Cavg) and steady-state pharmacokinetic parameters in patients following administrathree times a day and 400 mg twice daily of the oral suspension are provided in **Table 13**. Table 13: The Mean (%CV) [min-max] Posaconazole Steady-State Pharmacokinetic Parameters

in Patients Following Oral Administration of Noxafil Oral Suspension 200 mg Three Times a Day and 400 mg Twice Daily Dose* CL/F (L/hr) V/F (L) t₁, (hr)

(ng/mL) (ng·hr/mL) 1103 (67) ND§ ND§ ND§ ND§ 200 mg three times a day[‡] (n=252) [21.5-3650] 200 mg three times a day¶ (n=215) 15,900 (62) 51.2 (54) 2425 (39) 37.2 (39)
 [89.7-2200]
 [4100-56,100]
 [10.7-146]
 [828-5702]
 [19.1-148]
 76.1 (78) 400 mg twice daily# (n=23) 723 (86) 9093 (80) [6.70-2256] [1564-26,794] [14.9-256] [407-13,140] [12.4-67.3] Cavo = the average posaconazole concentration when measured at steady state AUC $_{(0.24 \text{ hr})}$ for 200 mg three times a day and AUC $_{(0.12 \text{ hr})}$ for 400 mg twice daily HSCT recipients with GVHD Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia

Febrile neutropenic patients or patients with refractory invasive fungal infections, Cavg n=24

The variability in average plasma posaconazole concentrations in patients was relatively higher than the

myelodysplastic syndromes

healthy subjects

Patient Information Posaconazole delayed-release tablets Posaconazole oral suspension

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Posaconazole (which refers to delayed-release tablets and oral suspension) is a prescription medicine used in adults and children to help prevent or treat fungal infections that can spread throughout your body (invasive fungal infections). These infections are caused by fungi called *Aspergillus* or *Candida*. Posaconazole 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 or those with a low white blood cell count due to chemotherapy for blood cancers (hematologic malignancies).

Posaconazole delayed-release tablets are used for: prevention of fungal infections in adults and children 2 years of

age and older who weigh greater than 88 lbs (40 kg). treatment of fungal infections in adults and children 13 years of Posaconazole oral suspension is used for:

• prevention of fungal infections in adults and children 13 years of

called "thrush" caused by Candida in your mouth or throat area. **Posaconazole oral suspension** can be used as the first treatment for thrush, or as another treatment for thrush after itraconazole or fluconazole

Posaconazole oral suspension is also used to treat a fungal infection

Posaconazole oral suspension is for adults and children 13 years of age and older.

It is not known if posaconazole is safe and effective in children under Who should not take posaconazole?

age and older.

Do not take posaconazole if you: are allergic to posaconazole, any of the ingredients in posaconazole,

or other azole antifungal medicines. See the end of this leaflet for a complete list of ingredients in posaconazole.

are taking any of the following medicines: sirolimus

 pimozide auinidine certain statin medicines that lower cholesterol (atorvastatin,

lovastatin, simvastatin) ergot alkaloids (ergotamine, dihydroergotamine)

have chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) and you have just started taking venetoclax or your venetoclax dose is being slowly increased. 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 posaconazole?

Before you take posaconazole, 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 posaconazole levels in your body. Efavirenz and fosamprenavir should not be taken with posaconazole.

are taking midazolam, a hypnotic and sedative medicine. are taking vincristine, vinblastine and other "vinca alkaloids" (medicines used to treat cancer). are taking venetoclax, a medicine used to treat cancer.

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 posaconazole will harm your unborn baby. are breastfeeding or plan to breastfeed. It is not known if posaconazole passes into your breast milk. You and your healthcare provider should decide if you will take posaconazole or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Posaconazole can affect the way other medicines work, and other medicines can affect the way posaconazole works, and can cause Especially tell your healthcare provider if you take: rifabutin or phenytoin. If you are taking these medicines, you should

not take Posaconazole delayed-release tablets or Posaconazole oral

cimetidine or esomeprazole. If you are taking these medicines, you

should not take Posaconazole oral suspension Ask your healthcare provider or pharmacist for a list of these medicines if 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 will I take posaconazole? Do not switch between Posaconazole oral suspension and Posaconazole delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension. Take posaconazole exactly as your healthcare provider tells you to

take it. Your healthcare provider will tell you how much posaconazole to take and when to take it. Take posaconazole for as long as your healthcare provider tells you to

If you take too much posaconazole, call your healthcare provider or go to the nearest hospital emergency room right away. Posaconazole delayed-release tablets: Take Posaconazole delayed-release tablets with or without food. • Take Posaconazole delayed-release tablets whole. Do not break, crush, or chew Posaconazole delayed-release tablets before swallowing. If you cannot swallow Posaconazole 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 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. Posaconazole oral suspension: Shake Posaconazole oral suspension well before use. o Take each dose of Posaconazole oral suspension during or within 20 minutes after a full meal. If you cannot eat a full meal, take each dose of Posaconazole oral suspension with a liquid

ginger ale. A measured dosing spoon comes with your Posaconazole oral

nutritional supplement or an acidic carbonated beverage, like

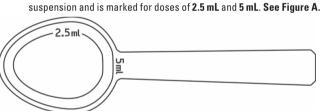


Figure A o Rinse the spoon with water after each dose of Posaconazole oral suspension and before you store it away. o If you miss a dose, take it as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and go back

to the regular dosing schedule. Do not take a double dose to make up for the missed dose. Follow the instructions from your healthcare provider on how much

posaconazole you should take and when to take it. What are the possible side effects of posaconazole?

Posaconazole may cause serious side effects, including: drug interactions with cyclosporine or tacrolimus. If you take posaconazole 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 posaconazole. 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 posaconazole, 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. **changes in body salt (electrolytes) levels in your blood.** Your healthcare provider should check your electrolytes while you are taking posaconazole.

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 posaconazole. Your healthcare

provider should do blood tests to check your liver while you are taking posaconazole. Call your healthcare provider right away if you have any of the following symptoms of liver problems: itchv skin feeling very tired nausea or vomiting flu-like symptoms

posaconazole with midazolam, posaconazole 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 posaconazole.

increased amounts of midazolam in your blood. If you take

The most common side effects of posaconazole include: headache diarrhea nausea coughing fever vomiting

vellowing of your eyes or skin

low potassium levels in the blood If you take Posaconazole delayed-release tablets or Posaconazole oral suspension, tell your healthcare provider right away if you have diarrhea or

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 posaconazole. 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 posaconazole? Posaconazole delayed-release tablets Store Posaconazole delayed-release tablets at room temperature

Posaconazole oral suspension Store Posaconazole oral suspension at room temperature between 68°F to 77°F (20°C to 25°C). Do not freeze Posaconazole oral suspension

between 68°F to 77°F (20°C to 25°C).

Safely throw away medicine that is out of date or no longer needed. Keep posaconazole and all medicines out of the reach of children. General information about the safe and effective use of posaconazole. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use posaconazole for a condition

for which it was not prescribed. Do not give posaconazole to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about posaconazole that is written for health professionals. What are the ingredients in posaconazole?

Active ingredient: posaconazole

Inactive ingredients: Posaconazole delayed-release tablets: croscarmellose sodium, hydroxypropylcellulose, hypromellose acetate succinate, iron oxide yellow, Macrogol/PEG 3350, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol partially hydrolyzed, silicon dioxide, talc, and titanium dioxide. Posaconazole oral suspension: artificial cherry flavor, citric acid

monohydrate, glycerin, liquid glucose, polysorbate 80, purified water, simethicone, sodium benzoate, sodium citrate dihydrate, titanium dioxide, and xanthan gum. Manufactured for: Par Pharmaceutical, Chestnut Ridge, NY 10977, USA Delayed-Release Tablets: Manuf. by: N. V. Organon, Kloosterstraat 6, 5349 AB Oss. Netherlands

Oral Suspension: Manuf. by: Patheon Inc., Whitby, Ontario, Canada L1N5Z5

PI1016-01-78-02 This Patient Information has been approved by the U.S. Food and Drug Administration.

usppi-gmk5592-mf-2205r004

Revised: 05/2022

Posaconazole Delayed-Release Tablets

When given orally in healthy volunteers, Noxafil 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 (once daily after twice daily loading dose at Day 1). The absolute bioavailability of the oral delayed-release tablet is approximately 54% under fasted conditions. The C_{max} and AUC of posaconazole following administration of Noxafil delayed-release tablets is increased 16% and 51%, respectively,

when given with a high fat meal compared to a fasted state (see **Table 14**). Table 14: Statistical Comparison of Plasma Pharmacokinetics of Posaconazole Following Single Oral

Dose Administration of 30	00 mg Noxafi	l Delayed-Release Fed Conditio		ealthy Subjects u	nder Fasting and
	Fasti	ng Conditions		Conditions Fat Meal)*	Fed/Fasting
Pharmacokinetic Parameter	N	Mean (%CV)	N	Mean (%CV)	GMR (90% CI)
C _{max} (ng/mL)	14	935 (34)	16	1060 (25)	1.16 (0.96, 1.41)
AUC _{0-72hr} (hr·ng/mL)	14	26200 (28)	16	38400 (18)	1.51 (1.33, 1.72)
T _{max} † (hr)	14	5.00 (3.00, 8.00)	16	6.00 (5.00, 24.00)	N/A

Median (Min, Max) reported for T_{max}

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Concomitant administration of Noxafil delayed-release tablets with drugs affecting gastric pH or gastric motility did not demonstrate any significant effects on posaconazole pharmacokinetic exposure

Table 15: The Effect of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the

Pharmacokinet	ics of Noxafil Delayed-Release T	ablets in Healthy Vol	unteers
		Change in C _{max} (ratio estimate*; 90% CI of the	Change in AUC _{0-last} (ratio estimate*; 90% CI of the
Coadministered Drug	Administration Arms	ratio estimate)	ratio estimate)
Mylanta® Ultimate strength liquid (Increase in gastric pH)	25.4 meq/5 mL, 20 mL	↑6%	↑4%
iiquiu (iiicrease iii gastiic pri/		(1.06; 0.90 -1.26)↑	(1.04; 0.90 -1.20)
Ranitidine (Zantac®)	150 mg (morning dose of 150 mg	↑4%	↓3%
(Alteration in gastric pH)	Ranitidine twice daily)	(1.04; 0.88 -1.23)↑	(0.97; 0.84 -1.12)
Esomeprazole (Nexium®)	40 mg (every morning for 5 days,	↑2%	↑5%
(Increase in gastric pH)	Day -4 to 1)	(1.02; 0.88-1.17) ↑	(1.05; 0.89 -1.24)
Metoclopramide (Reglan®)	15 mg four times daily for 2 days	↓14%	↓7%
(Increase in gastric motility)	(Day -1 and 1)	(0.86, 0.73,1.02)	(0.93, 0.803,1.07)
* Ratio Estimate is the ratio o	f coadministered drug plus Noxafil	to Noxafil alone for C	max or AUC _{0-last} .

Posaconazole Oral Suspension Noxafil 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 Noxafil oral suspension 400 mg, the mean AUC and Cmax of posaconazole are approximately 3-times higher when administered with a liquid nutritiona supplement (14 gm fat) relative to the fasted state (see **Table 16**). In addition, the effects of varying gastric administration conditions on the C_{max} and AUC of Noxafil oral suspension in healthy volunteers have been investigated and are shown in **Table 17**.

In order to assure attainment of adequate plasma concentrations, it is recommended to administer Posaconazole oral suspension during or immediately following a full meal. In patients who cannot ear a full meal, Posaconazole oral suspension should be taken with a liquid nutritional supplement or an acidic ted beverage (e.g., ginger ale).

Dose (mg)	C _{max}	T _{max} *	AUC (I)	CL/F	t _½
	(ng/mL)	(hr)	(ng·hr/mL)	(L/hr)	(hr)
200 mg fasted	132 (50)	3.50	4179 (31)	51 (25)	23.5 (25)
(n=20)†	[45-267]	[1.5-36‡]	[2705-7269]	[28-74]	[15.3-33.7]
200 mg nonfat	378 (43)	4 [3-5]	10,753 (35)	21 (39)	22.2 (18)
(n=20)†	[131-834]		[4579-17,092]	[12-44]	[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	121 (75)	4 [2-12]	5258 (48)	91 (40)	27.3 (26)
(n=23)§	[27-366]		[2834-9567]	[42-141]	[16.8-38.9]
400 mg with liquid utritional 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]

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 (I), CL/F, and $t_{1/2}$,	, , , , , , , , , , , , , , , , , , , ,	
Table 17: The Effect of Varying Gastric Adm Suspension	inistration Conditions on on in Healthy Volunteers³		C of Noxafil Oral
		Change in C _{max}	Change in AUC
			(ratio estimate†;
		90% CI of the	90% CI of the
Study Description	Administration Arms	ratio estimate)	ratio estimate)
	5 minutes before	↑96%	↑111%
	high-fat meal	(1.96; 1.48-2.59)	(2.11; 1.60-2.78)
400 ma single deservite a bigh fot most		♦330%	↑382%

		90% CI of the	90% CI of the
Study Description	Administration Arms	ratio estimate)	ratio estimate)
-	5 minutes before	↑96%	↑111%
	high-fat meal	(1.96; 1.48-2.59)	(2.11; 1.60-2.78)
400-mg single dose with a high-fat meal	Desire high for some	↑339%	↑382%
relative to fasted state (n=12)	During high-fat meal	(4.39; 3.32-5.80)	(4.82; 3.66-6.35)
	20 minutes after	↑333%	↑387%
	high-fat meal	(4.33; 3.28-5.73)	(4.87; 3.70-6.42)
400 mg twice daily and 200 mg four times	400 mg twice daily	↑65%	↑66%
daily for 7 days in fasted state and with	with B00ST	(1.65; 1.29-2.11)	(1.66; 1.30-2.13)
liquid nutritional supplement (BOOST®) (n=12)	200 mg four times daily with BOOST	No Effect	No Effect
Divided daily dose from 400 mg twice daily	Fasted state	↑136%	↑161%
to 200 mg four times daily for 7 days	rasted state	(2.36; 1.84-3.02)	(2.61; 2.04-3.35)
regardless of fasted conditions or	With BOOST	↑137%	↑157%
with BOOST (n=12)	With BUUST	(2.37; 1.86-3.04)	(2.57; 2.00-3.30)
	Cinnerale	↑92%	↑70%
400-mg single dose with carbonated acidic	Ginger ale	(1.92; 1.51-2.44)	(1.70; 1.43-2.03)
beverage (ginger ale) and/or proton pump inhibitor (esomeprazole) (n=12)	F	↓32%	↓30%
minutes (occuraçãos) (n=12)	Esomeprazole	(0.68; 0.53-0.86)	(0.70; 0.59-0.83)
400-mg single dose with a prokinetic agent	With metoclopramide +	↓21%	↓19%
(metoclopramide 10 mg three times a day	BOOST	(0.79; 0.72-0.87)	(0.81; 0.72-0.91)
for 2 days) + BOOST or an antikinetic agent (loperamide 4-mg single dose) + BOOST	With loperamide +	↓3%	↑11%
(n=12)	BOOST	(0.97; 0.88-1.07)	(1.11; 0.99-1.25)
400-mg single dose either orally with BOOST	Via NO to bat	↓19%	↓23%
or via an NG tube with BOOST (n=16)	Via NG tube‡	(0.81; 0.71-0.91)	(0.77; 0.69-0.86)
* In 5 subjects, the C _{max} and AUC decrease respectively) when Noxafil was administe administered orally. It is recommended to when posaconazole is administered via an	red via an NG tube comp closely monitor patients n NG tube because a low	ared to when Nox for breakthrough f	afil was ungal infections

NG = nasogastric Concomitant administration of Noxafil oral suspension with drugs affecting gastric pH or gastric motility results in lower posaconazole exposure. (See Table 18.) Table 18: The Effect of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the

Pharmacokinetics of Noxafil Oral Suspension in Healthy Volunteers

Ratio Estimate is the ratio of coadministered drug plus Noxafil to coadministered drug alone for C_{max} or AUC.

associated with an increased risk of treatment failure

				availability of onazole
Coadministered Drug (Postulated Mechanism of Interaction)	Coadministered Drug Dose/Schedule	Noxafil Dose/Schedule	Change in Mean C _{max} (ratio estimate*; 90% Cl of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% Cl of the ratio estimate)
Cimetidine (Alteration of gastric pH)	400 mg twice daily × 10 days	200 mg (tablets) once daily × 10 days†	↓ 39% (0.61; 0.53-0.70)	↓ 39% (0.61; 0.54-0.69)
Esomeprazole (Increase in gastric pH)‡	40 mg every morning × 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 three times a day × 2 days	400 mg (oral suspension) single dose	↓ 21% (0.79; 0.72-0.87)	↓ 19% (0.81; 0.72-0.91)
† The tablet refers ‡ The drug intera	s to a non-commercial ctions associated with	red drug plus Noxafil to coa tablet formulation without the oral suspension are a zole and Metoclopramide.	polymer.	

Posaconazole is highly bound to human plasma proteins (>98%), predominantly to albumin. 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 with the oral suspension or an early tablet formulation, which affect posaconazole concentrations, is provided in

				availability of onazole
Coadministered Drug (Postulated Mechanism of Interaction)	Coadministered Drug Dose/Schedule	Noxafil Dose/Schedule	Change in Mean C _{max} (ratio estimate*; 90% Cl of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)
Efavirenz (UDP-G Induction)	400 mg once daily × 10 and 20 days	400 mg (oral suspension) twice daily × 10 and 20 days	↓45% (0.55; 0.47-0.66)	\$ 50% (0.50; 0.43-0.60)
Fosamprenavir (unknown mechanism)	700 mg twice daily x 10 days	200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days	↓21% 0.79 (0.71-0.89)	\$23% 0.77 (0.68-0.87)
Rifabutin (UDP-G Induction)	300 mg once daily x 17 days	200 mg (tablets) once daily × 10 days†	↓ 43% (0.57; 0.43-0.75)	↓ 49% (0.51; 0.37-0.71)
Phenytoin (UDP-G Induction)	200 mg once daily x 10 days	200 mg (tablets) once daily × 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 Noxafil to Noxafil alone for $C_{\text{\scriptsize max}}$ 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 20** [see Contraindications (4) and Drug Interactions (7.1) including recommendations].

Table 20: Summary of the Effect of Noxafil on Coadministered Drugs in Healthy Volunteers and Patients

Effect on Bioavailability of

Drug (Postulated				nistered ugs
Mechanism of Interaction			Change in Mean C _{max}	Change in Mean
is Inhibition			(ratio estimate*;	(ratio estimate*;
of CYP3A4 by	Coadministered Drug	Noxafil Dose/	90% CI of the	90% CI of the
Posaconazole)	Dose/Schedule	Schedule	ratio estimate)	ratio estimate)
Sirolimus	2-mg single oral dose	400 mg (oral suspension)	↑ 572% (6.72; 5.62-8.03)	↑ 788% (8.88; 7.26-10.9)
		twice daily x 16 days	(0.72, 5.02-6.03)	(0.00, 7.20-10.3)
Cyclosporine	Stable maintenance	200 mg (tablets)		hole blood trough
	dose in heart transplant recipients	once daily x 10 days†		trations e reductions of up
	ti anapiant recipienta			re required
Tacrolimus	0.05-mg/kg	400 mg	↑ 121%	↑ 358%
	single oral dose	(oral suspension) twice daily × 7 days	(2.21; 2.01-2.42)	(4.58; 4.03-5.19)
Simvastatin	40-mg single oral dose	100 mg	Simvastatin	Simvastatin
		(oral suspension)	↑ 841%	↑ 931%
		once daily x 13 days	(9.41, 7.13-12.44) Simvastatin Acid	(10.31, 8.40-12.67 Simvastatin Acid
			↑ 817%	↑634%
			(9.17, 7.36-11.43)	(7.34, 5.82-9.25)
		200 mg	Simvastatin	Simvastatin
		(oral suspension)	↑ 1041%	↑ 960%
		once daily x 13 days	(11.41, 7.99-16.29)	(10.60, 8.63-13.02
			Simvastatin Acid	Simvastatin Acid
			↑851% (9.51, 8.15-11.10)	↑ 748% (8.48, 7.04-10.23)
Midazolam	0.4-mg single	200 mg	↑ 30%	↑ 362%
iviiuazoiaiii	intravenous dose‡	(oral suspension)	(1.3; 1.13-1.48)	(4.62; 4.02-5.3)
		twice daily x 7 days	(110, 1110,	(,
	0.4-mg single	400 mg	↑62%	↑524%
	intravenous dose‡	(oral suspension)	(1.62; 1.41-1.86)	(6.24; 5.43-7.16)
		twice daily x 7 days		
	2-mg single oral dose‡	200 mg	↑ 169%	↑ 470%
		(oral suspension)	(2.69; 2.46-2.93)	(5.70; 4.82-6.74)
		once daily x 7 days		
	2-mg single oral dose‡	400 mg	↑ 138%	↑ 397%
		(oral suspension)	(2.38; 2.13-2.66)	(4.97; 4.46-5.54)
		twice daily x 7 days		
Rifabutin	300 mg	200 mg (tablets)	↑ 31%	↑ 72%
	once daily x 17 days	once daily × 10 days†	(1.31; 1.10-1.57)	(1.72;1.51-1.95)
Phenytoin	200 mg once daily PO x 10 days	200 mg (tablets) once daily x 10 days†	16% (1.16; 0.85-1.57)	16% (1.16; 0.84-1.59)
Ritonavir	100 mg	400 ma	↑ 49%	↑ 80%
IIItoriavii	once daily x 14 days	(oral suspension)	(1.49; 1.04-2.15)	(1.8;1.39-2.31)
		twice daily x 7 days	(,	(**************************************
		twice dully A 7 days		
Atazanavir	300 mg	400 mg	↑ 155%	↑ 268%
	300 mg once daily x 14 days	400 mg (oral suspension)	↑ 155% (2.55; 1.89-3.45)	↑ 268% (3.68; 2.89-4.70)
Atazanavir/ ritonavir		400 mg		
Atazanavir Atazanavir/ ritonavir boosted regimen	once daily x 14 days	400 mg (oral suspension) twice daily x 7 days	(2.55; 1.89-3.45)	(3.68; 2.89-4.70)
Atazanavir/ ritonavir		400 mg (oral suspension)		

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 Additional clinical studies demonstrated that no clinically significant effects on zidovudine,

lamivudine, indinavir, or caffeine were observed when administered with Noxafil 200 mg once daily

therefore, no dose adjustments are required for these coadministered drugs when coadministered

Excretion: wing administration of Noxafil oral suspension, 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). Specific Populations No clinically significant differences in the pharmacokinetics of posaconazole were observed based on age, sex, renal impairment, and indication (prophylaxis or treatment). Race/Ethnicity:

In a population pharmacokinetic analysis of posaconazole, AUC was found to be 25% higher in Chinese patients relative to patients from other races/ethnicities. This higher exposure is not expected to be clinically relevant given the expected variability in posaconazole exposure. Patients Weighing More Than 120 kg:

Veight has a clinically significant effect on posaconazole clearance. Relative to 70 kg patients, the Cavq is decreased by 25% in patients greater than 120 kg. Patients administered posaconazole

weighing more than 120 kg may be at higher risk for lower posa to lower weight patients [see Use in Specific Populations (8.10)]. 12.4 Microbiolog Mechanism of Action:

with posaconazole 200 mg once daily.

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Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-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

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

Antimicrobial Activity:
Posaconazole has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections [see Indications and Usage (1)]. Microorganisms:

Asperaillus spp. and Candida spp. Susceptibility Testing: For specific information regarding susceptibility test interpretive criteria and associated test methods and

ality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC . 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

<u>Carcinogenesis</u>

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 twice daily oral suspension regimen, respectively, based on steady-state AUC in healthy volunteers administered a high-fat meal (400-mg twice daily 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 twice daily 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.

Impairment of Fertility
Posaconazole had no effect on fertility of male rats at a dose up to 180 mg/kg (1.7 x the 400-mg twice daily 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 twice daily oral suspension regimen).

13.2 Animal Toxicology and/or Pharmacology In a nonclinical study using intravenous administration of posaconazole in very young dogs (dosed from 2 to 8 weeks of age), an increase in the incidence of brain ventricle enlargement was observed in treated animals as compared with concurrent control animals. No difference in the incidence of brain ventricle enlargement between control and treated animals was observed following the subsequent 5-month treatment-free period. There were no neurologic, behavioral or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to juvenile dogs (4 days to 9 months of age). There were no drug-related increases in the incidence of brain ventricle enlargement when treated, and control animals were compared in a separate study of 10-week old dogs dosed with intravenous posaconazole for 13 weeks with a 9-week recovery period or a follow-up study of 31-week old dogs dosed for 3 months. 14 CLINICAL STUDIES

14.1 Treatment of Invasive Aspergillosis with Noxafil Injection and Noxafil Delayed-Release Tablets

Aspergillosis Treatment Study (NCT01782131) was a randomized, double-blind, controlled trial which evaluated the safety and efficacy of Noxafil injection and Noxafil delayed-release tablets versus voriconazole for primary treatment of invasive fungal disease caused by Aspergillus species. Eligible patients had proven, probable, or possible invasive fungal infections per the European Organization for Research and Treatment of Cancer/Mycoses Study Group, EORTC/MSG criteria. Patients were stratified by risk for mortality or poor outcome where high risk included a history of allogeneic bone marrow transplant, liver transplant, or relapsed leukemia undergoing salvage chemotherapy. The median age of patients was 57 years (range 14-91 years), with 27.8% of patients aged ≥65 years; 5 patients were pediatric patients 14-16 years of age, of whom 3 were treated with Noxafil and 2 with voriconazole The majority of patients were male (59.8%) and white (67.1%). With regard to risk factors for invasive aspergillosis, approximately two-thirds of the patients in the study had a recent history of neutropenia, while approximately 20% with a history of an allogeneic stem cell transplant. Over 80% of subjects in each treatment group had infection limited to the lower respiratory tract (primarily lung), while approximately 11% to 13% also had infection in another organ. Invasive aspergillosis was proven or probable in 58.1% of patients as classified by independent adjudicators blinded to study treatment assignment. At least one Aspergillus species was identified in 21% of the patients; A. fumigatus and A. flavus were the most Patients randomized to receive Noxafil were given a dose of 300 mg once daily (twice daily on

Day 1) IV or tablet. Patients randomized to receive voriconazole were given a dose of 6 mg/kg twice daily.

Day 1 followed by 4 mg/kg twice daily IV, or oral 300 mg twice daily Day 1 followed by 200 mg twice daily. The recommended initial route of administration was IV; however, patients could begin oral therapy if clinically stable and able to tolerate oral dosing. The transition from IV to oral therapy occurred when the patient was clinically stable. The protocol recommended duration of therapy was 84 days with a maximum allowed duration of 98 days. Median treatment duration was 67 days for Noxafii patients and 64 days for voriconazole patients. Overall, 55% to 60% of patients began treatment with the IV formulation with a median duration of 9 days for the initial IV dosing.

The Intent to Treat (ITT) population included all patients randomized and receiving at least one

dose of study treatment. All-cause mortality through Day 42 in the overall population (ITT) was 15.3% for Noxafil patients compared to 20.6% for voriconazole patients for an adjusted treatment difference of -5.3% with a 95% confidence interval of -11.6 to 1.0%. Consistent results were seen in patients with proven or probable invasive aspergillosis per EORTC criteria (see Table 21). Table 21: Noxafil Injection and Noxafil Delayed-Release Tablets Invasive

Aspergillosis Treatment Study: All-Cause Mortality Through Day 42						
	Noxafil		Voriconazole			
	Injecti	Injection and				
	Delayed-Release					
	Tab	lets				
Population	N	n (%)	N	n (%)	Difference* (95% CI)	
Intent to Treat	288	44 (15.3)	287	59 (20.6)	-5.3 (-11.6, 1.0)	
Proven/Probable Invasive Aspergillosis	163	31 (19.0)	171	32 (18.7)	0.3 (-8.2, 8.8)	
* Adjusted treatment difference based on Miettinen and Nurminen's method stratified by randomization						

factor (risk for mortality/poor outcome), using Cochran-Mantel-Haenszel weighting scheme. Global clinical response at Week 6 was assessed by a blinded, independent adjudication committee based upon prespecified clinical, radiologic, and mycologic criteria. In the subgroup of patients with proven or probable invasive aspergillosis per EORTC criteria, the global clinical response of success (complete or partial response) at Week 6 was seen in 44.8% for Noxafil-treated patients compared to 45.6% for voriconazole-treated patients (see **Table 22**).

Table 22: Noxafil Injection and Noxafil Delayed-Release Tablets Invasive

Aspergillosis Treatment Study	: Succes	ssful Globa	l Clinical	Response ³	^k at Week 6
	Posad	Posaconazole Voriconazole			
pulation	N	Success	N	Success	Difference [†] (95% CI)
oven/Probable Invasive Aspergillosis	163	73 (44.8)	171	78 (45.6)	-0.6 (-11.2, 10.1)
Successful Global Clinical Response wa Adjusted treatment difference based or factor (risk for mortality/poor outcome)	Miettin	en and Nur	minen's r	nethod stra	atified by randomization
2 Prophylaxis of Aspergillus and Ca	<i>ndida</i> In	fections w	ith Noxa	il Oral Sus	pension

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

The first study (Noxafil Oral Suspension Study 1) was a randomized, double-blind trial that compared Noxafil 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 een the 2 treatment groups (80 days, Noxafil oral suspension; 77 days, fluconazole). **Table 23** contains the results from Noxafil Oral Suspension Study 1.

Table 23: 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):

Noxafil Oral Suspension Study 1

	Posaconazole n=301		Fluconazole n=299				
On therapy plus 7 days							
Clinical Failure*	50 (17%)		55 (18%)				
Failure due to:	Failure due to:						
Proven/Probable IFI	7 (2%)		22 (7%)				
(Aspergillus)		3 (1%)		17 (6%)			
(Candida)		1 (<1%)		3 (1%)			
(Other)		3 (1%)		2 (1%)			
All Deaths Proven/probable fungal infection prior to death		2 (<1%)	24 (8%)	6 (2%)			
SAF†	27 (9%)		25 (8%)				
Through 16 weeks							
Clinical Failure*,‡	99 (33%)		110 (37%)				
Failure due to:							
Proven/Probable IFI	16 (5%)		27 (9%)				
(Aspergillus)		7 (2%)		21 (7%)			
(Candida)		4 (1%)		4 (1%)			
(Other)		5 (2%)		2 (1%)			
All Deaths Proven/probable fungal infection prior to death		10 (3%)	59 (20%)	16 (5%)			
SAF†	26 (9%)		30 (10%)				
Event free lost to follow-up§	24 (8%)		30 (10%)				
* Patients may have met more that Use of systemic antifungal the usage >4 consecutive days). ‡ 95% confidence interval (posace of the patients)	erapy (SAF) criterion is onazole-fluconazole) = (-1	based or 1.5%, +3.7	%).				
§ Patients who are lost to follow-	up (not observed for 112 c	iaysį, and	who did not meet anothe	ir cimicai			

The second study (Noxafil Oral Suspension Study 2) was a randomized, open-label study that compared Noxafil 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 Noxafil 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 24** contains the results from Noxafil Oral Suspension Study 2.

failure endpoint. These patients were considered failures.

Table 24: Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients

	Posaconazole n=304	Fluconazole/Itraconazole n=298
	On therapy plus 7 days	
Clinical Failure*,†	82 (27%)	126 (42%)
Failure due to:		
Proven/Probable IFI	7 (2%)	25 (8%)
(Aspergillus)	2 (1%)	20 (7%)
(Candida)	3 (1%)	2 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	17 (6%)	25 (8%)
Proven/probable fungal infection prior to death	1 (<1%)	2 (1%)
SAF [‡]	67 (22%)	98 (33%)
Clinical Failure†	Through 100 days postrandomizatio 158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(Aspergillus)	2 (1%)	26 (9%)
(Candida)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	44 (14%)	64 (21%)
Proven/probable fungal infection prior to death	2 (1%)	16 (5%)
SAF‡	98 (32%)	125 (42%)
Event free lost to follow-up§	34 (11%)	24 (8%)
† Patients may have met more tha	onazole-fluconazole/itraconazole) = on one criterion defining failure. erapy (SAF) criterion is based o	

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 Noxafil oral suspension As seen in the accompanying tables (**Tables 23 and 24**), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Noxafi Oral Suspension Study 1 (**Table 23**), the clinical failure rate of posaconazole (33%) was similar to fluconazole (37%),

Study 2 (**Table 24**) 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 posaconazolecomparator -22.9% to -7.8%). All-cause mortality was similar at 16 weeks for both treatment arms in Noxafil Oral Suspension Study 1 [POS 58/301 (19%) vs. FLU 59/299 (20%)]; all-cause mortality was lower at 100 days for Noxafil-treated patients in Noxafil Oral Suspension Study 2 [POS 44/304 (14%) vs. FLU/ITZ 64/298 (21%)]. Both studies demonstrated fewer breakthrough infections caused by Aspergillus species in patients

(95% CI for the difference posaconazole-comparator -11.5% to 3.7%) while in Noxafil Oral Suspension

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

receiving Noxafil prophylaxis when compared to patients receiving fluconazole or itraconazole.

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 25). The majority of the subjects had C alhicans as the has Clinical success at Day 14 (complete or partial resolution of all ulcers and/or plagues 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 25**).

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 25).

Table 25: Noxafil Oral Suspension Clinical Success, Mycological Eradication, and Relapse Rates in Oropharyngeal Candidiasis Noxafil 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%) ycological 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 (Noxafil 68.0%, onazole 68.1%). The clinical significance of this finding is unknown. 14.4 Noxafil Oral Suspension Treatment of Oropharyngeal Candidiasis Refractory to Treatment

with Fluconazole or Itraconazole
Noxafil Oral Suspension Study 4 was a noncomparative study of Noxafil 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 Noxafil. 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 Noxafil oral suspension 400 mg twice daily for 3 days, followed by 400 mg once daily 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 Noxafil 400 mg twice daily for 28 days. The efficacy of Noxafil 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). HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied Posaconazole Delayed-Release Tablets

Posaconazole delayed-release tablets are available as yellow, coated, oblong, debossed with "100" on one side containing 100 mg of posaconazole. Bottles with child-resistant closures of 60 delayed-release tablets (NDC 0254-2045-02). Posaconazole Oral Suspension

Posaconazole oral suspension is available as a white, cherry-flavored suspension in 4-ounce (123 mL) amber glass bottles with child-resistant closures (NDC 0254-1016-36) 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. 16.2 Storage and Handling

Posaconazole Delayed-Release Tablets Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Posaconazole Oral Suspension

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 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). Important Administration Instructions

Posaconazole Delayed-Release Tablets Advise patients that Posaconazole delayed-release tablets must be swallowed whole and not

Advise patients to inform their physician immediately if they:

or increase the plasma concentrations of posaconazole.

develop severe diarrhea or vomiting.

Drug Interactions

divided, crushed, or chewed. Instruct 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 Posaconazole Oral Suspension Advise patients to take each dose of Posaconazole 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 Posaconazole oral suspension should be administered with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in order to enhance absorption. Instruct patients that if they miss a dose, they should take it as soon as they remember. However if it is almost time for 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

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

• are currently taking drugs that are known to prolong the QTc interval and are metabolized

Serious and Potentially Serious Adverse Reactions

Advise patients 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 proarrhythm

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, Manufactured for: Par Pharmaceutical, Chestnut Ridge, NY 10977, USA

Delayed-Release Tablets: Manuf. by: N. V. Organon, Kloosterstraat 6, 5349 AB Oss, Netherlands Oral Suspension: Manuf. by: Patheon Inc., Whitby, Ontario, Canada L1N5Z5 The trademarks referenced herein are owned by their respective companies. uspi-gmk5592-mf-2205r005 OS1016-01-78-02