NOXAFIL- posaconazole suspension
NOXAFIL- posaconazole tablet, coated
NOXAFIL- posaconazole solution
NOXAFIL- posaconazole powder, for suspension
Merck Sharp & Dohme LLC

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

NOXAFIL® (posaconazole) injection, for intravenous use
NOXAFIL® (posaconazole) delayed-release tablets, for oral use
NOXAFIL® (posaconazole) oral suspension
NOXAFIL® POWDERMIX (posaconazole) for delayed-release oral suspension
Initial U.S. Approval: 2006

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2)	1/2026
Dosage and Administration (2)	1/2026

INDICATIONS AND USAGE

Noxafil is an azole antifungal indicated as follows:

- Noxafil is indicated for the treatment of invasive aspergillosis as follows: (1.1)
  - Noxafil injection: adults and pediatric patients 2 years of age and older who weigh 10 kg or greater
  - Noxafil delayed-release tablets: adults and pediatric patients 2 years of age and older who weigh greater than 40 kg
  - Noxafil PowderMix for delayed-release oral suspension: pediatric patients 2 years of age and older who weigh 10 kg to 40 kg
- Noxafil is indicated for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 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)
  - Noxafil injection: adults and pediatric patients 2 years of age and older who weigh 10 kg or greater.
  - Noxafil delayed-release tablets: adults and pediatric patients 2 years of age and older who weigh greater than 40 kg
  - Noxafil oral suspension: adults and pediatric patients 13 years of age and older
  - Noxafil PowderMix for delayed-release oral suspension: pediatric patients 2 years of age and older who weigh 10 kg to 40 kg
- Noxafil oral suspension is indicated for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory (rOPC) to itraconazole and/or fluconazole in adults and pediatric patients 13 years of age and older (1.3)

DOSAGE AND ADMINISTRATION

- Noxafil formulations are supplied in different dose strengths of posaconazole, are approved for different indications, age groups, and weights, have different dosages and duration of therapy; and have different preparation and administration instructions. (2.1)
- Noxafil oral suspension is not substitutable with Noxafil delayed-release tablets or 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. (2.1, 2.2, 2.3)
- Noxafil injection must be administered through an in-line filter. (2.6)
- Administer Noxafil injection by intravenous infusion over approximately 90 minutes via a central venous line. (2.1, 2.6)
- Do NOT administer Noxafil injection as an intravenous bolus injection. (2.1)
- Administer Noxafil delayed-release tablets with or without food. (2.1)
- Administer Noxafil oral suspension with a full meal. (2.1)

- Administer Noxafil PowderMix for delayed-release oral suspension with food. (2.1)
- Administer Noxafil PowderMix for delayed-release oral suspension with the provided notched tip syringes only. (2.1)
- See the full prescribing information for important administration instructions and preparation instructions for Noxafil (injection, delayed-release tablets, and oral suspension) and Noxafil PowderMix delayed-release oral suspension (2.5, 2.6, 2.7, 2.8, 2.9, 2.10)

- For adult and pediatric patients aged 2 years of age and older, see the Full Prescribing Information for dosing recommendations for Noxafil injection, Noxafil delayed-release tablets, Noxafil oral suspension, and/or Noxafil PowderMix for delayed-release oral suspension based on the indication, age, and weight associated with the dosage form (1.1, 1.2, 1.3, 2.1, 2.2, 2.3, 2.4)

DOSAGE FORMS AND STRENGTHS

- Noxafil injection: 300 mg per vial (18 mg per mL) in a single-dose vial (3)
- Noxafil delayed-release tablet: 100 mg (3)
- Noxafil oral suspension: 40 mg per mL (3)
- Noxafil PowderMix for delayed-release oral suspension: 300 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to posaconazole or other azole antifungal agents. (4.1)
- Coadministration of Noxafil with the following drugs is contraindicated; Noxafil increases concentrations and toxicities of:
  - Sirolimus (4.2, 7.2)
  - CYP3A4 substrates (pimozide, quinidine): can result in QTc interval prolongation and cases of torsades de pointes (TdP) (4.3, 5.2, 7.2)
  - HMG-CoA Reductase Inhibitors Primarily Metabolized through CYP3A4 (4.4, 7.2)
  - Ergot alkaloids (4.5, 7.2)
  - Venetoclax: In patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) at initiation and during the ramp-up phase (4.6, 5.11, 7.2)
- Noxafil PowderMix for delayed-release oral suspension is contraindicated in patients with known or suspected Hereditary Fructose Intolerance (HFI). (4.7, 5.9, 8.4)

WARNINGS AND PRECAUTIONS

- Calcineurin-Inhibitor Toxicity: Noxafil increases concentrations of cyclosporine or tacrolimus; reduce dose of cyclosporine and tacrolimus and monitor concentrations frequently. (5.1)
- Arrhythmias and QTc Prolongation: Noxafil has been shown to prolong the QTc interval and cause cases of TdP. Administer with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs known to prolong QTc interval and metabolized through CYP3A4. (5.2, 7.2)
- Electrolyte Disturbances: Monitor and correct, especially those involving potassium (K^+), magnesium (Mg^{++}), and calcium (Ca^{++}), before and during Noxafil therapy. (5.3)
- Pseudoaldosteronism: Manifested by the onset or worsening of hypertension, and abnormal laboratory findings. Monitor blood pressure and potassium levels, and manage as necessary. (5.4)
- 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. (5.5)
- Renal Impairment: Noxafil injection should be avoided in patients with moderate or severe renal impairment (eGFR less than 50 mL/min/1.73 m^2), unless an assessment of the benefit/risk to the patient justifies the use of Noxafil injection. (5.6, 8.6)
- Concomitant Use with Midazolam: Noxafil can prolong hypnotic/sedative effects. Monitor patients and benzodiazepine receptor antagonists should be available. (5.7, 7.2)
- Vincristine Toxicity: Concomitant administration of azole antifungals, including Noxafil, with vincristine has been associated with neurotoxicity and other serious adverse reactions; reserve azole antifungals, including Noxafil, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options. (5.8, 7.2)
- Risk in Patients with Hereditary Fructose Intolerance (HFI): Noxafil PowderMix for delayed-release oral suspension contains sorbitol. Risk of metabolic crisis with life-threatening hypoglycemia, hypophosphatemia, lactic acidosis, and hepatic failure. Obtain history of HFI symptoms in pediatric patients before Noxafil PowderMix for delayed-release oral suspension administration. (5.9, 8.4)
- Breakthrough Fungal Infections: Monitor patients with severe diarrhea or vomiting when receiving Noxafil delayed-release tablets, Noxafil oral suspension, and Noxafil PowderMix for delayed-release oral suspension. (5.10)
- Venetoclax Toxicity: Concomitant administration of Noxafil with venetoclax may increase venetoclax toxicities, including the risk of tumor lysis syndrome, neutropenia, and serious infections; monitor for

toxicity and reduce venetoclax dose. (4.6, 5.11, 7.2)

ADVERSE REACTIONS

- Adult Patients: Common adverse reactions in studies with Noxafil in adults are diarrhea, nausea, fever, vomiting, headache, coughing, and hypokalemia. (6.1)
- Pediatric Patients: Common adverse reactions (incidence >20% receiving 6 mg/kg Noxafil injection and Noxafil PowderMix for delayed-release oral suspension) in a study in pediatric patients are pyrexia, febrile neutropenia, vomiting, mucosal inflammation, pruritus, hypertension, hypokalemia, and stomatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch .

DRUG INTERACTIONS

Interaction Drug	*Interaction*
Rifabutin, phenytoin, efavirenz, cimetidine, esomeprazole*	*Avoid coadministration unless the benefit outweighs the risks (7.1, 7.2)*
Other drugs metabolized by CYP3A4	*Consider dosage adjustment and monitor for adverse effects and toxicity (7.2)*
Digoxin	*Monitor digoxin plasma concentrations (7.2)*
Fosamprenavir, metoclopramide*	*Monitor for breakthrough fungal infections (7.1)*

* The drug interactions with esomeprazole and metoclopramide do not apply to Noxafil tablets or Noxafil PowderMix *(7.3, 12.3).*

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Pediatrics: Safety and effectiveness in patients younger than 2 years of age have not been established. (8.4)
- Severe Renal Impairment: Monitor closely for breakthrough fungal infections. (8.6)

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

Revised: 1/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Invasive Aspergillosis

Noxafil is indicated for the treatment of invasive aspergillosis as follows:

- **Noxafil injection:** adults and pediatric patients 2 years of age and older who weigh 10 kg or greater
- **Noxafil delayed-release tablets:** adults and pediatric patients 2 years of age and older who weigh greater than 40 kg
- **Noxafil PowderMix for delayed-release oral suspension:** pediatric patients 2 years of age and older who weigh 10 to 40 kg

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

Noxafil is indicated for the prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 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:

- **Noxafil injection:** adults and pediatric patients 2 years of age and older who weigh 10 kg or greater
- **Noxafil delayed-release tablets:** adults and pediatric patients 2 years of age and older who weigh greater than 40 kg
- **Noxafil oral suspension:** adults and pediatric patients 13 years of age and older
- **Noxafil PowderMix for delayed-release oral suspension:** pediatric patients 2 years of age and older who weigh 10 kg to 40 kg

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

Noxafil oral suspension is indicated for the treatment of oropharyngeal candidiasis, including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole in adults and pediatric patients 13 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Noxafil injection, Noxafil delayed-release tablets, Noxafil oral suspension and Noxafil PowderMix for delayed-release oral suspension are supplied in different dose strengths of posaconazole, are approved for different indications, age groups and weights; have different dosages and duration of therapy; and have different preparation and administration instructions.

Therefore, select the recommended dosage form based on the indication, age group, and weight and carefully follow the recommended dosage, preparation and administration instructions described for each product *[see Dosage and Administration (2.2 to 2.11)]*, and the following important administration instructions described below.

Non-substitutable

Noxafil oral suspension is not substitutable with Noxafil delayed-release tablets or 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)].*

Noxafil injection

- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC), by slow intravenous infusion over approximately 90 minutes *[see Dosage and Administration (2.6)]*.
- Do NOT administer Noxafil injection as an intravenous bolus injection.

Noxafil delayed-release tablets

- Swallow tablets whole. Do not divide, crush, or chew.
- Administer with or without food *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)]*.
- For patients who cannot eat a full meal, Noxafil delayed-release tablets should be used instead of Noxafil oral suspension for the prophylaxis indication. Noxafil delayed-release tablets generally provide higher plasma drug exposures than Noxafil oral suspension under both fed and fasted conditions *[see Dosage and Administration (2.8)]*.

Noxafil oral suspension

- 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 (2.8)].*

Noxafil PowderMix for delayed-release oral suspension

- Administer with food *[see Clinical Pharmacology (12.3)]*.

- To ensure delivery of the correct dose, ONLY the provided notched tip syringes must be used for preparation and administration. The design of the notched tip syringe prevents aggregation of the suspension during preparation and administration *[see Dosage and Administration (2.10)]*.

2.2 Recommended Dosage of Noxafil in Adult Patients

The recommended dosage of Noxafil (injection, delayed-release tablets, and oral suspension) in adult patients for the treatment of invasive aspergillosis, prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, or for the treatment of oropharyngeal candidiasis (OPC) is shown in Table 1 *[see Dosage and Administration (2.5, 2.6, 2.7,2.8, 2.9) and Clinical Pharmacology (12.3)].*

Noxafil PowderMix for delayed-release oral suspension is not recommended for use in adults *[see Indications and Usage (1.1, 1.2)].*

Table 1: Recommended Dosage of Noxafil Injection, Noxafil Delayed-Release Tablets, and Noxafil Oral Suspension in Adult Patients

Dosage	Duration of Therapy
Treatment of Invasive Aspergillosis*	
Noxafil Injection: Loading dose: 300 mg Noxafil injection intravenously twice a day on the first day. Maintenance dose: 300 mg Noxafil injection intravenously once a day, starting on the second day. **Noxafil 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.
Prophylaxis of Invasive *Aspergillus* and *Candida* Infections	
Noxafil Injection: Loading dose: 300 mg Noxafil injection intravenously twice a day on the first day. Maintenance dose: 300 mg Noxafil injection intravenously once a day thereafter. **Noxafil Delayed-Release Tablets:** Loading dose: 300 mg (three 100 mg delayed-release tablets) twice a day on the	Loading dose: 1 day Maintenance dose: Duration of therapy

first day. Maintenance dose: 300 mg (three 100 mg delayed-release tablets) once a day, starting on the second day. **Noxafil Oral Suspension:** 200 mg (5 mL) three times a day.	is based on recovery from neutropenia or immunosuppression
Oropharyngeal Candidiasis (OPC)	
Noxafil 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	
Noxafil 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.

* Switching between the Noxafil injection and delayed-release tablets is acceptable. A loading dose is not required when switching between dosage forms.

2.3 Recommended Dosage of Noxafil for the Treatment of Invasive Aspergillosis and Prophylaxis of Invasive *Aspergillus* and *Candida* Infections in Pediatric Patients 2 Years of Age and Older

Noxafil injection and Noxafil delayed-release tablets

The recommended dosage of (1) Noxafil injection in pediatric patients 2 years of age and older who weigh 10 kg or greater, and (2) Noxafil delayed-release tablets in pediatric patients 2 years of age and older who weigh greater than 40 kg for the treatment of invasive aspergillosis and prophylaxis of invasive *Aspergillus and Candida* infections is shown in Table 2 *[see Dosage and Administration (2.5, 2.6, 2.7, 2.9) and Clinical Pharmacology (12.3)].*

Noxafil delayed-release tablets are not recommended for use in pediatric patients who weigh 40 kg or less because the recommended dosage cannot be achieved with this dosage form.

Table 2: Recommended Dosage of Noxafil Injection and Noxafil Delayed-Release Tablets for the Treatment of Invasive Aspergillosis* and Prophylaxis of Invasive Aspergillus and Candida Infections in Pediatric Patients (2 Years of Age and Older)

Recommended Pediatric Dosage by Formulation	Duration of Therapy
Noxafil Injection (patients weighing 10 kg or greater):	

Loading dose: 6 mg/kg up to a maximum of 300 mg twice daily on the first day Maintenance dose: 6 mg/kg up to a maximum of 300 mg once daily, starting on the second day. **Noxafil Delayed-Release Tablets (patients weighing greater than 40 kg):** 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.	Treatment of invasive aspergillosis: Recommended total duration of therapy is 6 to 12 weeks Prophylaxis of invasive *Aspergillus* and *Candida* infections: Duration of therapy is based on recovery from neutropenia or immunosuppression.

* Switching between the intravenous and delayed-release tablets is acceptable. A loading dose is not required when switching between formulations.

Noxafil Oral Suspension

The recommended dosage of Noxafil oral suspension in pediatric patients 13 years of age and older for the prophylaxis of invasive *Aspergillus and Candida* Infections is shown in Table 3.

Table 3: Recommended Dosage of Noxafil Oral Suspension for the Prophylaxis of Invasive Aspergillus and Candida Infections in Pediatric Patients (13 Years of Age and Older)

Recommended Pediatric Dosage of Noxafil Oral Suspension	Duration of Therapy
200 mg (5 mL) three times a day	Duration of therapy is based on recovery from neutropenia or immunosuppression.

Noxafil PowderMix

The recommended dosage of Noxafil PowderMix for delayed-release oral suspension in pediatric patients 2 years of age and older who weigh 10 kg to 40 kg, for the treatment of invasive aspergillosis, and the prophylaxis of invasive *Aspergillus* and *Candida* infections, is shown in Table 4 and Table 5. The dosing for these indications is the same, except for patients weighing 10 to less than 12 kg *[see Dosage and Administration (2.9, 2.10) and Clinical Pharmacology (12.3)].*

Noxafil PowderMix for delayed-release oral suspension is not recommended for use in

pediatric patients who weigh greater than 40 kg because the recommended dosage cannot be achieved with this dosage form.

Table 4: Recommended Dosage for Noxafil PowderMix for Delayed-Release Oral Suspension for the Treatment of Invasive Aspergillosis in Pediatric Patients (2 Years of Age and Older)

Weight (kg)	Recommended Pediatric Dosage of Noxafil PowderMix for Delayed-Release Oral Suspension	Duration of Therapy
10 to less than 17	Loading Dose: 120 mg (4 mL) twice daily on the first day Maintenance Dose: 120 mg (4 mL) once daily	Recommended total duration of therapy is 6 to 12 weeks.
17 to less than 21	Loading Dose: 150 mg (5 mL) twice daily on the first day Maintenance Dose: 150 mg (5 mL) once daily	
21 to less than 26	Loading Dose: 180 mg (6 mL) twice daily on the first day Maintenance Dose: 180 mg (6 mL) once daily	
26 to less than 36	Loading Dose: 210 mg (7 mL) twice daily on the first day Maintenance Dose: 210 mg (7 mL) once daily	
36 to 40	Loading Dose: 240 mg (8 mL) twice daily on the first day Maintenance Dose: 240 mg (8 mL) once daily	

Table 5: Recommended Dosage for Noxafil PowderMix for Delayed-Release Oral Suspension for the Prophylaxis of Invasive Aspergillus and Candida infections in Pediatric Patients (2 Years of Age and Older)

Weight	Recommended Pediatric Dosage of Noxafil	Duration of

(kg)	PowderMix for Delayed-Release Oral Suspension	Therapy
10 to less than 12	Loading Dose: 90 mg (3 mL) twice daily on the first day Maintenance Dose: 90 mg (3 mL) once daily	Duration of therapy is based on recovery from neutropenia or immunosuppression.
12 to less than 17	Loading Dose: 120 mg (4 mL) twice daily on the first day Maintenance Dose: 120 mg (4 mL) once daily	
17 to less than 21	Loading Dose: 150 mg (5 mL) twice daily on the first day Maintenance Dose: 150 mg (5 mL) once daily	
21 to less than 26	Loading Dose: 180 mg (6 mL) twice daily on the first day Maintenance Dose: 180 mg (6 mL) once daily	
26 to less than 36	Loading Dose: 210 mg (7 mL) twice daily on the first day Maintenance Dose: 210 mg (7 mL) once daily	
36 to 40	Loading Dose: 240 mg (8 mL) twice daily on the first day Maintenance Dose: 240 mg (8 mL) once daily	

2.4 Recommended Dosage of Noxafil Oral Suspension for the Treatment of Oropharyngeal Candidiasis in Pediatric Patients 13 Years of Age and Older

The recommended dosage of Noxafil oral suspension for the treatment of oropharyngeal candidiasis (OPC) and OPC refractory (rOPC) to itraconazole and/or fluconazole in pediatric patients 13 years of age and older is shown in Table 6.

The Noxafil injection, Noxafil delayed-release tablets, and Noxafil PowderMix for delayed-release oral suspension products are not approved for the treatment of oropharyngeal candidiasis in pediatric patients.

Table 6: Recommended Dosage of Noxafil Oral Suspension for the Treatment of OPC and rOPC in Pediatric Patients (13 Years of Age and Older)

Recommended Pediatric Dosage of Noxafil Oral Suspension	Duration of Therapy
Oropharyngeal Candidiasis (OPC)	
Loading Dose: 100 mg (2.5 mL) twice daily on the first day Maintenance Dose: 100 mg (2.5 mL) once daily	Loading dose: 1 day Maintenance dose: 13 days
OPC Refractory (rOPC) to Itraconazole and/or Fluconazole	
400 mg (10 mL) twice daily	Duration of therapy is based on the severity of the patient's underlying disease and clinical response.

2.5 Preparation of Noxafil Injection

Preparation of Noxafil Injection:

- Remove the vial of Noxafil injection from the refrigerator and allow to equilibrate to room temperature prior to use.
- To prepare the required dose, aseptically transfer one vial of Noxafil injection (containing 300 mg of posaconazole in 16.7 mL of solution) to an intravenous bag or bottle of one of the following compatible diluents to achieve a final posaconazole concentration between 1 mg/mL and 2 mg/mL:
  - 0.45% Sodium Chloride Injection
  - 0.9% Sodium Chloride Injection
  - 5% Dextrose Injection
  - 5% Dextrose and 0.45% Sodium Chloride Injection
  - 5% Dextrose and 0.9% Sodium Chloride Injection
  - 5% Dextrose and 20 mEq Potassium Chloride Injection

Use of other diluents is not recommended because they may result in particulate formation.

- Discard any unused Noxafil injection from the vial.
- Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit. Once admixed, the diluted Noxafil infusion solution ranges from colorless to yellow (variations of color within this range do not affect the quality of the product).
- Immediately use the diluted Noxafil infusion solution, once admixed. If not used immediately, refrigerate (2 to 8°C (36 to 46°F)) the diluted Noxafil infusion solution up

to 24 hours. Discard any unused portion.

Incompatible Diluents

Co-administration of drug products besides the infusion solutions or products stated above are not recommended because this may result in particulate formation. The following diluents were determined to be incompatible with Noxafil injection; thus, do **not** dilute Noxafil injection with them:

- Lactated Ringer's Injection
- Lactated Ringer's and 5% Dextrose Injection
- 4.2% Sodium Bicarbonate Injection

2.6 Administration of Diluted Noxafil Infusion Solution

See *Dosage and Administration (2.5)* for the preparation instructions for the diluted Noxafil Solution.

Important Administration Instructions for the Diluted Noxafil Infusion Solution

- Must administer diluted Noxafil Infusion Solution through a 0.22-micron polyethersulfone (PES) or polyvinylidene difluoride (PVDF) filter.
- Administer diluted Noxafil infusion solution via a central venous line, including a central venous catheter (CVC) or peripherally inserted central catheter (PICC), by slow intravenous infusion over approximately 90 minutes *[see Adverse Reactions (6.1)]*
- If a CVC or PICC are not available, may administer diluted Noxafil solution **once** through a peripheral venous catheter by intravenous infusion over approximately 30 minutes to bridge the period during which a CVC or PICC are replaced, inserted, or unavailable for use (e.g., the CVC is being used for intravenous treatment with another product). However, do not administer diluted Noxafil infusion solution more than once via peripheral venous catheter because in clinical trials, multiple peripheral infusions given through the same vein resulted in infusion site reactions *[see Adverse Reactions (6.1)].*
- When multiple dosing is required, the infusion should be done via a central venous line.

Additional Administration Instructions for the Diluted Noxafil Infusion Solution

- Administer diluted Noxafil infusion solution intravenously through the same intravenous line (or cannula) with the following compatible infusion solutions:
  - 0.45% Sodium Chloride Injection
  - 0.9% Sodium Chloride Injection
  - 5% Dextrose Injection
  - 5% Dextrose and 0.45% Sodium Chloride Injection
  - 5% Dextrose and 0.9% Sodium Chloride Injection
  - 5% Dextrose and 20 mEq potassium chloride Injection
- Administer diluted Noxafil infusion solution intravenously at the same time through the same intravenous line (or cannula) with the following intravenous drug products prepared in 5% Dextrose Injection or 0.9% Sodium Chloride Injection:
  - Amikacin Sulfate Injection
  - Caspofungin Acetate for Injection
  - Ciprofloxacin Injection
  - Daptomycin for Injection

- Dobutamine Injection
- Famotidine Injection
- Filgrastim Injection
- Gentamicin Injection
- Hydromorphone Hydrochloride Injection
- Levofloxacin Injection
- Lorazepam Injection
- Meropenem for Injection
- Micafungin for Injection
- Morphine Sulfate Injection
- Norepinephrine Bitartrate Injection
- Potassium Chloride Injection
- Vancomycin Hydrochloride for Injection

2.7 Administration Instructions for Noxafil Delayed-Release Tablets

- Swallow the Noxafil delayed-release tablets whole. Do not divide, crush, or chew.
- Administer Noxafil delayed-release tablets orally with or without food *[see Clinical Pharmacology (12.3)].*

2.8 Administration Instructions for Noxafil Oral Suspension

Administer Noxafil oral suspension 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.

For patients who cannot eat a full meal, use Noxafil delayed-release tablets instead of the Noxafil oral suspension for the prophylaxis of invasive *Aspergillus* and *Candida* infections in those who are at high risk of developing these infections due to being severely immunocompromised. This is because Noxafil delayed-release tablets provide higher plasma drug exposures than Noxafil oral suspension under fasted condition *[see Dosage and Administration (2.1)].*

For those patients using the Noxafil oral suspension:

- Shake Noxafil oral suspension well before use.
- Administer with measured dosing spoon provided in the package (see Figure 1).

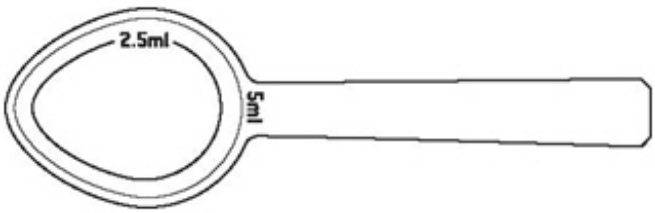


Figure 1: Measured dosing spoon provided in the package marked for doses of 2.5 mL and 5 mL.

- Administer each dose of Noxafil oral suspension during or immediately (i.e., within 20 minutes) following a full meal *[see Clinical Pharmacology (12.3)].*
- In patients who cannot eat a full meal and for whom Noxafil delayed-release tablets or Noxafil injection are not options, administer each dose of Noxafil oral suspension with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger

ale). If these patients cannot tolerate an oral nutritional supplement or an acidic carbonated beverage either use:
  - An alternative antifungal therapy, or
  - Noxafil oral suspension and closely monitor patients for breakthrough fungal infections.
- Rinse the spoon with water after each administration and before storage.

2.9 Non-substitutability between Noxafil Oral Suspension and Other Formulations

Noxafil oral suspension is not substitutable with Noxafil delayed-release tablets or 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)].*

2.10 Preparation and Administration Instructions for Noxafil PowderMix for Delayed-Release Oral Suspension

For details on preparation and administration of Noxafil PowderMix for delayed-release oral suspension, see Instructions for Use.

Preparation Instructions for Noxafil PowderMix for Delayed-Release Oral Suspension

- Do not open the Noxafil PowderMix packet until ready to prepare the drug.
- Remove cap from the mixing liquid and push the bottle adapter into the neck of the bottle. Once in place, the bottle adapter stays in the bottle.
- Remove 9 mL of mixing liquid using the provided **blue** syringe. Put the cap back on the bottle.**Only use the mixing liquid in the kit to prepare Noxafil PowderMix.**
- Using the provided mixing cup, combine 9 mL of mixing liquid and the entire contents of one packet in the Noxafil PowderMix kit and mix (containing 300 mg of posaconazole).
- Shake the mixing cup vigorously for 45 seconds to mix the powder and mixing liquid from the Noxafil PowderMix kit. The final concentration of the reconstituted Noxafil PowderMix delayed-release suspension is approximately 30 mg/mL of posaconazole. Check to make sure the powder is mixed (the mixture should look cloudy and free of clumps).
- Must use the reconstituted Noxafil PowderMix delayed-release suspension within 1 hour of reconstitution. Discard unused portion of the reconstituted Noxafil PowderMix delayed-release suspension.

Administration Instructions for Noxafil PowderMix Delayed-Release Reconstituted Suspension

- To ensure delivery of the correct reconstituted Noxafil PowderMix Delayed-release dose, **only** use the provided notched tip syringes for preparation and administration because its design reduces the risk of aggregation of the product during preparation and administration.
- Choose the correct syringe based on the prescribed Noxafil PowderMix dose:
  - Use 3 mL (**green**) notched tip syringe (provided with the kit) if dose is 3 mL or less.
  - Use 10 mL (**blue**) notched tip syringe (provided with the kit) if dose is more than 3 mL.

- Administer reconstituted Noxafil PowderMix suspension orally with food within 1 hour of reconstitution *[see Clinical Pharmacology (12.3)].*
- The maximum dose that can be accurately withdrawn from the mixing cup after reconstitution is 240 mg (8 mL).

Discarding Unused Reconstituted Noxafil PowderMix Suspension and Reuse of Syringes

- Not all the reconstituted Noxafil PowderMix suspension in the mixing cup will be used; there will be some left over in the mixing cup.
- Discard any remaining reconstituted Noxafil PowderMix suspension.
- The mixing cup may be hand washed and reused. Alternatively, the mixing cup may be discarded, and a similar mixing cup with a lid may be used for subsequent doses.
- The notched tip syringes may be hand washed and reused.

2.11 Dosage Modifications in Patients with Renal Impairment

The recommended dosage of Noxafil oral suspension, Noxafil delayed-release tablets, and Noxafil PowderMix for delayed-release oral suspension is the same in patients with renal impairment compared to those with normal renal function.

Avoid the use of Noxafil injection in patients with eGFR less than 50 mL/minute/1.73 m^2, unless an assessment of the benefit/risk to the patient justifies its use. If the decision is made to use Noxafil injection in patients with eGFR less than 50 mL/minute/1.73 m^2, closely monitor serum creatinine levels, and, if increases occur, consider changing to oral Noxafil therapy. The recommended dosage of Noxafil injection in patients with eGFR 50 to 90 mL/minute/1.73 m^2 is the same as those with normal renal function.

3 DOSAGE FORMS AND STRENGTHS

Noxafil injection

300 mg/16.7 mL (18 mg/mL) of posaconazole: Clear, colorless to yellow sterile liquid in a single-dose vial.

Noxafil Delayed-Release Tablets

100 mg of posaconazole: Yellow, coated, oblong tablets, debossed with "100" on one side.

Noxafil Oral Suspension

4,200 mg/105 mL (40 mg/mL) of posaconazole: White, cherry-flavored suspension in amber glass bottles with child-resistant closures.

Noxafil PowderMix for Delayed-Release Oral Suspension

300 mg: Off-white to yellowish powder for delayed-release oral suspension and a mixing liquid in a kit. The kit contains (1) Package A that contains single-use packets of Noxafil PowderMix, green notched tip syringes, blue notched tip syringes, mixing cups, mixing liquid bottle, and one bottle adapter for the mixing liquid bottle; and (2) Package B that contains green and blue notched tip syringes for additional supply *[see How Supplied/Storage and Handling (16.1)].*

4 CONTRAINDICATIONS

4.1 Hypersensitivity

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

4.2 Use with Sirolimus

Noxafil is contraindicated with sirolimus. Concomitant administration of Noxafil with sirolimus increases the sirolimus blood concentrations by approximately 9-fold and can result in sirolimus toxicity *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

4.3 QT Prolongation with Concomitant Use with CYP3A4 Substrates

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

4.4 HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 (e.g., atorvastatin, lovastatin, and simvastatin) is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

4.5 Use with Ergot Alkaloids

Noxafil may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism *[see Drug Interactions (7.2)]*.

4.6 Use with Venetoclax

Coadministration of Noxafil with venetoclax at initiation and during the ramp-up phase is 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 (5.11) and Drug Interactions (7.2)].*

4.7 Use of Noxafil PowderMix for Delayed-Release Oral Suspension in Patients with Hereditary Fructose Intolerance

Noxafil PowderMix for delayed-release oral suspension is contraindicated in patients with known or suspected hereditary fructose intolerance (HFI) *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Calcineurin-Inhibitor Toxicity

Concomitant administration of Noxafil with cyclosporine or tacrolimus increases the whole blood trough concentrations of these calcineurin-inhibitors *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*. Nephrotoxicity and leukoencephalopathy

(including deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine or tacrolimus concentrations. Frequent monitoring of tacrolimus or cyclosporine whole blood trough concentrations should be performed during and at discontinuation of Noxafil treatment and the tacrolimus or cyclosporine dose adjusted accordingly.

5.2 Arrhythmias and QT Prolongation

Some azoles, including Noxafil, 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 Noxafil.

Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval. Multiple, time-matched ECGs collected over a 12-hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18-85 years of age) administered 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 (n=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 increase ≥60 msec in their QTc(F) interval from baseline.

Noxafil should be administered with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4 *[see Contraindications (4.3) and Drug Interactions (7.2)]*.

5.3 Electrolyte Disturbances

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during Noxafil therapy.

5.4 Pseudoaldosteronism

Pseudoaldosteronism, manifested by the onset of hypertension or worsening of hypertension, and abnormal laboratory findings (hypokalemia, low serum renin and aldosterone, and elevated 11-deoxycortisol), has been reported with posaconazole use in the postmarket setting. Monitor blood pressure and potassium levels and manage as necessary. Management of pseudoaldosteronism may include discontinuation of Noxafil, substitution with an appropriate antifungal drug that is not associated with pseudoaldosteronism, or use of aldosterone receptor antagonists.

5.5 Hepatic Toxicity

Hepatic reactions (e.g., mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and/or clinical hepatitis) have been reported in clinical trials. The elevations in liver 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 Noxafil. These severe hepatic reactions were seen primarily in subjects receiving the Noxafil oral suspension 800 mg daily (400 mg twice daily or 200 mg four times a day) in clinical trials.

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

5.6 Renal Impairment

Due to the variability in exposure with Noxafil delayed-release tablets, Noxafil oral suspension, and Noxafil PowderMix for delayed-release oral suspension, patients with severe renal impairment should be monitored closely for breakthrough fungal infections *[see Dosage and Administration (2.11) and Use in Specific Populations (8.6)].*

Noxafil injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), unless an assessment of the benefit/risk to the patient justifies the use of Noxafil injection. In patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), receiving the Noxafil injection, accumulation of the intravenous vehicle, SBECD, is expected to occur. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral Noxafil therapy *[see Dosage and Administration (2.11) and Use in Specific Populations (8.6)]*.

5.7 Midazolam Toxicity

Concomitant administration of Noxafil with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Patients must be monitored closely for adverse effects associated with high plasma concentrations of midazolam and benzodiazepine receptor antagonists must be available to reverse these effects *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

5.8 Vincristine Toxicity

Concomitant administration of azole antifungals, including Noxafil, 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 Noxafil, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options *[see Drug Interactions (7.2)]*.

5.9 Risk in Patients with Hereditary Fructose Intolerance (HFI)

Noxafil PowderMix for delayed-release oral suspension contains sorbitol, an inactive ingredient, and may precipitate a metabolic crisis that may include, but is not limited to life-threatening hypoglycemia, hypophosphatemia, lactic acidosis, and hepatic failure in patients with HFI. Obtain careful history of HFI symptoms (nausea, vomiting, abdominal pain) with sorbitol/fructose/sucrose exposure prior to Noxafil PowderMix for delayed-

release oral suspension administration because a diagnosis of HFI may not yet be established in pediatric patients *[see Contraindications (4) and Use in Specific Populations (8.4)]*.

5.10 Breakthrough Fungal Infections

Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections when receiving Noxafil delayed-release tablets, Noxafil oral suspension, or Noxafil PowderMix for delayed-release oral suspension.

5.11 Venetoclax Toxicity

Concomitant administration of Noxafil, a strong CYP3A4 inhibitor, with venetoclax may increase venetoclax toxicities, including the risk of tumor lysis syndrome (TLS), neutropenia, and serious infections. In patients with CLL/SLL, administration of Noxafil 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.

For patients with acute myeloid leukemia (AML), dose reduction and safety monitoring are recommended across all dosing phases when coadministering Noxafil with venetoclax *[see Drug Interactions (7.2)].* Refer to the venetoclax prescribing information for dosing instructions.

6 ADVERSE REACTIONS

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

- Arrhythmias and QT Prolongation *[see Warnings and Precautions (5.2)]*
- Electrolyte Disturbances *[see Warnings and Precautions (5.3)]*
- Pseudoaldosteronism *[see Warnings and Precautions (5.4)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.5)]*

6.1 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.

Treatment of Invasive Aspergillosis in Adults and Adolescents (Noxafil injection and Noxafil Delayed-Release Tablets)

The safety of Noxafil injection and Noxafil delayed-release tablets 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 adult and pediatric patients 14 years of age and older (288 in the Noxafil group, 287 in voriconazole group (voriconazole for injection or voriconazole tablets)) with proven, probable or possible invasive aspergillosis were included. The median duration of treatment was 67 days for Noxafil injection or Noxafil delayed-release tablets and 64 days for voriconazole. In this study, 55% to 60% of patients started intravenous treatment with Noxafil (Noxafil injection) or voriconazole (voriconazole for injection). The median duration of the first instance of intravenous

treatment (before switching to oral treatment or discontinuing or completing study treatment) was 9 days for both groups. Table 7 presents adverse reactions reported at an incidence of ≥10% in either one of the treatment groups in the Aspergillosis Treatment Study.

Adverse reactions leading to treatment discontinuation were reported for 34% of patients. The most commonly reported adverse reactions (>2% of patients) leading to treatment discontinuation were septic shock, respiratory failure, and bronchopulmonary aspergillosis in the Noxafil group, and septic shock and acute myeloid leukemia in the voriconazole group. The most frequently reported adverse reactions in the Noxafil-treated group were pyrexia (28%), hypokalemia (28%), and nausea (23%).

Table 7: Adverse Reactions in at least 10% of Adults and Adolescents Receiving Noxafil Injection or Noxafil Delayed-Release Tablets for the Treatment of Invasive Aspergillosis

Adverse Reactions	Noxafil injection or Noxafil delayed-release tablets n=288 (%)	Voriconazole for injection or Voriconazole tablets n=287 (%)
Percentage of Patients Reporting any Adverse Reaction	97.6	97.6
Hypokalemia	28.5	17.1
Pyrexia	28.1	25.1
Nausea	22.6	17.8
Diarrhea	18.1	18.1
Vomiting	18.1	13.6
Alanine aminotransferase increased	14.6	12.9
Febrile neutropenia	14.6	13.2
Aspartate aminotransferase increased	13.2	12.5
Pneumonia	12.5	9.1
Headache	12.2	8.7
Constipation	11.1	8.0
Edema peripheral	11.1	8.4
Epistaxis	11.1	5.9
Cough	10.4	8.4
Abdominal pain	10.1	8.4
Hypomagnesemia	10.1	6.3

Clinical Trial Experience with Noxafil Injection for Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

Administration of multiple doses of Noxafil injection via a peripheral venous catheter were associated with thrombophlebitis (60% incidence). Therefore, in subsequent studies, Noxafil injection was administered via central venous catheter *[see Dosage and Administration (2.6)].*

The safety of Noxafil injection has been assessed in 268 patients in a clinical trial. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of Noxafil injection when given as antifungal prophylaxis (Noxafil Injection Study). Patients were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 55% male, had a mean age of 51 years (range: 18-82 years, 19% of patients were ≥65 years of age), and were 95% White and 8% Hispanic. In this study, 10 patients received a single dose of 200 mg Noxafil injection, 21 patients received 200 mg daily dosage for a median of 14 days, and 237 patients received 300 mg daily dosage for a median of 9 days (the 200 mg dosage is not a recommended dosage for prophylaxis of invasive *Aspergillus* and *Candida* infections in adults *[see Dosage and Administration (2.2)].* In the 300 mg daily dosage group each patient received a loading intravenous dose of Noxafil injection 300 mg twice on Day 1, then intravenous Noxafil injection therapy, and finally Noxafil oral suspension to complete 28 days of total Noxafil therapy.

Table 8 presents adverse reactions observed in patients treated with the Noxafil injection 300 mg daily dosage group in the Noxafil Injection Study.

The most frequently reported adverse reactions with an onset during the intravenous Noxafil injection phase of dosing with 300 mg once daily were diarrhea (32%), hypokalemia (22%), pyrexia (21%), and nausea (19%). These adverse reactions were consistent with those seen in studies with Noxafil oral suspension.

Table 8: Adverse Reactions in at least 10% of Adults Receiving Noxafil Injection for the Prophylaxis of Invasive Aspergillus and Candida infections

Adverse Reactions	**Noxafil Injection Treatment Phase n=237[*] (%)**	**Noxafil Injection Treatment Phase or Subsequent Noxafil Oral Suspension Treatment Phase n=237[†] (%)**
Percentage of Patients Reporting any Adverse Reaction	93	99
Diarrhea	32	39
Hypokalemia	22	28
Pyrexia	21	31
Nausea	19	30
Rash	15	24
Headache	14	21

Epistaxis	14	17
Abdominal Pain	13	17
Chills	12	16
Edema Peripheral	12	15
Vomiting	12	19
Hypomagnesemia	11	13
Decreased appetite	10	12
Cough	9	13
Constipation	8	13
Fatigue	8	10
Hypertension	8	11
Petechiae	8	10
Anemia	7	10
Dyspnea	7	10
Thrombocytopenia	7	11
Abdominal Pain Upper	6	11

* Adverse reactions reported in patients with an onset during the Noxafil intravenous dosing phase of the study.

† Adverse reactions reported with an onset at any time during the study in patients who were treated for up to 28 days of Noxafil therapy.

Clinical Trial Experience with Noxafil Delayed-Release Tablets for Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

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. Noxafil delayed-release tablets were given for a median duration of 28 days. In this study, 20 adult patients received 200 mg daily dosage (this is not a recommended dosage *[see Dosage and Administration (2.2)]*) and 210 adult patients received 300 mg daily dosage (following twice daily dosing on Day 1 in each cohort). Table 9 presents adverse reactions (incidence of ≥ 10%) observed in patients treated with the Noxafil delayed-release tablets 300 mg daily dosage in the Noxafil Delayed-Release Tablet Study.

The most frequently reported adverse reactions (>25%) in patients treated 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 tablets 300 mg once daily was nausea (2%).

Table 9: Adverse Reactions in at least 10% of Adults Receiving Noxafil Delayed-Release Tablets (300 mg Daily Dosage) for the Prophylaxis of Invasive Aspergillus and Candida infections

	Noxafil delayed-

Adverse Reactions	release tablet (300 mg) n=210 (%)
Percentage of Patients Reporting any Adverse Reaction	99
Diarrhea	29
Pyrexia	28
Nausea	27
Hypokalemia	22
Cough	17
Edema Peripheral	16
Rash	16
Epistaxis	14
Headache	14
Mucosal Inflammation	14
Thrombocytopenia	14
Vomiting	13
Abdominal Pain	11
Hypertension	11
Anemia	10
Asthenia	10
Chills	10
Constipation	10
Hypomagnesemia	10

Clinical Trials Safety Experience with Noxafil Oral Suspension

The safety of Noxafil oral suspension has been assessed in 1,844 patients, including:

- 605 patients in the active-controlled studies for the prophylaxis of invasive *Aspergillus* and *Candida* infections
- 557 patients in the active-controlled OPC studies (not refractory to itraconazole or fluconazole)
- 239 patients in refractory OPC studies (refractory to itraconazole or fluconazole) (rOPC), and
- 443 patients in other patient populations

These studies included 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, 14% Black, 16% Hispanic. Noxafil oral suspension therapy was given to 171 patients for ≥6 months, including 58 patients who received Noxafil oral suspension therapy for ≥12 months. Table 10 presents adverse reactions observed at an incidence of >10% in the studies for prophylaxis of invasive *Aspergillus* and *Candida* infections. Table 11 presents adverse reactions observed at an incidence of at least 10% in the OPC/rOPC studies.

Prophylaxis of Invasive *Aspergillus* and *Candida* Infections (Noxafil oral suspension)

In the two randomized, comparative studies for prophylaxis of invasive *Aspergillus* and *Candida* infections in those at high risk of developing these infections due to being severely immunocompromised (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 immunocompromised patients. The most frequently reported adverse reactions (>30%) in these trials were fever, diarrhea, and nausea. The most common adverse reactions leading to discontinuation of Noxafil oral suspension were GI adverse reactions, specifically, nausea (2%), vomiting (2%), and increased hepatic enzymes (2%).

Table 10: Adverse Reactions in at least 10% of Patients Receiving Noxafil Oral Suspension for the Prophylaxis of Invasive Aspergillus and Candida Infections

Adverse Reactions	Noxafil Oral Suspension n=605 (%)	Fluconazole n=539 (%)	Itraconazole n=58 (%)
Percentage of Patients Reporting any Adverse Reaction	98	99	100
Fever	45	47	55
Diarrhea	42	39	60
Nausea	38	37	52
Hypokalemia	30	26	52
Thrombocytopenia	29	27	34
Vomiting	29	32	41
Headache	28	26	40
Abdominal Pain	27	27	36
Anemia	25	23	28
Coughing	24	24	24
Neutropenia	23	23	40
Constipation	21	17	17
Dyspnea	20	22	26
Rigors	20	16	29
Rash	19	18	43
Hypertension	18	16	5
Hypomagnesemia	18	16	19
Fatigue	17	18	9
Insomnia	17	17	19
Musculoskeletal Pain	16	15	16
Anorexia	15	17	28
Edema Legs	15	12	19
Epistaxis	14	14	21
Hypotension	14	15	17
Pharyngitis	12	11	21

Tachycardia	12	14	5
Arthralgia	11	12	9
Dizziness	11	10	9
Hyperglycemia	11	14	3
Petechiae	11	10	16
Pruritus	11	12	19
Back Pain	10	12	7
Bilirubinemia	10	9	19
Dyspepsia	10	9	10
Vaginal Hemorrhage*	10	9	12

* Percentages of sex-specific adverse reactions are based on the number of males/females.

Treatment of Nonrefractory OPC and Refractory OPC (Noxafil oral suspension)

In two randomized comparative studies for the treatment of nonrefractory OPC, the safety of Noxafil oral suspension (less than or equal to 400 mg once daily) in 557 HIV-infected patients was compared to the safety of fluconazole (100 mg once daily) in 262 HIV-infected patients.

An additional 239 HIV-infected patients with refractory OPC (rOPC) received Noxafil oral suspension in two non-comparative trials for rOPC. Of these patients, 149 received the 800 mg/day dosage and the remainder received the less than or equal to 400 mg once daily dosage.

In the nonrefractory OPC and rOPC studies, the most common adverse reactions in patients treated with Noxafil oral suspension were fever, diarrhea, nausea, headache, vomiting, and coughing.

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

Table 11: Adverse Reactions in at least 10% of Patients Receiving Noxafil Oral Suspension for the Treatment of Nonrefractory and Refractory OPC

Adverse Reactions	Controlled OPC Pool		Refractory OPC Pool
	Noxafil Oral Suspension	Fluconazole	Noxafil Oral Suspension
	n=557 (%)	n=262 (%)	n=239 (%)
Percentage of Patients that Reported any Adverse Reaction*	64	67	92
Diarrhea	10	13	29
Nausea	9	11	29

Headache	8	9	20
Vomiting	7	7	28
Fever	6	8	34
Abdominal Pain	5	6	18
Neutropenia	4	3	16
Coughing	3	4	25
Fatigue	3	5	13
Herpes Simplex	3	3	11
Pneumonia	3	2	10
Rash	3	4	15
Anemia	2	2	14
Anorexia	2	2	19
Asthenia	2	2	13
Sweating Increased	2	2	10
Candidiasis, Oral	1	<1	12
Dehydration	1	3	11
Dyspnea	1	3	12
Insomnia	1	1	16
Pain	1	1	11
Weight Decrease	1	<1	14
Rigors	<1	2	12

OPC=oropharyngeal candidiasis

* Based on patients reporting adverse reactions at least once during the study, without regard to relationship to treatment. Patients may have reported more than 1 adverse reaction.

Additional Adverse Reactions Reported in Less Than 5% of Noxafil-Treated Patients in Clinical Trials

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
- *Gastrointestinal disorders:* pancreatitis
- *Liver and Biliary System Disorders:* hepatic enzymes increased, hepatic function abnormal, hepatitis, hepatomegaly, jaundice
- *Renal & Urinary System Disorders:* renal failure acute

Liver Test Abnormalities in the Clinical Trials of Noxafil Oral Suspension

Liver Test Abnormalities in the Clinical Trials with Noxafil Oral Suspension for Prophylaxis of Invasive Aspergillus and Candida Infections

In the prophylaxis of invasive *Aspergillus* and *Candida* infections studies, the number and

percentage of patients with changes in liver tests from Common Toxicity Criteria (CTC) Grade 0, 1, or 2 at baseline to Grade 3 or 4 at the end of the studies is presented in Table 12**.**

Table 12: Changes in Liver Test Results from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4 in Prophylaxis of Invasive Aspergillus and Candida Infections Studies (Noxafil Oral Suspension Studies 1 and 2)

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

CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase;

ALT= Alanine Aminotransferase.

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

Liver Test Abnormalities in the Clinical Trials with Noxafil Oral Suspension for the Treatment of OPC

The number and percentage of patients treated for OPC with clinically significant liver test abnormalities at any time during the studies is provided in Table 13 (liver test abnormalities were present in some of these patients prior to initiation of the study drug).

Table 13: Clinically Significant Liver Test Abnormalities without Regard to Baseline Value (Noxafil Oral Suspension

Studies for the Treatment of OPC)

Laboratory Test	Nonrefractory OPC		Refractory OPC
	Noxafil Oral Suspension	Fluconazole	Noxafil Oral Suspension
	n=557 (%)	n=262 (%)	n=239 (%)
ALT > 3.0 x ULN	16/537 (3)	13/254 (5)	25/226 (11)
AST > 3.0 x ULN	33/537 (6)	26/254 (10)	39/223 (17)
Total Bilirubin > 1.5 x ULN	15/536 (3)	5/254 (2)	9/197 (5)
Alkaline Phosphatase > 3.0 x ULN	17/535 (3)	15/253 (6)	24/190 (13)

ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase.

Liver Test Abnormalities in the Clinical Trials with Noxafil Oral Suspension for the Treatment of Invasive Aspergillosis

The number and percentage of patients treated for invasive aspergillosis with clinically significant liver test abnormalities at any time during the Aspergillosis Treatment Study is provided in Table 14. Liver test abnormalities present prior to the initiation of study drug included: ALT (22% of the patients), AST (13% of the patients), and bilirubin (13% of the patients).

Table 14: Changes in Liver Test Results from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4 (Aspergillosis Treatment Study)

Number (%) of Patients with Change*		
Laboratory Parameter	**Noxafil n/N (%)**	**Voriconazole n/N (%)**
AST	22/281 (8)	21/285 (7)
ALT	29/281(10)	23/282 (8)
Bilirubin	26/280 (9)	25/284 (9)
Alkaline Phosphatase	12/282 (4)	20/284 (7)

N=Number of patients for a given laboratory test with a baseline value of CTC Grade 0, 1, or 2 and at least one post-baseline value.

CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase;

ALT= Alanine Aminotransferase.

* 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, where n represents the number of patients who met the criterion as indicated, and N represents the number of patients who had a baseline observation and at least one post-baseline observation.

In healthy volunteers and patients, elevation of liver test values did not appear to be associated with higher plasma posaconazole concentrations.

Clinical Trials in Pediatric Patients 2 Years of Age and Older

The safety of Noxafil injection and Noxafil PowderMix (for delayed-release oral suspension) for prophylaxis of invasive fungal infections was evaluated in an open-label uncontrolled dose-ranging pharmacokinetic and safety study of Noxafil injection and Noxafil PowderMix (Pediatric Study 1, NCT02452034). In this study, 115 immunocompromised pediatric patients 2 to less than 18 years of age with known or expected neutropenia initially received Noxafil injection (up to 6 mg/kg twice daily for the first day and then up to 6 mg/kg for at least 7 days), and then 63 patients were transitioned to Noxafil PowderMix (up to 6 mg/kg once daily). The mean overall treatment duration was 21 days including a mean duration of 14 days (range: 1 to 28 days) on Noxafil injection and a mean duration of 12 days (range: 2 to 18 days) on Noxafil PowderMix *[see Clinical Pharmacology (12.3)].* In this study, the reported adverse reaction profile of Noxafil injection and Noxafil PowderMix in pediatric patients was consistent with the safety profile of Noxafil in adults. The most common adverse reactions that occurred in greater than 20% of pediatric patients who received Noxafil injection and Noxafil PowderMix were pyrexia, febrile neutropenia, vomiting, mucosal inflammation, pruritus, hypertension, hypokalemia, and stomatitis.

The safety of Noxafil injection, Noxafil delayed-release tablets, and Noxafil PowderMix for delayed-release oral suspension for the treatment of invasive aspergillosis was evaluated in an open-label, non-comparative clinical study in 31 pediatric patients 2 to less than 18 years of age with a diagnosis of possible, probable, or proven invasive aspergillosis (Pediatric Study 2, NCT04218851). In this study, all 31 pediatric patients initially received Noxafil injection (6 mg/kg twice daily on the first day and then 6 mg/kg once daily) for the treatment of invasive aspergillosis; 12 patients were transitioned to Noxafil delayed-release tablets (300 mg once daily) if they weighed ≥40 kg, and 10 patients were transitioned to Noxafil PowderMix (based on weight) if they weighed 10 to 40 kg *[see Dosage and Administration (2.3)]*. The mean overall treatment duration was 50 days including 15 days (range: 2 to 78 days) on Noxafil injection, 54 days (range: 6 to 80 days) on Noxafil delayed-release tablets, and 44 days (range: 7 to 76 days) on Noxafil PowderMix. The reported adverse reaction profile of Noxafil injection, Noxafil delayed-release tablets, and Noxafil PowderMix in pediatric patients was consistent with the known safety profile of Noxafil in adults. The most common adverse reactions that occurred in greater than 20% of pediatric patients who received any of the three formulations of Noxafil were vomiting, pyrexia, abdominal pain, liver test abnormalities, and hypertension.

6.2 Postmarketing Experience

The following adverse reaction has been identified during the post-approval use of Noxafil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Endocrine Disorders: Pseudoaldosteronism

7 DRUG INTERACTIONS

Table 15 and Table 17 include drugs with clinically important drug interactions when administered concomitantly with Noxafil and Noxafil PowderMix and instructions for preventing or managing them. Table 16 includes important drug interactions specific to

the absorption of posaconazole administered as either Noxafil oral suspension or Noxafil PowderMix.

These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse reactions or loss of efficacy *[see Clinical Pharmacology (12.3)]*.

The following information was derived from data with Noxafil oral suspension or another posaconazole tablet formulation unless otherwise noted. All clinically important drug interactions with Noxafil oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility), are considered relevant to clinically important drug interactions with Noxafil injection, Noxafil delayed-release tablets, and Noxafil PowderMix for delayed-release oral suspension *[see Clinical Pharmacology (12.3)]*.

Consult the labeling of concomitantly used drugs to obtain further information about interactions with posaconazole.

7.1 Effects of Other Drugs on Noxafil and Noxafil PowderMix

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. Concomitant use of Noxafil with drugs that can decrease the plasma posaconazole concentrations should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections.

Table 15: Drug Interactions Affecting Noxafil and Noxafil PowderMix When Administered Concomitantly with Other Drugs

UDP-Glucuronidase Inducers		
Mechanism and Clinical Effect(s)	Posaconazole is a UDP-glucuronosyltransferase substrate. Concomitant use of Noxafil with UDP-glucuronidase inducers may decrease posaconazole exposure *[see Clinical Pharmacology (12.3)],* which may reduce the effectiveness of posaconazole.	
Prevention or Management	*Efavirenz*	Avoid concomitant use of posaconazole with efavirenz, unless the benefit outweighs the risks.
	Rifabutin	Avoid concomitant use of posaconazole with rifabutin unless the benefit to the patient outweighs the risk. If concomitant use is needed, monitor closely for breakthrough fungal infections. *See Table 17 for rifabutin monitoring considerations when posaconazole affects rifabutin via CYP3A4 inhibition.*
		Avoid concomitant use of posaconazole with phenytoin unless the benefit to the patient outweighs the

	Phenytoin	risk. If concomitant use is needed, monitor for breakthrough fungal infections. *See Table 17 for phenytoin monitoring considerations when posaconazole affects phenytoin via CYP3A4 inhibition.*
Fosamprenavir		
Mechanism and Clinical Effect(s)	Concomitant use of Noxafil with fosamprenavir may lead to decreased posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)],* which may reduce effectiveness of posaconazole.	
Prevention or Management	If concomitant use of posaconazole with fosamprenavir is needed, monitor closely for breakthrough fungal infections.	

Table 16: Drug Interactions Affecting Noxafil Oral Suspension and Noxafil PowderMix Absorption When Administered Concomitantly with Other Drugs

Noxafil Oral Suspension	
Cimetidine and Esomeprazole	
Mechanism and Clinical Effect(s)	Concomitant use of Noxafil oral suspension with cimetidine or esomeprazole resulted in decreased posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)],* which may reduce effectiveness of Noxafil.
Prevention or Management	Avoid concomitant use of Noxafil oral suspension with cimetidine or esomeprazole unless the benefit outweighs the risks. If concomitant use is needed, monitor closely for breakthrough fungal infections.
Metoclopramide	
Mechanism and Clinical Effect(s)	Concomitant use of Noxafil oral suspension with metoclopramide decreased posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)],* which may reduce effectiveness of Noxafil oral suspension.
Prevention or Management	If Noxafil oral suspension is concomitantly administered with metoclopramide, closely monitor for breakthrough fungal infections.
Noxafil Oral PowderMix	
Alcohol	
Mechanism and Clinical Effect(s)	Posaconazole releases faster from Noxafil PowderMix in the presence of alcohol, which may interfere with Noxafil PowderMix's delayed-release characteristics *[see Clinical Pharmacology (12.3)].*
Prevention or Management	Administration of Noxafil PowderMix with alcohol is not recommended.

7.2 Effects of Noxafil and Noxafil PowderMix on Other Drugs

Posaconazole is a strong CYP3A4 inhibitor. Therefore, concomitant use of Noxafil may increase plasma concentrations of drugs that are CYP3A4 substrates *[see Clinical Pharmacology (12.3)]*.

Table 17: Drug Interactions Affecting Drugs Administered Concomitantly with Noxafil and Noxafil PowderMix

Digoxin		
Clinical Effect(s)	Increased digoxin plasma concentrations have been reported in patients who received concomitant posaconazole and digoxin.	
Prevention or Management	Monitor digoxin plasma concentrations during concomitant use of posaconazole.	
Glipizide		
Clinical Effect(s)	No dosage modification of glipizide is needed when used concomitantly with Noxafil. However, glucose concentrations decrease in some patients concomitantly administered posaconazole and glipizide.	
Prevention or Management	Increase monitoring of glucose concentrations when used concomitantly.	
CYP3A Substrates		
Immunosuppressants that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Posaconazole is a strong CYP3A4 inhibitor. Therefore, plasma concentrations of CYP3A4 substrates may be increased by posaconazole use *[see Clinical Pharmacology (12.3)].*	
Prevention or Management	Sirolimus	Posaconazole is contraindicated with sirolimus *[see Clinical Pharmacology (12.3)]*.
	Tacrolimus	• At initiation of posaconazole treatment, reduce the tacrolimus dosage to approximately one-third of the original tacrolimus dosage. • Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dosage should be modified accordingly *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

	Cyclosporine	• At initiation of posaconazole treatment reduce the cyclosporine dosage to approximately three-fourths of the original dosage. • Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dosage should be modified accordingly *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.
CYP3A4 Substrates that Prolong QTc Interval		
Mechanism and Clinical Effect(s)	Concomitant use of posaconazole with CYP3A4 substrates such as pimozide and quinidine may result in increased plasma concentrations of the CYP3A4 substrates leading to QTc interval prolongation and torsades de pointes *[see Warnings and Precautions (5.2)].*	
Prevention or Management	Pimozide Quinidine	Concomitant use with posaconazole is contraindicated.
HMG-CoA Reductase Inhibitors (Statins) that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Concomitant use of posaconazole with simvastatin increased simvastatin plasma concentrations which can lead to rhabdomyolysis *[see Clinical Pharmacology (12.3)].*	
Prevention or Management	Atorvastatin, Lovastatin, Simvastatin	Concomitant use with posaconazole is contraindicated.
Benzodiazepines that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Concomitant use of posaconazole with midazolam increased midazolam plasma concentrations which could potentiate and prolong hypnotic and sedative effects *[see Clinical Pharmacology (12.3)]*.	
Prevention or Management	Midazolam, Alprazolam, Triazolam	Closely monitor for adverse reactions associated with high plasma concentrations of benzodiazepines that are CYP3A4 substrates during concomitant use, and a benzodiazepine receptor antagonist should be available to reverse effects *[see Warnings and Precautions (5.7)].*
Calcium Channel Blockers that are CYP3A4 Substrates		

Mechanism and Clinical Effect(s)	Posaconazole may increase the plasma concentrations of calcium channel blockers that are substrates of CYP3A4.	
Prevention or Management	Verapamil, Diltiazem, Nifedipine, Nicardipine, Felodipine	Monitor frequently for adverse reactions and toxicity with concomitant use of posaconazole with calcium channel blockers that are CYP3A4 substrates. Dosage reduction of the calcium channel blocker may be needed.
Anti-HIV Drugs that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Ritonavir and atazanavir are CYP3A4 substrates and posaconazole increased plasma concentrations of these drugs *[see Clinical Pharmacology (12.3)].*	
Prevention or Management	Ritonavir and Atazanavir	Monitor frequently for adverse reactions and toxicity of ritonavir and atazanavir during concomitant use.
Antineoplastic Drugs that are CYP3A4 Substrates		
Mechanism and Clinical Effect(s)	Posaconazole may increase plasma concentrations of oncology drugs that are CYP3A4 substrates, which may increase the risk of serious adverse reactions.	
Prevention or Management	Venetoclax	*CLL/SLL patients:* Concomitant use of posaconazole with venetoclax during initiation and ramp-up phase is contraindicated. *AML patients:* With concomitant use, venetoclax dosage reduction and safety monitoring is recommended across all dosing phases *[see Warnings and Precautions (5.11)]*.
	Vinca alkaloids (e.g., vincristine, vinblastine)	Reserve concomitant use for patients with no alternative antifungal treatment options *[see Warnings and Precautions (5.8)].*
Ergot Alkaloids		
Mechanism and Clinical Effect(s)	Most of the ergot alkaloids are CYP3A4 substrates. Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism.	
Prevention or Management	Ergotamine, Dihydroergotamine	Concomitant use with posaconazole is contraindicated.
Phenytoin		
Mechanism	Phenytoin is a CYP3A4 substrate. Concomitant use	

Mechanism and Clinical Effect(s)	of posaconazole with phenytoin increased phenytoin plasma concentrations *[see Clinical Pharmacology (12.3)].*
Prevention or Management	Avoid concomitant use of posaconazole with phenytoin unless the benefit outweighs the risk. frequently monitor phenytoin concentrations and consider a dosage reduction of phenytoin. *See Table 15 for additional monitoring considerations when phenytoin affects posaconazole via UDP-glucuronosyltransferase inhibition.*
Rifabutin	
Mechanism and Clinical Effect(s)	Rifabutin is a CYP3A4 substrate. Concomitant use of posaconazole with rifabutin increased rifabutin plasma concentrations *[see Clinical Pharmacology (12.3)].*
Prevention or Management	Avoid concomitant use of posaconazole with rifabutin unless the benefit outweighs the risk. Frequent monitoring of full blood counts and adverse reactions due to increased rifabutin plasma concentrations (e.g., uveitis, leukopenia) during concomitant use are recommended. *See Table 15 for additional monitoring considerations when rifabutin affects posaconazole via UDP-glucuronosyltransferase inhibition.*

7.3 Absence of Clinically Important Interaction with Noxafil and Noxafil PowderMix

Additional clinical studies demonstrated that no clinically important 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 drugs when coadministered with Noxafil 200 mg once daily.

No clinically relevant effects on the pharmacokinetics of Noxafil delayed-release tablets were observed during concomitant use with antacids, H_2-receptor antagonists and proton pump inhibitors, and metoclopramide *[see Clinical Pharmacology (12.3)]*. No dosage adjustment of Noxafil delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension is required during concomitant use with these drugs.

No clinically relevant effects on the pharmacokinetics of Noxafil oral suspension were observed during concomitant use with antacids, H_2-receptor antagonists (other than cimetidine), and loperamide *[see Clinical Pharmacology (12.3)]*. No dosage adjustment of Noxafil oral suspension is required during concomitant use with these drugs (other than cimetidine).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal data, Noxafil 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 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, doses of ≥ 3 times the clinical exposure caused an increase in resorptions *(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 populations 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 recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data: 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 healthy volunteers). The no-effect dose for malformations and maternal toxicity in rats was 9 mg/kg, which is 0.7 times the exposure achieved with the 400 mg twice daily oral suspension regimen. No malformations 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 no-effect dose was 20 mg/kg, while high doses of 40 mg/kg and 80 mg/kg (3 or 5 times the clinical exposure) caused an increase in resorptions. In rabbits dosed at 80 mg/kg, a reduction in body weight gain of females and a reduction in litter size were seen.

8.2 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 Noxafil and any potential adverse effects on the breastfed child from Noxafil or from the underlying maternal condition.

8.4 Pediatric Use

The three Noxafil dosage forms (injection, delayed-release tablets, oral suspension) and one Noxafil PowderMix (for delayed-release oral suspension) dosage form are different products; are approved for different pediatric indications, age groups, and weights; have different dosing regimens; and have different preparation and administration instructions. Therefore, select the recommended dosage form based on the pediatric indication, age group, and weight *[see Dosage and Administration (2.1)].*

Noxafil PowderMix for delayed-release oral suspension is contraindicated in patients with HFI. Because a diagnosis of HFI may not yet be established in pediatric patients, obtain a careful history of HFI symptoms with sorbitol/fructose/sucrose exposure prior to administration of Noxafil PowderMix *for delayed-release oral suspension [see Warnings and Precautions (5.9)].*

Treatment of Invasive Aspergillosis

The safety and effectiveness of Noxafil (injection and delayed-release tablets) have been established for the treatment of invasive aspergillosis in pediatric patients 2 years of age and older .

The safety and effectiveness of Noxafil PowderMix have been established for the treatment of invasive aspergillosis in pediatric patients 2 years of age and older who weigh 10 kg to 40 kg.

Use of Noxafil and Noxafil PowderMix for these pediatric indications is supported by evidence from adequate and well-controlled studies of Noxafil in adults and safety and pharmacokinetic (PK) data from two pediatric studies *[see Adverse Reactions (6.1)* and *Clinical Pharmacology (12.3)]*. The safety of Noxafil and Noxafil PowderMix in pediatric patients for these pediatric indications was consistent with the known safety profile of Noxafil in adults *[see Adverse Reactions (6.1)].*

Noxafil PowderMix for delayed-release oral suspension is not recommended for use in patients who weigh greater than 40 kg because the recommended dosage cannot be achieved with this dosage form.

The safety and effectiveness of Noxafil and Noxafil PowderMix have not been established in pediatric patients less than 2 years of age**.**

Prophylaxis of Invasive *Aspergillus* and *Candida* Infections

The safety and effectiveness of Noxafil (injection and delayed-release tablets) have been established for the prophylaxis of invasive *Aspergillus* and *Candida* infections in pediatric patients 2 years of age and older who are at high risk of developing these infections due to being severely immunocompromised.

The safety and effectiveness of Noxafil oral suspension have been established for the prophylaxis of invasive *Aspergillus* and *Candida* infections in pediatric patients 13 years of age and older who are at high risk of developing these infections due to being severely immunocompromised.

The safety and effectiveness of Noxafil PowderMix have been established for the prophylaxis of invasive *Aspergillus* and *Candida* infections in pediatric patients 2 years of age and older who weigh 10 kg to 40 kg who are at high risk of developing these infections due to being severely immunocompromised.

Use of Noxafil and Noxafil PowderMix for these pediatric indications is supported by adequate and well controlled studies of Noxafil in adults and pediatric patients aged 13 years of age and older and additional PK and safety data in pediatric patients 2 years of age and older *[see Clinical Pharmacology (12.3) and Clinical studies (14)*].

Noxafil PowderMix is not recommended for use in patients who weigh greater than 40 kg because the recommended dosage cannot be achieved with this dosage form.

The safety and effectiveness of Noxafil and Noxafil PowderMix have not been

established in pediatric patients less than 2 years of age.

Treatment of Oropharyngeal Candidiasis, including Refractory to Itraconazole and/or Fluconazole

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

Use of Noxafil oral suspension for this pediatric indication is supported by adequate and well controlled studies in adults and pediatric patients 13 years of age and older *[see Clinical studies (14.4)].*

The Noxafil injection, Noxafil delayed-release tablets, and Noxafil PowderMix products are not approved for the treatment of oropharyngeal candidiasis in pediatric patients. Noxafil Oral Suspension is the only dosage form approved for the treatment of OPC and rOPC in pediatric patients *[see Dosage and Administration (2.4)].*

The safety and effectiveness of Noxafil oral suspension for the treatment of OPC and rOPC have not been established in pediatric patients less than 13 years of age.

8.5 Geriatric Use

No overall differences in the safety or effectiveness of Noxafil injection, Noxafil delayed-release tablets, and Noxafil oral suspension have been observed between geriatric patients and younger adult patients in the clinical trials; therefore, the recommended dosage in geriatric patients is the same as that for younger adult patients. No clinically meaningful differences in posaconazole pharmacokinetics were observed in Noxafil-treated geriatric patients compared to Noxafil-treated younger adult patients during clinical trials *[see Clinical Pharmacology (12.3)]*.

- Of the 279 patients treated with Noxafil injection in the Noxafil Injection Study (prophylaxis of invasive *Aspergillus* and *Candida* infections in those at high risk of developing these infections due to being severely immunocompromised), 52 (19%) patients were >65 years of age.
- Of the 230 patients treated with Noxafil delayed-release tablets, 38 (17%) patients were >65 years of age.
- Of the 605 patients treated with Noxafil oral suspension in Noxafil Oral Suspension Study 1 and Study 2 (prophylaxis of invasive *Aspergillus* and *Candida* infections in those at high risk of developing these infections due to being severely immunocompromised), 63 (10%) patients were ≥65 years of age.
- In studies of Noxafil for an unapproved indication, 48 patients treated with Noxafil oral suspension (greater than or equal to 800 mg/day (eight times the maximum recommended maintenance dosage for the treatment of OPC)) were ≥65 years of age.
- Of the 288 patients treated with Noxafil injection or Noxafil delayed-release tablets in the Aspergillosis Treatment Study, 85 (29%) patients were ≥65 years of age.

8.6 Renal Impairment

Noxafil Oral Suspension and Noxafil Delayed-Release Tablets

No dosage adjustment is required for patients with eGFR 20 mL/minute/1.73 m^2 or higher.
Due to variability in posaconazole exposure, closely monitor patients with eGFR less than

Due to variability in posaconazole exposure, closely monitor patients with eGFR less than 20 mL/minute/1.73 m^2 for breakthrough fungal infections. *[see Clinical Pharmacology (12.3)]*.

Noxafil Injection

Avoid use of Noxafil injection in patients with eGFR less than 50 mL/minute/1.73 m^2 unless the benefit/risk to the patient justifies its use. The inactive ingredient in Noxafil injection, Betadex Sulfobutyl Ether Sodium (SBECD) is expected to accumulate in patients with reduced renal function. Safety and effectiveness of Noxafil injection have not been established in patients with less than 50 mL/minute/1.73 m^2.

If treatment with Noxafil injection is unavoidable in patients with eGFR less than 50 mL/minute/1.73 m^2, monitor serum creatinine levels. If serum creatinine increases, consider changing to oral Noxafil therapy.

8.7 Hepatic Impairment

No dosage adjustment is recommended for Noxafil oral suspension, Noxafil delayed-release tablets, Noxafil PowderMix for delayed-release oral suspension, and Noxafil injection in patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) *[see Clinical Pharmacology (12.3)]*.

However, a specific hepatic impairment study has not been conducted with the Noxafil delayed-release tablets, Noxafil PowderMix for delayed-release oral suspension, or Noxafil injection.

8.8 Sex

No adjustment in the dosage of Noxafil is necessary based on sex.

8.9 Race

No adjustment in the dosage of Noxafil is necessary based on race.

8.10 Weight

Pharmacokinetic modeling suggests that patients who weigh greater than 120 kg may have lower posaconazole plasma drug exposure. Therefore, consider closely monitoring for breakthrough fungal infections particularly when using Noxafil oral suspension in patients weighing greater than 120 kg *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no experience with overdosage of Noxafil injection and Noxafil delayed-release tablets.

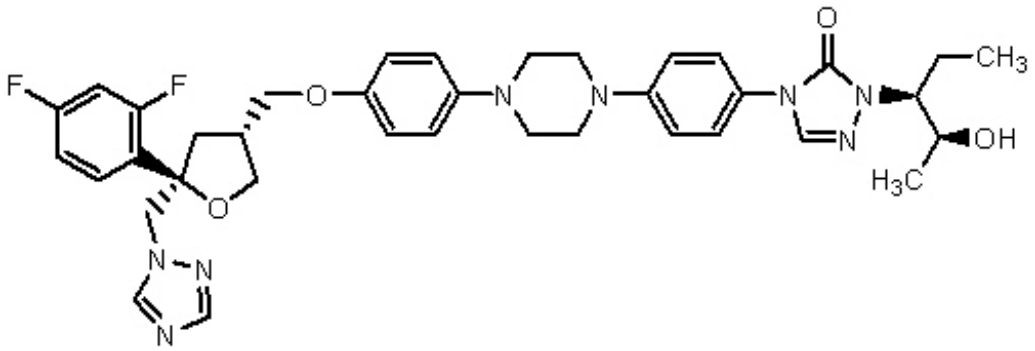
During the clinical trials, some patients received Noxafil oral suspension up to 1,600 mg/day with no adverse reactions noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg twice daily Noxafil oral suspension for 3 days. No related adverse reactions were noted by the investigator.

Posaconazole is not removed by hemodialysis.

11 DESCRIPTION

Noxafil and Noxafil PowderMix contain posaconazole, an azole antifungal agent.

Posaconazole is designated chemically as 4-[4-[4-[4-[[(3*R*,5*R*)-5- (2,4-difluorophenyl)tetrahydro-5- (1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1*S*,2*S*)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one with an empirical formula of $C_{37}H_{42}F_2N_8O_4$ and a molecular weight of 700.8. The chemical structure is:



Posaconazole is a white powder with a low aqueous solubility.

Noxafil (posaconazole) Injection

Noxafil injection, for intravenous use, is a clear colorless to yellow, without preservatives sterile liquid essentially free of foreign matter. Each vial contains 300 mg of posaconazole and the following inactive ingredients: 6.68 g Betadex Sulfobutyl Ether Sodium (SBECD), 0.0033 g edetate disodium, hydrochloric acid and sodium hydroxide to adjust the pH to 2.6, and water for injection.

Noxafil (posaconazole) Delayed-Release Tablets

Noxafil delayed-release tablet, for oral use, is yellow, coated, and oblong and contains 100 mg of posaconazole. Each delayed-release tablet contains the following inactive ingredients: 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.

Noxafil (posaconazole) Oral Suspension

Noxafil oral suspension is a white, cherry-flavored immediate-release suspension that contains 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.

Noxafil PowderMix (posaconazole) for Delayed-Release Oral Suspension

Noxafil PowderMix for delayed-release oral suspension is supplied as a component of a kit. Each kit contains Noxafil as an off-white to yellowish powder for delayed-release oral suspension, a bottle of mixing liquid, two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, and one bottle adapter for the mixing liquid bottle.

- Noxafil PowderMix for delayed-release oral suspension contains 300 mg of posaconazole and the following inactive ingredient: hypromellose acetate succinate.
- The mixing liquid contains: anhydrous citric acid, antifoam Af emulsion, berry citrus sweet flavor, carboxymethylcellulose sodium, carrageenan calcium sulfate trisodium phosphate, glycerin, methylparaben, microcrystalline cellulose, potassium sorbate, propylparaben, purified water, sodium citrate, sodium phosphate monobasic monohydrate, sodium saccharin, sorbitol solution, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Exposure Response Relationship: Prophylaxis of invasive *Aspergillus* and *Candida* Infections in Adults Who Are at High Risk of Developing These Infections Due to Being Severely Immunocompromised

In clinical studies of neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) or hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD), a wide range of plasma posaconazole exposures 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 18). A lower Cavg may be associated with an increased risk of treatment failure, defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive fungal infections.

Table 18: 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‡ (%)
Quartile 1	90-322	54.7	22-557	44.4
Quartile 2	322-490	37.0	557-915	20.6
Quartile 3	490-734	46.8	915-1563	17.5
Quartile 4	734-2200	27.8	1563-3650	17.5

Cavg = the average posaconazole concentration when measured at steady state

* Neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS

† HSCT recipients with GVHD

‡ Defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive fungal infections

Exposure Response Relationship: Treatment of Invasive Aspergillosis in Adult and Adolescent Patients:

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 adult and pediatric patients aged 14 years and older treated for invasive 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 a range of population pharmacokinetic model-predicted steady-state plasma average concentrations (Cavg, range: 589 to 6315 ng/mL), there was no association between posaconazole Cavg and treatment efficacy.

12.3 Pharmacokinetics

General Pharmacokinetic Characteristics

General Pharmacokinetic Characteristics of Noxafil Injection

Noxafil injection exhibits dose proportional pharmacokinetics after single doses between 200 and 300 mg in healthy volunteers and patients. The mean pharmacokinetic parameters after single doses with Noxafil injection in healthy volunteers and patients are shown in Table 19.

Table 19: Summary of Mean Pharmacokinetic Parameters (%CV) in Healthy Volunteers (30 minute infusion via peripheral venous line) and Patients (90 minute infusion via central venous line) after Dosing with Noxafil Injection on Day 1

	Dose (mg)	n	$AUC_{0-\infty}$ (ng·hr/mL)	AUC_{0-12} (ng·hr/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	CL (L/hr)
Healthy Volunteers	200	9	35400 (50)	8840 (20)	2250 (29)	23.6 (23)	6.5 (32)
	300	9	46400 (26)	13000 (13)	2840 (30)	24.6 (20)	6.9 (27)
Patients	200	30	N/D	5570 (32)	954 (44)	N/D	N/D
	300	22	N/D	8240 (26)	1590 (62)	N/D	N/D

$AUC_{0-\infty}$ = Area under the plasma concentration-time curve from time zero to infinity; AUC_{0-12} = Area under the plasma concentration-time curve from time zero to 12 hr after the first dose on Day 1; C_{max} = maximum observed concentration; $t_{½}$ = terminal phase half-life; CL = total body clearance; N/D = Not Determined

Table 20 displays the pharmacokinetic parameters of posaconazole in patients following administration of Noxafil injection 300 mg taken once a day for 10 or 14 days following twice daily dosing on Day 1.

Table 20: Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Patients Following Dosing of Noxafil

Injection (300 mg)*

Day	N	C_{max} (ng/mL)	T_{max}† (hr)	AUC_{0-24} (ng*hr/mL)	Cav (ng/mL)	C_{min} (ng/mL)
10/14	49	3280 (74)	1.5 (0.98-4.0)	36100 (35)	1500 (35)	1090 (44)

AUC_{0-24} = area under the concentration-time curve over the dosing interval (i.e., 24 hours); Cav= time-averaged concentrations (i.e., AUC_{0-24h}/24hr);
C_{min} = POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; C_{max} = observed maximum plasma concentration; CV = coefficient of variation, expressed as a percent (%); Day = study day on treatment; T_{max} = time of observed maximum plasma concentration.

* 300 mg dose administered over 90 minutes once a day following twice daily dosing on Day 1
† Median (minimum-maximum)

General Pharmacokinetic Characteristics of Noxafil Delayed-Release Tablets

Noxafil delayed-release tablets exhibit dose proportional pharmacokinetics after single and multiple dosing up to 300 mg. The mean pharmacokinetic parameters of posaconazole at steady state following administration of Noxafil delayed-release tablets 300 mg twice daily on Day 1, then 300 mg once daily thereafter in healthy volunteers and in neutropenic patients who are receiving cytotoxic chemotherapy for AML or MDS or HSCT recipients with GVHD are shown in Table 21.

Table 21: Arithmetic Mean (%CV) of Steady State PK Parameters in Healthy Volunteers and Patients Following Administration of Noxafil Delayed-Release Tablets (300 mg)*

	N	$AUC_{0-24\ hr}$ (ng·hr/mL)	Cav† (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max}‡ (hr)	$t_{1/2}$ (hr)	CL/F (L/hr)
Healthy Volunteers	12	51618 (25)	2151 (25)	2764 (21)	1785 (29)	4 (3-6)	31 (40)	7.5 (26)
Patients	50	37900 (42)	1580 (42)	2090 (38)	1310 (50)	4 (1.3-8.3)	-	9.39 (45)

CV = coefficient of variation expressed as a percentage (%CV); AUC_{0-T} = Area under the plasma concentration-time curve from time zero to 24 hr; C_{max} = maximum observed concentration; C_{min} = minimum observed plasma concentration; T_{max} = time of maximum observed concentration; $t_{½}$ = 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., $AUC_{0-24\ hr/24\ hr}$)
‡ Median (minimum-maximum)

General Pharmacokinetic Characteristics of Noxafil 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 concentrations (Cavg) and steady-state pharmacokinetic parameters in patients following administration of 200 mg three times a day and 400 mg twice daily of the oral suspension are provided in Table 22.

Table 22: 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*	Cavg (ng/mL)	AUC† (ng·hr/mL)	CL/F (L/hr)	V/F (L)	$t_{½}$ (hr)
200 mg three times a day‡ (n=252)	1103 (67) [21.5-3650]	ND§	ND§	ND§	ND§
200 mg three times a day¶ (n=215)	583 (65) [89.7-2200]	15,900 (62) [4100-56,100]	51.2 (54) [10.7-146]	2425 (39) [828-5702]	37.2 (39) [19.1-148]
400 mg twice daily# (n=23)	723 (86) [6.70-2256]	9093 (80) [1564-26,794]	76.1 (78) [14.9-256]	3088 (84) [407-13,140]	31.7 (42) [12.4-67.3]

Cavg = the average posaconazole concentration when measured at steady state

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

* Oral suspension administration
† $AUC_{(0\text{-}24\ hr)}$ for 200 mg three times a day and $AUC_{(0\text{-}12\ hr)}$ for 400 mg twice daily
‡ HSCT recipients with GVHD
§ Not done
¶ Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes
# Febrile neutropenic patients or patients with refractory invasive fungal infections, Cavg n=24

Absorption:

Absorption of Noxafil 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 are increased 16% and 51%, respectively, when given with a high fat meal compared to a fasted state (see Table 23).

Table 23: Statistical Comparison of Plasma Pharmacokinetics of Posaconazole Following Single Oral Dose Administration of 300 mg Noxafil Delayed-Release Tablet to Healthy Subjects under Fasting and Fed Conditions

	Fasting Conditions		Fed Conditions (High 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)
$AUC_{0\text{-}72hr}$ (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

GMR=Geometric least-squares mean ratio; CI=Confidence interval
* 48.5 g fat
† Median (Min, Max) reported for T_{max}

Absorption of Noxafil PowderMix for Delayed-Release Oral Suspension

The absolute bioavailability of the Noxafil PowderMix for delayed-release oral suspension is approximately 70-80%. The effect of food on the pharmacokinetics of the Noxafil PowderMix for delayed-release oral suspension has not been determined.

Absorption of Noxafil 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 C_{max} of posaconazole are approximately 3 times higher when administered with a liquid nutritional supplement (14 gm fat) relative to the fasted state (see Table 24). 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 25.

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

nutritional supplement or an acidic carbonated beverage (e.g., ginger ale).

Table 24: The Mean (%CV) [min-max] Posaconazole Pharmacokinetic Parameters Following Single-Dose Noxafil Oral Suspension Administration of 200 mg and 400 mg Under Fed and Fasted Conditions

Dose (mg)	C_{max} (ng/mL)	T_{max}* (hr)	AUC (I) (ng·hr/mL)	CL/F (L/hr)	$t_{½}$ (hr)
200 mg fasted (n=20)†	132 (50) [45-267]	3.50 [1.5-36‡]	4179 (31) [2705-7269]	51 (25) [28-74]	23.5 (25) [15.3-33.7]
200 mg nonfat (n=20)†	378 (43) [131-834]	4 [3-5]	10,753 (35) [4579-17,092]	21 (39) [12-44]	22.2 (18) [17.4-28.7]
200 mg high fat (54 gm fat) (n=20)†	512 (34) [241-1016]	5 [4-5]	15,059 (26) [10,341-24,476]	14 (24) [8.2-19]	23.0 (19) [17.2-33.4]
400 mg fasted (n=23)§	121 (75) [27-366]	4 [2-12]	5258 (48) [2834-9567]	91 (40) [42-141]	27.3 (26) [16.8-38.9]
400 mg with liquid nutritional supplement (14 gm fat) (n=23)§	355 (43) [145-720]	5 [4-8]	11,295 (40) [3865-20,592]	43 (56) [19-103]	26.0 (19) [18.2-35.0]

* Median [min-max].
† n=15 for AUC (I), CL/F, and $t_{½}$
‡ 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 $t_{½}$

Table 25: The Effect of Varying Gastric Administration Conditions on the C_{max} and AUC of Noxafil Oral Suspension in Healthy Volunteers*

Study Description	Administration Arms	Change in C_{max} (ratio estimate†; 90% CI of the ratio estimate)	Change in AUC (ratio estimate†; 90% CI of the ratio estimate)
400 mg single dose with a high-fat meal relative to fasted state (n=12)	5 minutes before high-fat meal	↑96% (1.96; 1.48-2.59)	↑111% (2.11; 1.60-2.78)
	During high-fat meal	↑339% (4.39; 3.32-5.80)	↑382% (4.82; 3.66-6.35)
	20 minutes	↑333%	↑387%

	after high-fat meal	(4.33; 3.28-5.73)	(4.87; 3.70-6.42)
400 mg twice daily and 200 mg four times daily for 7 days in fasted state and with liquid nutritional supplement (BOOST®) (n=12)	400 mg twice daily with BOOST	↑65% (1.65; 1.29-2.11)	↑66% (1.66; 1.30-2.13)
	200 mg four times daily with BOOST	No Effect	No Effect
Divided daily dose from 400 mg twice daily to 200 mg four times daily for 7 days regardless of fasted conditions or with BOOST (n=12)	Fasted state	↑136% (2.36; 1.84-3.02)	↑161% (2.61; 2.04-3.35)
	With BOOST	↑137% (2.37; 1.86-3.04)	↑157% (2.57; 2.00-3.30)
400 mg single dose with carbonated acidic beverage (ginger ale) and/or proton pump inhibitor (esomeprazole) (n=12)	Ginger ale	↑92% (1.92; 1.51-2.44)	↑70% (1.70; 1.43-2.03)
	Esomeprazole	↓32% (0.68; 0.53-0.86)	↓30% (0.70; 0.59-0.83)
400 mg single dose with a prokinetic agent (metoclopramide 10 mg three times a day for 2 days) + BOOST or an antikinetic agent (loperamide 4 mg single dose) + BOOST (n=12)	With metoclopramide + BOOST	↓21% (0.79; 0.72-0.87)	↓19% (0.81; 0.72-0.91)
	With loperamide + BOOST	↓3% (0.97; 0.88-1.07)	↑11% (1.11; 0.99-1.25)
400 mg single dose either orally with BOOST or via an NG tube with BOOST (n=16)	Via NG tube‡	↓19% (0.81; 0.71-0.91)	↓23% (0.77; 0.69-0.86)

* In 5 subjects, the C_{max} and AUC decreased substantially (range: -27% to -53% and -33% to -51%, respectively) when Noxafil was administered via an NG tube compared to when Noxafil was administered orally. It is recommended to closely monitor patients for breakthrough fungal infections when Noxafil is administered via an NG tube because a lower plasma exposure may be associated with an increased risk of treatment failure.

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

‡ NG = nasogastric

Distribution:

The mean volume of distribution of posaconazole after intravenous solution

administration was 261 L and ranged from 226-295 L between studies and dose levels.

Posaconazole is highly bound to human plasma proteins (>98%), predominantly to albumin.

Metabolism:

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

In vitro studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4.

Excretion:

Following 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).

Noxafil injection is eliminated with a mean terminal half-life ($t_{½}$) of 27 hours and a total body clearance (CL) of 7.3 L/h.

Noxafil delayed-release tablet is eliminated with a mean half-life ($t_{½}$) ranging between 26 to 31 hours.

Noxafil oral suspension is eliminated with a mean half-life ($t_{½}$) 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).

Patients with Renal Impairment:

After Noxafil oral administration, there were no significant differences in the posaconazole pharmacokinetics in patients with eGFR 20 mL/minute/1.73 m^2 or higher compared to those with eGFR >80 mL/minute/1.73 m^2. Although the mean posaconazole plasma exposure (AUC) was similar in patients with eGFR less than 20 mL/minute/1.73 m^2 treated with Noxafil oral suspension to those with eGFR >80 mL/minute/1.73 m^2 treated with Noxafil oral suspension, the range of the AUC estimates was highly variable (CV=96%) in patients with eGFR less than 20 mL/minute/1.73 m^2 compared to those with eGFR >80 mL/minute/1.73 m^2 (CV<40%).Similar posaconazole pharmacokinetic results are expected after administration of Noxafil delayed-release tablets *[see Use in Specific Populations (8.6)].*

Patients with 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 *[see Use in Specific Populations (8.7)].*

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 *[see Use in Specific Populations (8.9)]*.

Patients Weighing More Than 120 kg:

Weight has a clinically significant effect on posaconazole clearance. Relative to 70 kg patients, the Cavg is decreased by 25% in patients greater than 120 kg. Patients administered Noxafil weighing more than 120 kg may be at higher risk for lower posaconazole plasma concentrations compared to lower weight patients *[see Use in Specific Populations (8.10)]*.

Pediatric Patients:

Prophylaxis of invasive Aspergillus and Candida infections in pediatric patients 2 years of age and older: A total of 12 patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) of Noxafil oral suspension for prophylaxis of invasive fungal infections. Based on pharmacokinetic data in 10 of these pediatric patients, the mean steady-state Cav was similar between these patients and adults (≥18 years of age). In a study of 136 neutropenic pediatric patients 11 months to less than 18 years treated with Noxafil oral suspension, the exposure target of steady-state posaconazole Cavg between 500 ng/mL and less than 2500 ng/mL was attained in approximately 50% of patients instead of the pre-specified 90% of patients.

The mean pharmacokinetic parameters after multiple-dose administration of Noxafil injection and Noxafil PowderMix for delayed-release oral suspension in neutropenic pediatric patients 2 to less than 18 years of age (Pediatric Study 1) are shown in Table 26. Patients were enrolled into 2 age groups and received Noxafil injection and Noxafil PowderMix for delayed-release oral suspension doses at 6 mg/kg (0.6 to 1 times the recommended dose) with a maximum 300 mg dose once daily (twice daily on Day 1) *[see Adverse Reactions (6.1)]*.

Table 26: Summary of Steady-State Geometric Mean Pharmacokinetic Parameters (% Geometric CV) After Multiple Dosing with Noxafil Injection and Noxafil PowderMix for Delayed-Release Oral Suspension 6 mg/kg* in Pediatric Patients with Neutropenia or Expected Neutropenia

Age Group	Dose Type	N	$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	Cav† (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max}‡ (hr)	CL/F§ (L/hr)
2 to <7 years	IV	17	31100 (48.9)	1300 (48.9)	3060 (54.1)	626 (104.8)	1.75 (1.57-1.83)	3.27 (49.3)
	PFS	7	23000	960	1510	542	4.00 (2.17	4.60

			(47.3)	(47.3)	(43.4)	(68.8)	(2.17-7.92)	(35.2)
7 to 17 years	IV	24	44200 (41.5)	1840 (41.5)	3340 (39.4)	1160 (60.4)	1.77 (1.33-6.00)	4.76 (55.7)
	PFS	12	25000 (184.3)	1040 (184.3)	1370 (178.5)	713 (300.6)	2.78 (0.00-4.00)	8.39 (190.3)

IV= Noxafil injection; PFS= Noxafil PowderMix for delayed-release oral suspension; AUC_{0-24} = Area under the plasma concentration-time curve from time zero to 24 hr; C_{max} = maximum observed concentration; C_{min} = minimum observed plasma concentration; T_{max} = time of maximum observed concentration; CL/F = apparent total body clearance

* 0.6 to 1 times the recommended dose
† Cav = time-averaged concentrations (i.e., $AUC_{0-24\ hr/24\ hr}$)
‡ Median (minimum-maximum)
§ Clearance (CL for IV and CL/F for PFS)

Based on a population pharmacokinetic model evaluating posaconazole pharmacokinetics and predicting exposures in pediatric patients, the exposure of steady-state posaconazole average concentration greater than or equal to 700 ng/mL in approximately 90% of patients is attained with the recommended dose of Noxafil injection and Noxafil PowderMix for delayed-release oral suspension.

The population pharmacokinetic analysis of posaconazole in pediatric patients from Pediatric Study 1 suggests that age, sex, renal impairment and ethnicity have no clinically meaningful effect on the pharmacokinetics of posaconazole.

Treatment of invasive aspergillosis in pediatric patients 2 years of age and older: A total of 31 patients 2 to less than 18 years of age (body weight of ≥12 kg) received pediatric dosing based on body weight of Noxafil delayed-release tablets, Noxafil Injection, and Noxafil PowderMix for delayed-release oral suspension *[see Dosage and Administration (2.3].*

The mean population pharmacokinetic model parameters after multiple dose administration of Noxafil delayed-release tablets, Noxafil Injection, and Noxafil PowderMix for delayed-release oral suspension in pediatric patients 2 to less than 18 years of age for the treatment of invasive aspergillosis (Pediatric Study 2) are shown in Table 27. *[see Adverse Reactions (6.1)]*.

Table 27: Summary of Steady-State Geometric Mean Pharmacokinetic Parameters* (% Geometric CV) After Multiple Dosing with Noxafil Injection, Noxafil PowderMix for Delayed-Release Oral Suspension, and Noxafil Delayed-Release Tablets in Pediatric Patients being Treated for Invasive Aspergillosis

Age Group	Dose Type	N†	AUC_{0-24} hours (ng·hr/mL)	C_{av}‡ (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max}§ (hr)	CL/F¶ (L/hr)
2 to	IV	9					1.50	

2 to <12 years	IV	9	61900 (49.8)	2580 (49.8)	3630 (30.8)	1710 (82.2)	1.50 (1.25-1.77)	2.56 (47.8)
	PFS	6	45200 (30.2)	1880 (30.2)	2220 (26.5)	1370 (41.8)	7.00 (6.40-7.20)	3.25 (34.6)
12 to <18 years	IV	13	60800 (35.6)	2530 (35.6)	3510 (26.8)	1740 (48.5)	1.50 (1.30-1.63)	4.41 (41.8)
	Tablet	10	47800 (52.7)	1990 (52.7)	2250 (48.3)	1580 (62.6)	7.15 (6.70-7.30)	6.27 (52.7)

IV = Noxafil injection; PFS = Noxafil PowderMix for delayed-release oral suspension; Tablet = Noxafil delayed-release tablets; $AUC_{0\text{-}24\ hours}$ = Area under the plasma concentration-time curve from time zero to 24 hr; C_{max} = maximum observed concentration; C_{min} = minimum observed plasma concentration; T_{max} = time of maximum observed concentration; CL/F = apparent total body clearance

* Parameter estimates reported only for N>2 (excludes a single patient ≥2 to <12 receiving tablet and 2 patients ≥12 to <18 years receiving PFS)
† Some patients had 2 values (1 for IV dosing and 1 for oral dosing)
‡ Cav = time-averaged concentrations (i.e., $AUC_{0\text{-}24\ hours}$/24hr)
§ Median (minimum-maximum)
¶ Clearance (CL for IV and CL/F for PFS or Tablet)

The population pharmacokinetic analysis of posaconazole in pediatric patients, including Pediatric Study 2, suggests that age, sex, ethnicity, and disease status have no clinically meaningful effect on the pharmacokinetics of posaconazole

Drug Interaction Studies:

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 another tablet formulation, which affect posaconazole concentrations, is provided in Table 28.

Table 29 and Table 30 include a summary of the drug effects of concomitant medications that may impact the absorption of posaconazole when administered as either the oral suspension or delayed-release tablets.

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 31 *[see Contraindications (4)* and *Drug Interactions (7.2) including recommendations]*.

Effects of Other Drugs on Noxafil and Noxafil PowderMix:

Table 28: Summary of the Effects of Coadministered Drugs on Noxafil in Healthy Volunteers

Coadministered Drug (Postulated Mechanism of Interaction)	Coadministered Drug Dose/Schedule	Noxafil Dose/Schedule	Effect on Bioavailability of Posaconazole	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)
Efavirenz (UDP-G Induction)	400 mg 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 × 10 days	200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily × 8 Days	↓21% 0.79 (0.71-0.89)	↓23% 0.77 (0.68-0.87)
Rifabutin (UDP-G Induction)	300 mg once daily × 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 × 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_{max} or AUC.
† The tablet refers to a non-commercial tablet formulation without polymer.

Noxafil Oral Suspension: Concomitant administration of Noxafil oral suspension with drugs affecting gastric pH or gastric motility results in lower posaconazole exposure. (see Table 29.)

Table 29: The Effects of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Noxafil Oral Suspension in Healthy Volunteers

Coadministered Drug			Effect on Bioavailability of Posaconazole	
			Change in Mean C_{max} (ratio estimate*;	Change in Mean AUC (ratio estimate*; 90% CI of

(Postulated Mechanism of Interaction)	Coadministered Drug Dose/Schedule	Noxafil Dose/Schedule	90% CI of the ratio estimate)	90% CI 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)

* Ratio Estimate is the ratio of coadministered drug plus Noxafil to coadministered drug alone for C_{max} or AUC.
† The tablet refers to a non-commercial tablet formulation without polymer.
‡ The drug interactions associated with the oral suspension are also relevant for the delayed-release tablet with the exception of Esomeprazole and Metoclopramide.

Noxafil Delayed-Release Tablets: 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 (see Table 30).

Table 30: The Effects of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Noxafil Delayed-Release Tablets in Healthy Volunteers

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

gastric motility)	days (Day -1 and 1)	0.73,1.02)	0.803,1.07)

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

Noxafil PowderMix for Delayed-Release Oral Suspension: Concomitant administration of Noxafil PowderMix for delayed-release oral suspension with drugs affecting gastric pH or gastric motility would not be expected to demonstrate any significant effects on posaconazole pharmacokinetic exposure based on similarity to the delayed-release tablets.

An *in vitro* dissolution study was conducted to evaluate the impact of alcohol (5, 10, 20, and 40%) on the dissolution of Noxafil PowderMix delayed-release oral suspension. The study showed alcohol-induced dose-dumping potential with the Noxafil PowderMix delayed-release oral suspension *[see Drug Interactions (7.1)]*.

Effects of Noxafil and Noxafil PowderMix on Other Drugs:

Table 31: Summary of the Effects of Noxafil on Coadministered Drugs in Healthy Adult Volunteers and Patients

Coadministered Drug (Postulated Mechanism of Interaction is Inhibition of CYP3A4 by posaconazole)	**Coadministered Drug Dose/Schedule**	**Noxafil Dose/ Schedule**	**Effect on Bioavailability of Coadministered Drugs**	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	**Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)**
Sirolimus	2-mg single oral dose	400 mg (oral suspension) twice daily x 16 days	↑ 572% (6.72; 5.62-8.03)	↑ 788% (8.88; 7.26-10.9)
Cyclosporine	Stable maintenance dose in heart transplant recipients	200 mg (tablets) once daily x 10 days†	↑ Cyclosporine whole blood trough concentrations Cyclosporine dose reductions of up to 29% were required	
Tacrolimus	0.05-mg/kg single oral dose	400 mg (oral suspension) twice daily x 7 days	↑ 121% (2.21; 2.01-2.42)	↑ 358% (4.58; 4.03-5.19)
			Simvastatin ↑ 841%	Simvastatin ↑ 931%

Simvastatin	40-mg single oral dose	100 mg (oral suspension) once daily x 13 days	(9.41, 7.13-12.44) Simvastatin Acid ↑ 817% (9.17, 7.36-11.43)	↑ 931% (10.31, 8.40-12.67) Simvastatin Acid ↑634% (7.34, 5.82-9.25)
		200 mg (oral suspension) once daily x 13 days	Simvastatin ↑ 1041% (11.41, 7.99-16.29) Simvastatin Acid ↑851% (9.51, 8.15-11.10)	Simvastatin ↑ 960% (10.60, 8.63-13.02) Simvastatin Acid ↑ 748% (8.48, 7.04-10.23)
Midazolam	0.4-mg single intravenous dose‡	200 mg (oral suspension) twice daily x 7 days	↑ 30% (1.3; 1.13-1.48)	↑ 362% (4.62; 4.02-5.3)
	0.4-mg single intravenous dose‡	400 mg (oral suspension) twice daily x 7 days	↑62% (1.62; 1.41-1.86)	↑524% (6.24; 5.43-7.16)
	2-mg single oral dose‡	200 mg (oral suspension) once daily x 7 days	↑ 169% (2.69; 2.46-2.93)	↑ 470% (5.70; 4.82-6.74)
	2-mg single oral dose‡	400 mg (oral suspension) twice daily x 7 days	↑ 138% (2.38; 2.13-2.66)	↑ 397% (4.97; 4.46-5.54)
Rifabutin	300 mg once daily x 17 days	200 mg (tablets) once daily x 10 days†	↑ 31% (1.31; 1.10-1.57)	↑ 72% (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)
		400 mg (oral	↑ 49%	↑ 80%

Ritonavir	100 mg once daily x 14 days	(oral suspension) twice daily x 7 days	↑ 49% (1.49; 1.04-2.15)	↑ 80% (1.8;1.39-2.31)
Atazanavir	300 mg once daily x 14 days	400 mg (oral suspension) twice daily x 7 days	↑ 155% (2.55; 1.89-3.45)	↑ 268% (3.68; 2.89-4.70)
Atazanavir/ritonavir boosted regimen	300 mg/100 mg once daily x 14 days	400 mg (oral suspension) twice daily x 7 days	↑ 53% (1.53; 1.13-2.07)	↑ 146% (2.46; 1.93-3.13)

* Ratio Estimate is the ratio of coadministered drug plus Noxafil to coadministered drug alone for C_{max} or AUC.
† The tablet refers to a non-commercial tablet formulation without polymer.
‡ The mean terminal half-life of midazolam was increased from 3 hours to 7 to 11 hours during coadministration with Noxafil.

12.4 Microbiology

Mechanism of Action

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

Resistance

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

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

Aspergillus spp. and *Candida spp.*

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality 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

Carcinogenesis

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.

Mutagenesis

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).

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 common pathogens identified.

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 Noxafil 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 32).

Table 32: Noxafil Injection and Noxafil Delayed-Release Tablets Invasive Aspergillosis Treatment Study: All-Cause Mortality Through Day 42

	Noxafil Injection and Delayed-Release Tablets		Voriconazole		
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 33).

Table 33: Noxafil Injection and Noxafil Delayed-Release Tablets Invasive Aspergillosis Treatment Study: Successful Global Clinical Response* at Week 6

	Posaconazole		Voriconazole		
Population	N	Success	N	Success	Difference† (95% CI)
Proven/Probable Invasive Aspergillosis	163	73 (44.8)	171	78 (45.6)	-0.6 (-11.2, 10.1)

* Successful Global Clinical Response was defined as survival with a partial or complete response.
† 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.

14.2 Prophylaxis of *Aspergillus* and *Candida* Infections with Noxafil Oral Suspension

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 immune systems.

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 between the 2 treatment groups (80 days, Noxafil oral suspension; 77 days, fluconazole). Table 34 contains the results from Noxafil Oral Suspension Study 1.

Table 34: 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:		
Proven/Probable IFI	7 (2%)	22 (7%)
(*Aspergillus*)	3 (1%)	17 (6%)
(*Candida*)	1 (<1%)	3 (1%)
(Other)	3 (1%)	2 (1%)
All Deaths	22 (7%)	24 (8%)
Proven/probable fungal infection prior to death	2 (<1%)	6 (2%)
SAF†	27 (9%)	25 (8%)
Through 16 weeks		
Clinical Failure*,‡	99 (33%)	110 (37%)

Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(*Aspergillus*)	7 (2%)	21 (7%)
(*Candida*)	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths	58 (19%)	59 (20%)
Proven/probable fungal infection prior to death	10 (3%)	16 (5%)
SAF†	26 (9%)	30 (10%)
Event free lost to follow-up§	24 (8%)	30 (10%)

* Patients may have met more than one criterion defining failure.
† Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >4 consecutive days).
‡ 95% confidence interval (posaconazole-fluconazole) = (-11.5%, + 3.7%).
§ Patients who are lost to follow-up (not observed for 112 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

The second study (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 post-randomization. The mean duration of therapy was comparable between the 2 treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole). Table 35 contains the results from Noxafil Oral Suspension Study 2.

Table 35: Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and Prolonged Neutropenia: Noxafil Oral Suspension Study 2

	Posaconazole n=304	**Fluconazole/Itraconazole n=298**
On therapy plus 7 days		
Clinical Failure*,†	82 (27%)	126 (42%)
Failure due to:		
Proven/Probable IFI	7 (2%)	25 (8%)
(*Aspergillus*)	2 (1%)	20 (7%)
(*Candida*)	3 (1%)	2 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	17 (6%)	25 (8%)
Proven/probable fungal infection prior to death	1 (<1%)	2 (1%)

SAF‡	67 (22%)	98 (33%)
Through 100 days post-randomization		
Clinical Failure†	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(*Aspergillus*)	2 (1%)	26 (9%)
(*Candida*)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	44 (14%)	64 (21%)
Proven/probable fungal infection prior to death	2 (1%)	16 (5%)
SAF‡	98 (32%)	125 (42%)
Event free lost to follow-up§	34 (11%)	24 (8%)

∗ 95% confidence interval (posaconazole-fluconazole/itraconazole) = (-22.9%, -7.8%).
† Patients may have met more than one criterion defining failure.
‡ Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >3 consecutive days).
§ Patients who are lost to follow-up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

In summary, 2 clinical studies of prophylaxis were conducted with the Noxafil oral suspension. As seen in the accompanying tables (**Table 34 and Table 35**), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Noxafil Oral Suspension Study 1 (**Table 34**), the clinical failure rate of posaconazole (33%) was similar to fluconazole (37%), (95% CI for the difference posaconazole–comparator -11.5% to 3.7%) while in Noxafil Oral Suspension Study 2 (**Table 35**) clinical failure was lower for patients treated with posaconazole (27%) when compared to patients treated with fluconazole or itraconazole (42%), (95% CI for the difference posaconazole–comparator -22.9% to -7.8%).

All-cause mortality was similar at 16 weeks for both treatment arms in 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 receiving Noxafil prophylaxis when compared to patients receiving fluconazole or itraconazole.

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).

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 36**). The majority of the subjects had *C. albicans* as the baseline pathogen.

Clinical success at Day 14 (complete or partial resolution of all ulcers and/or plaques and symptoms) and clinical relapse rates (recurrence of signs or symptoms after initial cure or improvement) 4 weeks after the end of treatment were similar between the treatment arms (see **Table 36**).

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 36**).

Table 36: 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%)
Mycological Eradication (absence of CFU) at End of Therapy (Day 14)	88/169 (52.1%)	80/160 (50.0%)
Mycological Relapse (4 Weeks after End of Treatment)	49/88 (55.6%)	51/80 (63.7%)

Mycologic response rates, using a criterion for success as a posttreatment quantitative culture with ≤20 colony forming units (CFU/mL) were also similar between the two groups (Noxafil 68.0%, fluconazole 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 posaconazole 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).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Noxafil Injection

Noxafil injection is a clear, colorless to yellow sterile liquid in single-dose Type I glass vials closed with bromobutyl rubber stopper and aluminum seal containing 300 mg of posaconazole in 16.7 mL of solution (18 mg of posaconazole per mL) (NDC 0085-4331-01).

Noxafil Delayed-Release Tablets

Noxafil delayed-release tablets are 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 0085-4324-02).

Noxafil Oral Suspension

Noxafil oral suspension is a white, cherry-flavored oral suspension in 4-ounce (123 mL) amber glass bottles with child-resistant closures 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 (NDC 0085-1328-01).

Noxafil PowderMix for Delayed-Release Oral Suspension

Noxafil PowderMix for delayed-release oral suspension is supplied as:

- Package A: a kit with 8 child-resistant single-use packets of Noxafil PowderMix for delayed-release oral suspension 300 mg, two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, one mixing liquid bottle, one bottle adapter for the mixing liquid bottle and Instructions for Use.
- Package B: a box of six 3 mL (green) and six 10 mL (blue) notched tip syringes for additional supply.
- Packages A and B are supplied separately.

NDC 0085-2224-02 unit of use carton with 8 packets.

NDC 0085-2224-01 individual packet.

16.2 Storage and Handling

Noxafil Injection

Store Noxafil injection vial refrigerated at 2 to 8°C (36 to 46°F). Storage conditions for the diluted Noxafil infusion solution are presented in another section of the prescribing information [see Dosage and Administration (2.5)].

Noxafil Delayed-Release Tablets

Store at 20 to 25°C (68 to 77°F), excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Noxafil 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.**

Noxafil PowderMix for Delayed-Release Oral Suspension

Store the entire kit at 20 to 25°C (68 to 77°F), excursions permitted to 15 to 30°C (59 to 86°F) in a clean, dry place. Do not open foil packet containing Noxafil PowderMix for delayed-release oral suspension until ready for use. Storage conditions for the reconstituted solution are presented in another section of the prescribing information *[see Dosage and Administration (2.10)].*

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Important Administration Instructions

Noxafil Delayed-Release Tablets

Advise patients that Noxafil delayed-release tablets must be swallowed whole and not 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 the prescribed dose.

Noxafil Oral Suspension

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

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.

Noxafil PowderMix for Delayed-Release Oral Suspension

Instruct parents and/or caregivers that ONLY the provided notched tip syringes can be used to administer Noxafil PowderMix for delayed-release oral suspension to pediatric patients.

Advise patients to take Noxafil PowderMix for delayed-release oral suspension with food.

Drug Interactions

Advise patients to inform their physician immediately if they:

- develop severe diarrhea or vomiting.
- are currently taking drugs that are known to prolong the QTc interval and are metabolized through CYP3A4.
- are currently taking a cyclosporine or tacrolimus, or they notice swelling in an arm or leg or shortness of breath.

- are taking other drugs or before they begin taking other drugs as certain drugs can decrease or increase the plasma concentrations of posaconazole.

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. Noxafil can be administered with caution to patients with potentially proarrhythmic conditions.
- are pregnant, plan to become pregnant, or are nursing.
- have liver disease or develop itching, nausea or vomiting, their eyes or skin turn yellow, they feel more tired than usual or feel like they have the flu.
- have ever had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole, or voriconazole.

Hereditary Fructose Intolerance (HFI)

Inform patients and caregivers that Noxafil PowderMix for delayed-release oral suspension contains sorbitol and can be life-threatening when administered to patients with hereditary fructose intolerance (HFI) *[see Warnings and Precautions (5.9)]*. Inquire for symptoms of sorbitol/fructose and/or sucrose intolerance before administration.

Manuf. for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

uspi-mk5592-mf-2601r050

Patient Information
NOXAFIL® (**NOX**-a-fil)
(posaconazole) injection
NOXAFIL® (**NOX**-a-fil)
(posaconazole) delayed-release tablets
NOXAFIL® (**NOX**-a-fil)
(posaconazole) oral suspension
NOXAFIL® (**NOX**-a-fil) POWDERMIX
(posaconazole) for delayed-release oral suspension

What is Noxafil and Noxafil PowderMix?
Noxafil (which refers to injection, delayed-release tablets, and oral suspension) and Noxafil PowderMix (for delayed-release oral suspension) are prescription medicines 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*. Noxafil and Noxafil PowderMix are 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).

Noxafil injection is used for:
- prevention of fungal infections in adults and children 2 years of age and older who weigh 22 lbs (10 kg) or greater.
- treatment of fungal infections in adults and children 2 years of age and older who weigh 22 lbs (10 kg) or greater.

Noxafil 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 2 years of age and older who weigh greater than 88 lbs (40 kg).

Noxafil oral suspension is used for:
- prevention of fungal infections in adults and children 13 years of age and older.

Noxafil PowderMix for delayed-release oral suspension is used for:
- prevention of fungal infections in children 2 years of age and older who weigh 22 lbs to 88 lbs (10 kg to 40 kg).
- treatment of fungal infections in children 2 years of age and older who weigh 22 lbs to 88 lbs (10 kg to 40 kg).

Noxafil oral suspension is also used to treat a fungal infection called “thrush” caused by *Candida* in your mouth or throat area. **Noxafil oral suspension** can be used as the first treatment for thrush, or as another treatment for thrush after itraconazole or fluconazole treatment has not worked.
Noxafil oral suspension is for adults and children 13 years of age and older.
It is not known if Noxafil oral suspension is safe and effective in children under 13 years of age for the treatment of thrush as the first treatment for thrush, or as another treatment for thrush after itraconazole or fluconazole treatment has not worked.
It is not known if Noxafil or Noxafil PowderMix is safe and effective in children under 2 years of age.

Do not take Noxafil or Noxafil PowderMix if you:
- are allergic to posaconazole, any of the ingredients in Noxafil or Noxafil PowderMix, or other azole antifungal medicines. See the end of this Patient Information leaflet for a complete list of ingredients in Noxafil and Noxafil PowderMix.
- are taking any of the following medicines:
  - sirolimus
  - pimozide
  - quinidine
  - 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.
- are taking **Noxafil PowderMix for delayed-release oral suspension** and have hereditary fructose intolerance.

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.

Before you take Noxafil or Noxafil PowderMix, tell your healthcare provider about all of your medical conditions, including if you:

- are taking certain medicines that lower your immune system like cyclosporine or tacrolimus.
- are taking certain drugs for HIV infection, such as ritonavir, atazanavir, efavirenz, or fosamprenavir. Efavirenz and fosamprenavir can cause a decrease in the Noxafil levels in your body. Efavirenz and fosamprenavir should not be taken with Noxafil or Noxafil PowderMix.
- 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 Noxafil will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Noxafil passes into your breast milk. You and your healthcare provider should decide if you will take Noxafil or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Noxafil and Noxafil PowderMix can affect the way other medicines work, and other medicines can affect the way Noxafil and Noxafil PowderMix work, and can cause serious side effects.

Especially tell your healthcare provider if you take:

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

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.
Know the medicines you take. Keep a list of them with you to show your healthcare provider or pharmacist when you get a new medicine.

How should I take Noxafil or Noxafil PowderMix?

- **Do not switch between Noxafil oral suspension and Noxafil delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension**.
- Take Noxafil or Noxafil PowderMix exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much Noxafil or Noxafil PowderMix to take and when to take it.
- Take Noxafil or Noxafil PowderMix for as long as your healthcare provider tells you to

take it.

- If you take too much Noxafil or Noxafil PowderMix, call your healthcare provider or go to the nearest hospital emergency room right away.
- Noxafil injection is usually given over 30 to 90 minutes through a plastic tube placed in your vein.
- **Noxafil delayed-release tablets:**
  - Take Noxafil delayed-release tablets with or without food.
  - Take Noxafil delayed-release tablets whole. Do not break, crush, or chew Noxafil delayed-release tablets before swallowing. If you cannot swallow Noxafil delayed-release tablets whole, tell your healthcare provider. You may need a different medicine.
  - If you miss a dose, take it as soon as you remember and then take your next scheduled dose at its regular time. If it is within 12 hours of your next dose, do not take the missed dose. Skip the missed dose and go back to your regular schedule. Do not double your next dose or take more than your prescribed dose.
- **Noxafil oral suspension:**
  - Shake Noxafil oral suspension well before use.
  - Take each dose of Noxafil oral suspension during or within 20 minutes after a full meal. If you cannot eat a full meal, take each dose of Noxafil oral suspension with a liquid nutritional supplement or an acidic carbonated beverage, like ginger ale.
  - A measured dosing spoon comes with your Noxafil oral suspension and is marked for doses of **2.5 mL** and **5 mL**. **See Figure A.**

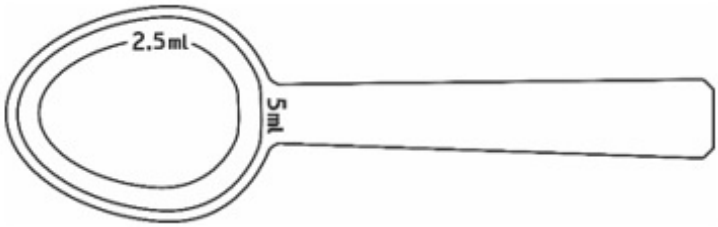


Figure A

  - Rinse the spoon with water after each dose of Noxafil oral suspension and before you store it away.
  - 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 or take more than your prescribed dose.
- **Noxafil PowderMix for delayed-release oral suspension:**
  - Before giving the first dose of Noxafil PowderMix for delayed-release oral suspension, **read the Instructions for Use booklet that comes with Noxafil PowderMix for delayed-release oral suspension** for information about the correct way to mix and give a dose of Noxafil PowderMix for delayed-release oral suspension to your child. **Keep the booklet and follow it each time you prepare the medicine. Bring this booklet to your child's appointments.**
  - If you have questions about how to mix or give Noxafil PowderMix, talk with your healthcare provider or pharmacist.
  - Only use the mixing liquid that comes with the kit to prepare Noxafil PowderMix.
  - After mixing, measure the prescribed dose with notched tip syringe provided with the kit. **Only use the notched tip syringes that come with the kit to prepare and give the medicine.**

- **Give the dose within 1 hour of mixing the suspension. Give with food.**
- **If your child does not take all of the prescribed dose or spits some of it out, call your healthcare provider to find out what to do.**

Follow the instructions from your healthcare provider on how much Noxafil or Noxafil PowderMix you should take and when to take it.

What are the possible side effects of Noxafil or Noxafil PowderMix?
Noxafil or Noxafil PowderMix may cause serious side effects, including:

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

  - itchy skin
  - nausea or vomiting
  - yellowing of your eyes or skin
  - feeling very tired
  - flu-like symptoms

- **increased amounts of midazolam in your blood.** If you take Noxafil or Noxafil PowderMix with midazolam, Noxafil or Noxafil PowderMix increases the amount of midazolam in your blood. This can make your sleepiness last longer. Your healthcare provider should check you closely for side effects if you take midazolam with Noxafil or Noxafil PowderMix.

The most common side effects of Noxafil in adults include:

- diarrhea
- nausea
- headache
- coughing

- fever
- vomiting
- coughing
- low potassium levels in the blood

The most common side effects of Noxafil injection and Noxafil PowderMix in children include:

- fever
- fever with low white blood cell count (febrile neutropenia)
- vomiting
- redness and sores of the lining of the mouth, lips, throat, stomach, and genitals (mucositis or stomatitis)
- itching
- high blood pressure
- low potassium levels in the blood

If you take Noxafil delayed-release tablets, Noxafil oral suspension, or Noxafil PowderMix for delayed-release oral suspension, tell your healthcare provider right away if you have diarrhea or vomiting.
Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of Noxafil or Noxafil PowderMix. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Noxafil or Noxafil PowderMix?
Noxafil injection

- Store Noxafil injection refrigerated between 36°F to 46°F (2°C to 8°C).

Noxafil delayed-release tablets

- Store Noxafil delayed-release tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Noxafil oral suspension

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

Noxafil PowderMix for delayed-release oral suspension

- Store the entire kit at room temperature between 68°F to 77°F (20°C to 25°C) in a clean, dry place.
- Do not open the foil packet until ready for use.

Safely throw away medicine that is out of date or no longer needed.
Keep Noxafil and Noxafil PowderMix and all medicines out of the reach of children.

General information about the safe and effective use of Noxafil and Noxafil PowderMix.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Noxafil or Noxafil PowderMix for a condition for which it was not prescribed. Do not give Noxafil or Noxafil PowderMix 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 Noxafil or Noxafil PowderMix

that is written for health professionals.

What are the ingredients in Noxafil and Noxafil PowderMix?
Active ingredient: posaconazole
Inactive ingredients:
Noxafil injection: Betadex Sulfobutyl Ether Sodium (SBECD), edetate sodium, hydrochloric acid, sodium hydroxide, and water for injection.
Noxafil 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.
Noxafil 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.
Noxafil PowderMix for delayed-release oral suspension: hypromellose acetate succinate. The mixing liquid contains: anhydrous citric acid, antifoam Af emulsion, berry citrus sweet flavor, carboxymethylcellulose sodium, carrageenan calcium sulfate trisodium phosphate, glycerin, methylparaben, microcrystalline cellulose, potassium sorbate, propylparaben, purified water, sodium citrate, sodium phosphate monobasic monohydrate, sodium saccharin, sorbitol solution, and xanthan gum.

Manuf. for: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA
For patent information: www.msd.com/research/patent

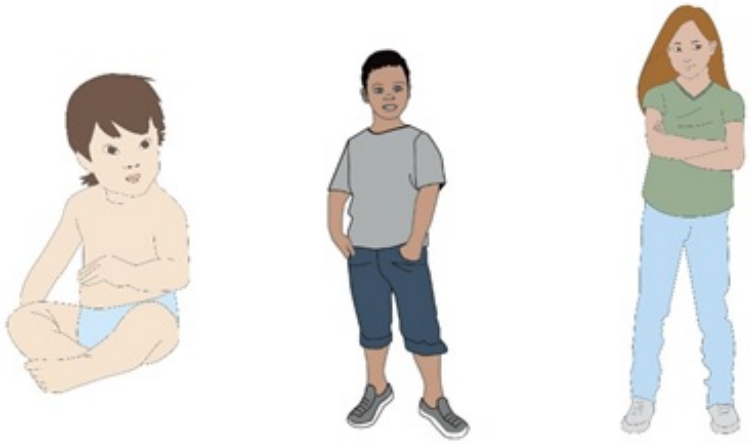
usppi-mk5592-mf-2601r024
For more information, go to www.noxafil.com or call 1-800-672-6372.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 1/2026

Important: Read This Booklet First
Noxafil PowderMix (posaconazole)
for delayed-release oral suspension

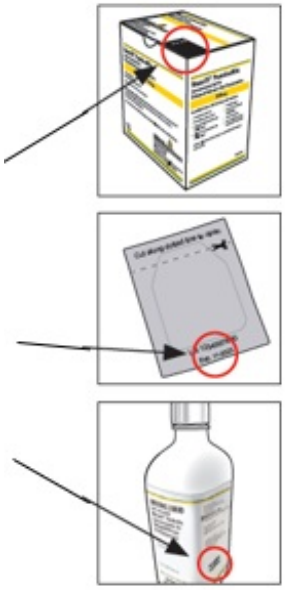
Instructions for Use

for caregivers and healthcare providers of toddlers and children



Before You Start

- Before you start, be sure that you read and understand all of these instructions. They may be different than those for medicines that you have used in the past.
- It is important that you make all measurements very carefully.
- Before you give Noxafil PowderMix, check all 3 expiration dates. The expiration date is printed on the box, the Noxafil PowderMix packets, and the mixing liquid.
- Do not open the Noxafil PowderMix packets until you are ready to mix the dose.
- Give Noxafil PowderMix with food.



Note: Put your child in a safe place. You will need both hands to prepare Noxafil PowderMix. Wash your hands with soap and water before preparing Noxafil PowderMix.

Before You Start

- The amount of Noxafil PowderMix you give depends on your child’s weight. Your healthcare provider will tell you the right dose to give your child. Be sure to keep your healthcare provider’s appointments so you get new dosing information as your child grows.

- This booklet tells you how to:
  - Make the Noxafil PowderMix into a liquid form.
  - Measure the right dose using the included notched-tip oral syringe. Only use the notched-tip syringes supplied with the kit. Do not use other oral syringes.
  - Give the Noxafil PowderMix to your child.
  - Clean up.

Note before adding Noxafil PowderMix: Make sure you and your child are ready! If you do not use Noxafil PowderMix within **1 hour**, you will need to throw it away and start over.

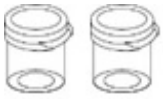
Note: If you have any questions, call your healthcare provider.

Kit Contents

- Prescription (on Noxafil PowderMix box)

- Instructions for Use (this booklet)

- Package insert
- 4 syringes (shown below)
- 2 mixing cups

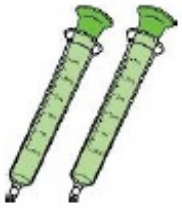


- 8 packets of Noxafil PowderMix

- Bottle adapter

- Bottle of Mixing Liquid for use with Noxafil PowderMix

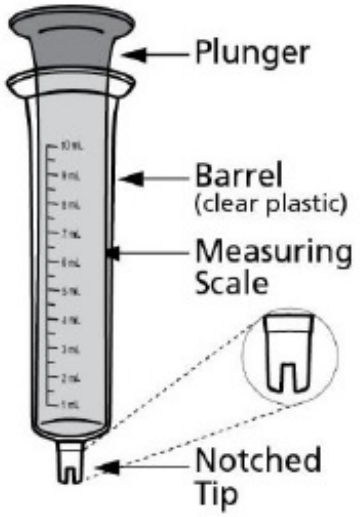
2 blue (10 mL) syringes



2 green (3 mL) syringes

The kit has an extra cup and set of syringes in case one is lost or damaged.
Do not use any damaged cups or syringes.

Get to Know the Oral Syringes



- Before you prepare a dose, review the parts of the syringe and how to use them.
- If you have any questions about measuring with a syringe, call your healthcare provider.
- Make sure the plunger is pushed all the way into the barrel before you start to measure the dose.

- Look for the number on the measuring scale that matches the amount of mixing liquid or Noxafil PowderMix that you need.
- Be sure to follow the directions in this booklet to remove air bubbles from the syringe. **Air bubbles can affect the amount of medicine that the child gets.**

Step 1. Get the mixing liquid ready.

Important: Noxafil PowderMix needs to be prepared using the mixing liquid. **Do not** mix Noxafil PowderMix with milk, juice, or water.

When you use the mixing liquid for the first time:

- Open the bottle and remove the safety seal.
- Place the bottle adapter on top of the bottle with the small hole facing up.
- **Push the bottle adapter all the way down.**
- After it is in place, the bottle adapter stays in the bottle.
- Put the cap back on the bottle.

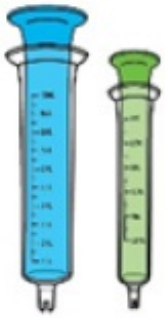
Step 2. Gather all your supplies and put on a clean surface.

Note: Put your child in a safe place. You will need both hands to prepare Noxafil PowderMix. Wash your hands with soap and water before preparing Noxafil PowderMix.

1 mixing cup (Using the tab on the mixing cup, pull open the lid.)

1 packet of Noxafil PowderMix powder

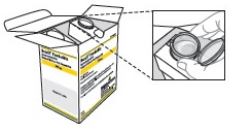
Mixing liquid



2 syringes (Have 1 of each size ready, but you may only use 1, depending on

Scissors (not included with kit: use sharp household scissors or kitchen scissors)

the dose.)



The Noxafil PowderMix box has a mixing cup holder inside to help tilt the cup when you are measuring the dose.

Step 3. Add Noxafil PowderMix to the mixing cup.

Note before adding Noxafil PowderMix:
Make sure you and your child are ready! If you do not use Noxafil PowderMix within **1 hour**, you will need to throw it away and start over.

- Take **1 packet** of Noxafil PowderMix and shake the powder to the bottom of the packet.

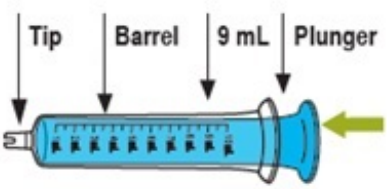
- Cut open the packet of Noxafil PowderMix at the dotted line and add all of the Noxafil PowderMix to the mixing cup.
  Make sure the packet of Noxafil PowderMix is completely empty.

Step 4. Shake the mixing liquid bottle.

- Shake the mixing liquid well before each time you prepare Noxafil PowderMix.

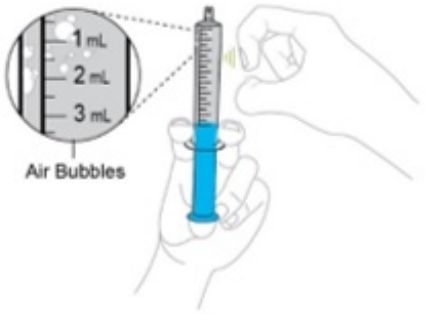
Step 5. Fill the blue syringe with 9 mL of mixing liquid.

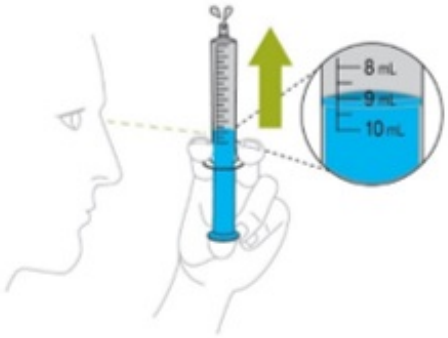
- Push the plunger of the **blue** syringe into the syringe barrel as far as it goes.
- Remove the cap from the bottle of mixing liquid.
- Push the notched tip of the syringe into the bottle adapter.
- With the syringe attached to the bottle, turn the bottle and syringe upside down. With your other hand, pull back the plunger to draw the mixing liquid back into the syringe.
- Stop when you get to the 9 mL line.
- Turn the bottle back over and remove the syringe to check your measurement.



Step 6. Check for air bubbles.

- Hold the syringe with notched tip up. Tap it with your finger to move any air bubbles up.
- Slowly push the plunger to make the air come out.





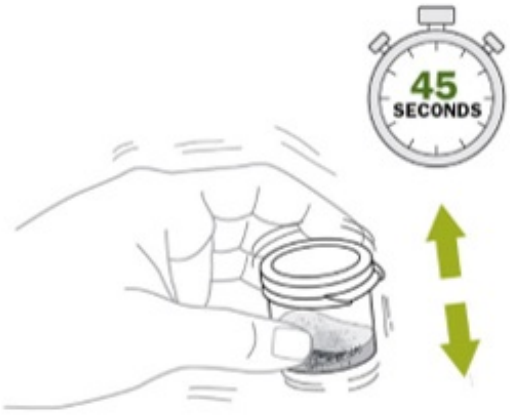
- Re-check the measurement of mixing liquid in the syringe. If it is less than 9 mL, put the notched tip back into the mixing liquid and pull the plunger back until you get to the 9 mL mark.

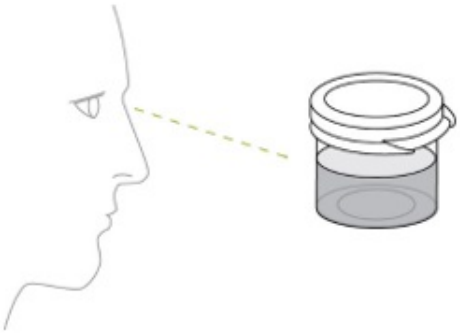
Step 7. Add the 9 mL of mixing liquid to the Noxafil PowderMix.

- Add the 9 mL of mixing liquid to the Noxafil PowderMix in the mixing cup by pushing all the way down on the plunger.

Step 8. Mix the Noxafil PowderMix.

- Snap the lid of the mixing cup shut.
- Shake the mixing cup really hard for 45 seconds to mix the Noxafil PowderMix.





- Check to make sure the Noxafil PowderMix powder is mixed. If it is not mixed, shake the mixing cup some more. Noxafil PowderMix should look cloudy and free of clumps.

Step 9. Check your prescription label.

- Find the dose amount (look for the 'mL' written on the prescription label on the box from your healthcare provider).

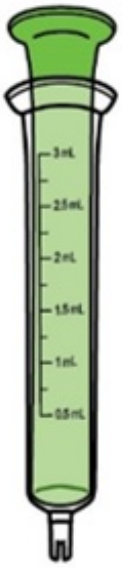
Note: The dose may change each time you go to the healthcare provider, so make sure you have all the recent information. Be sure to go to all of your child's healthcare provider appointments so your child gets the right dose.

Step 10. Choose the syringe you need.

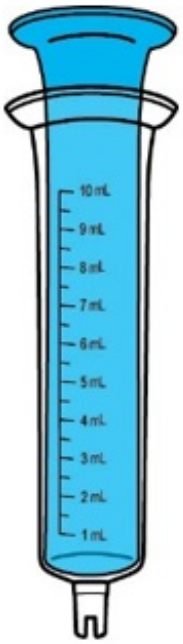
Note: Only use the syringes provided in the kit.

Choose the correct syringe for your child's dose:

For **1 mL** to **3 mL** **Green**



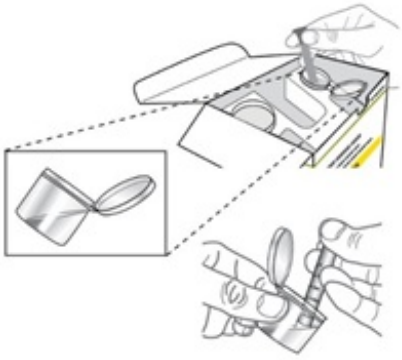
For **3 mL** to **10 mL** **Blue**



- Then find the mL mark on the syringe that matches your child's dose.

Step 11. Measure the Noxafil PowderMix.

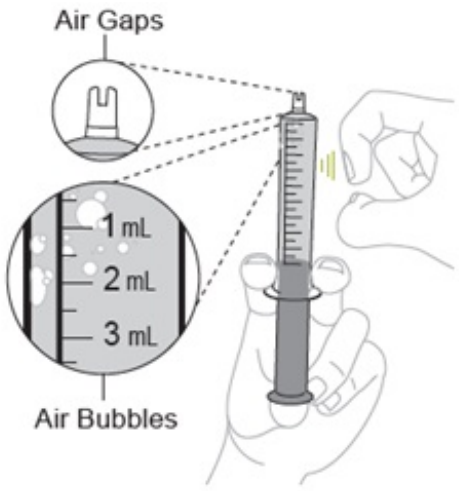
- Push the plunger into the dosing syringe as far as it goes.
- Tilt the cup by hand or use the mixing cup holder inside the Noxafil PowderMix box.
- Put the notched tip of the dosing syringe into the lowest part of the cup with the Noxafil PowderMix and pull back the plunger.
- Stop when you get to the line showing the prescribed dose.

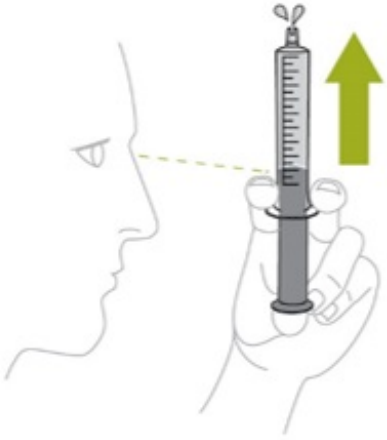


Important: You will not use all of the Noxafil PowderMix. There will be some left over in the mixing cup.

Step 12. Check for air bubbles.

- Be sure to follow the directions to remove air bubbles from the syringe.
  Air bubbles can affect the amount of
  medicine that the child gets.
- Hold the syringe with notched tip up.
  Tap it with your finger to move any air bubbles up. Check for air gaps in the tip of the syringe. Slowly push the plunger to make the air bubbles or air gaps come out.





- Re-check the measurement of Noxafil PowderMix in the syringe. If it is less than the prescribed dose, put the notched tip back into the mixing cup with the Noxafil PowderMix and pull the plunger back until you get to the right dose mark.

Step 13. Give the Noxafil PowderMix to your child.

- Gently place the syringe inside your child's mouth so that the notched tip touches one of his or her cheeks.
- Slowly push down on the plunger to give the dose of
  Noxafil PowderMix. It is important that your child takes
  all of the dose of Noxafil PowderMix (a little left in the
  syringe notched tip is ok).

Important:

- If your child does not take the whole dose or spits some of it out, call your healthcare provider to find out what to

do.
- Only use the mixing liquid from the kit. Do not mix Noxafil PowderMix with milk, juice, or water.

Step 14. Clean the cup and syringes.

Note: Syringes and mixing cups should be reused. Do not throw away syringes and mixing cups provided until all the Noxafil PowderMix packets are used.

- Pour the leftover Noxafil PowderMix from the mixing cup into the trash. **Do not pour it into the sink.**
- Pull the plungers out of any syringes you used.
- Hand wash the syringes, plungers, and mixing cup with warm water and dish soap. **Do not wash in the dishwasher.**
- Rinse with water and air dry.
- Put everything in a clean, dry place.

Step 15. After all packets of Noxafil PowderMix have been used.

- After you have used the last Noxafil PowderMix packet in this box, you will have leftover mixing liquid in the bottle. Throw away the leftover mixing liquid and all components of the kit.

How should I store Noxafil PowderMix?

- Store the entire kit at room temperature between 68°F to 77°F (20°C to 25°C) in a clean, dry place.
- Keep the mixing liquid at room temperature.
- Do not open the Noxafil PowderMix packet until you are ready to mix a dose.

Keep NOXAFIL PowderMix and all medicines out of the reach of children.

For more information go to www.Noxafil.com or call 1-800-622-4477.

Distributed by:

Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

ifu-mk5592-2209r002

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: September 2022

PRINCIPAL DISPLAY PANEL - 105 mL Bottle Carton

NDC 0085-1328-01
105 mL

NOXAFIL®
(posaconazole)

Oral Suspension

200 mg/5 mL

Each mL contains: 40 mg posaconazole.

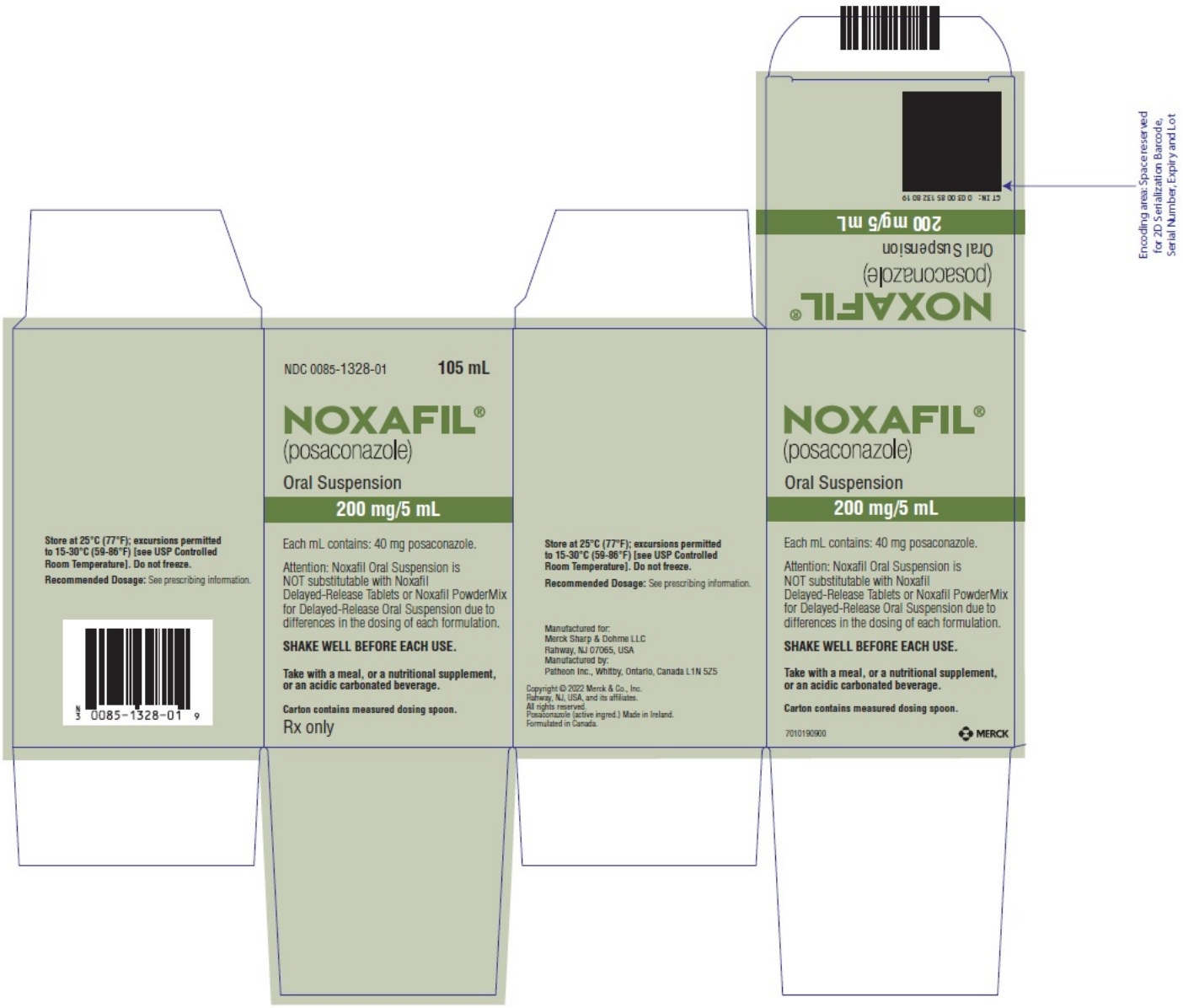
Attention: Noxafil Oral Suspension is NOT substitutable with Noxafil Delayed-Release Tablets or Noxafil PowderMix for Delayed-Release Oral Suspension due to differences in the dosing of each formulation.

SHAKE WELL BEFORE EACH USE.

Take with a meal, or a nutritional supplement, or an acidic carbonated beverage.

Carton contains measured dosing spoon.

Rx only



PRINCIPAL DISPLAY PANEL - 60 Tablet Bottle Label

NDC 0085-4324-02

Noxafil®
(posaconazole)
delayed-release tablets

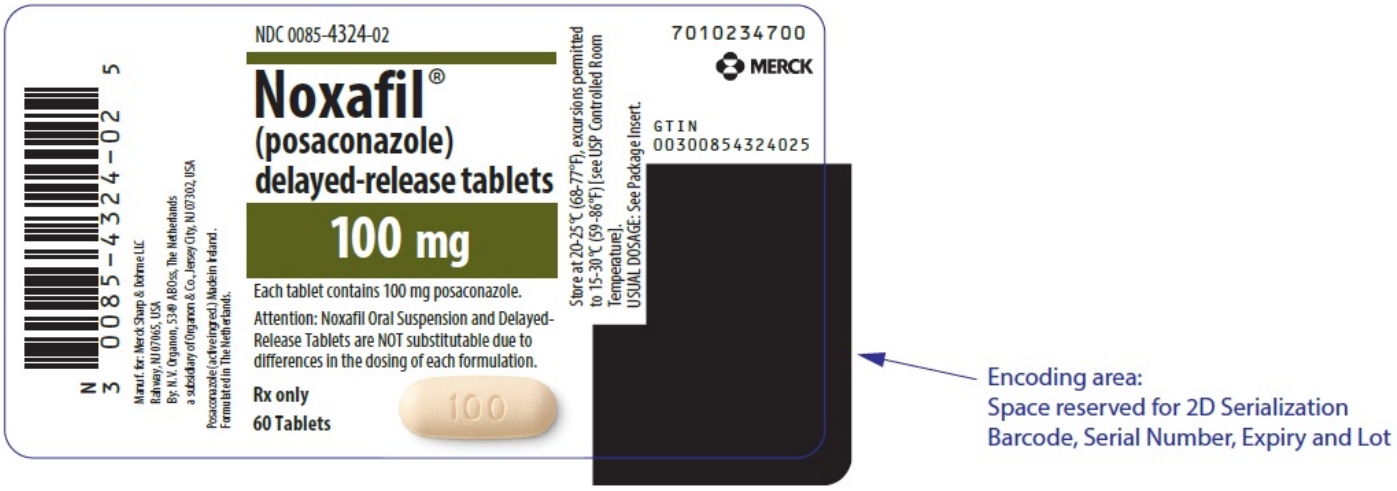
100 mg

Each tablet contains 100 mg posaconazole.

Attention: Noxafil Oral Suspension and Delayed-Release Tablets are NOT substitutable due to differences in the dosing of each formulation.

Rx only

60 Tablets



PRINCIPAL DISPLAY PANEL - 16.7 mL Vial Carton

NDC 0085-4331-01

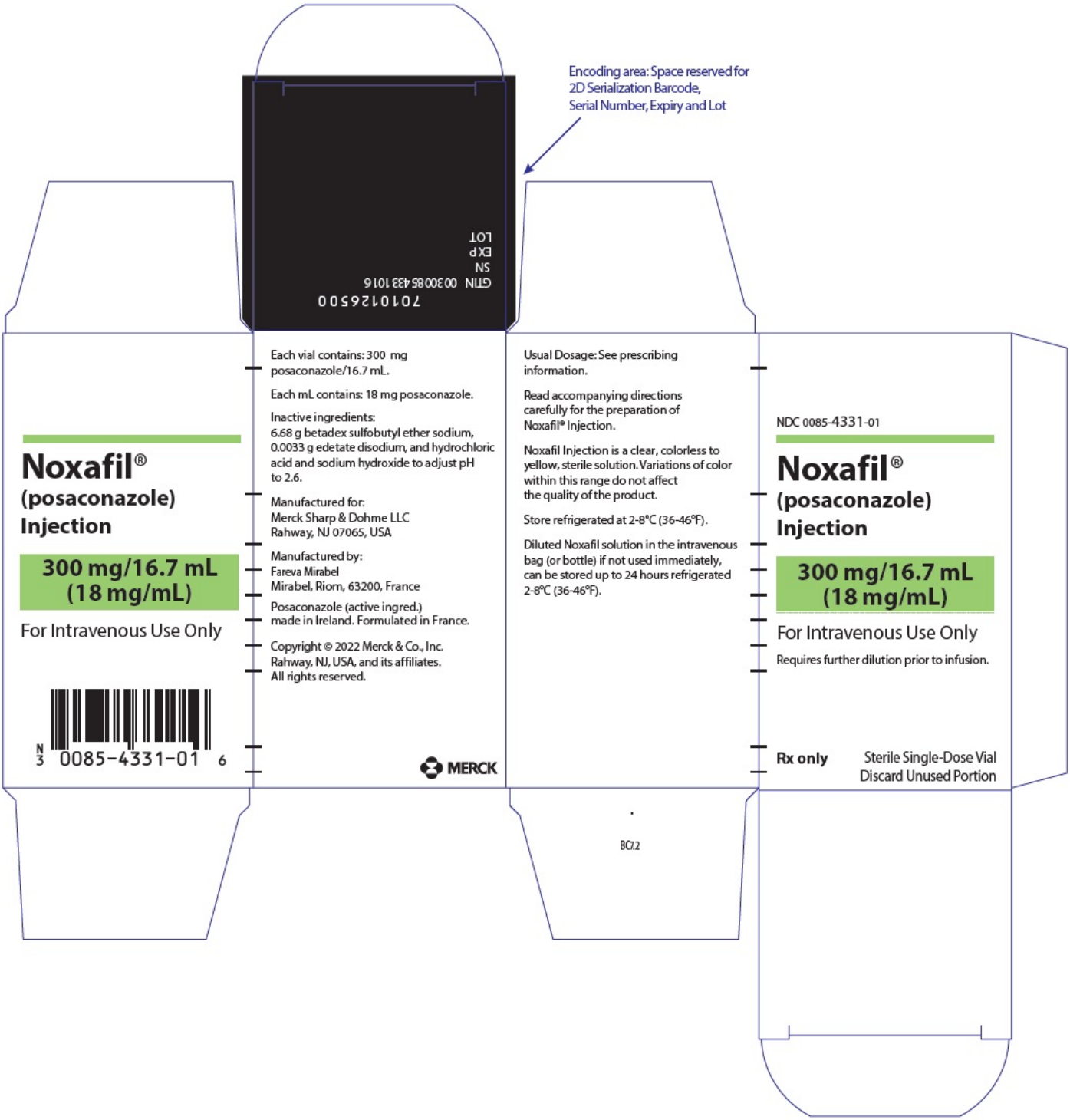
Noxafil®
(posaconazole)
Injection

300 mg/16.7 mL
(18 mg/mL)

For Intravenous Use Only

Requires further dilution prior to infusion.

Rx only
Sterile Single-Dose Vial
Discard Unused Portion



PRINCIPAL DISPLAY PANEL - 300 mg Carton

NDC 0085-2224-02

Noxafil® PowderMix
(posaconazole) for
Delayed-Release Oral Suspension

300 mg

For Pediatric Use
For Oral Administration Only

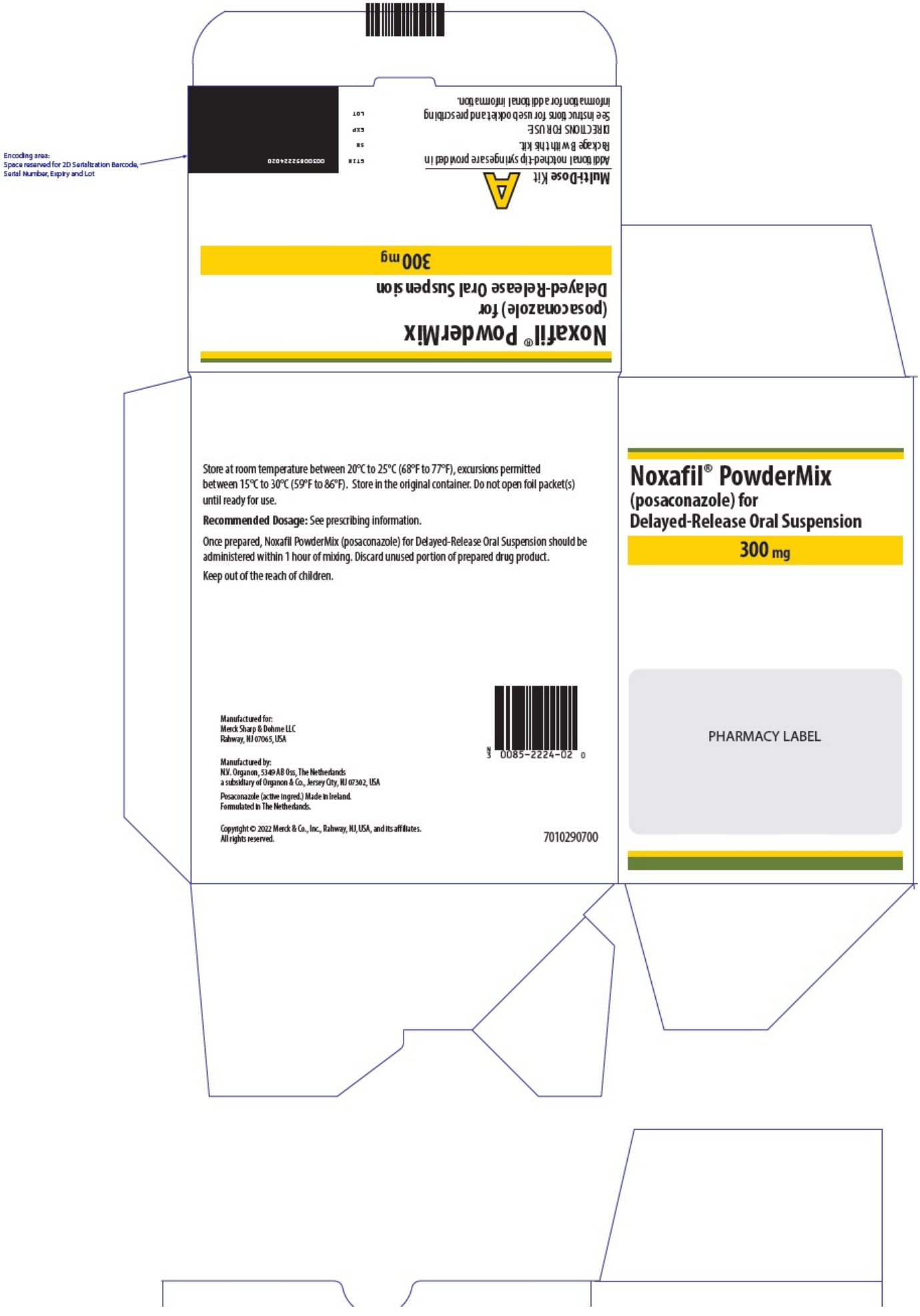
Each packet contains 300 mg posaconazole.

Attention: Noxafil PowderMix for Delayed-Release Oral Suspension is NOT substitutable with Noxafil Oral Suspension due to differences in the dosing of each formulation.

Use only the notched-tip syringes and mixing liquid provided with this kit.

Rx only
8 packets

Multi-Dose Kit A
Additional notched-tip syringes are provided in Package B with this kit.
DIRECTIONS FOR USE:
See instructions for use booklet and prescribing information for additional information.


Encoding area:
Space reserved for 2D Serialization Barcode,
Serial Number, Expiry and Lot
Noxafil® PowderMix
(posaconazole) for
Delayed-Release Oral Suspension
300 mg
Multi-Dose Kit
Additional notched-tip syringes are provided in
package B with this kit.
DIRECTIONS FOR USE:
See instructions for use booklet and prescribing
information for additional information.
Store at room temperature between 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F). Store in the original container. Do not open foil packet(s) until ready for use.
Recommended Dosage: See prescribing information.
Once prepared, Noxafil PowderMix (posaconazole) for Delayed-Release Oral Suspension should be administered within 1 hour of mixing. Discard unused portion of prepared drug product.
Keep out of the reach of children.
Manufactured for:
Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA
Manufactured by:
N.V. Organon, 5349 AB Oss, The Netherlands
a subsidiary of Organon & Co., Jersey City, NJ 07302, USA
Posaconazole (active ingred.) Made in Ireland.
Formulated in The Netherlands.
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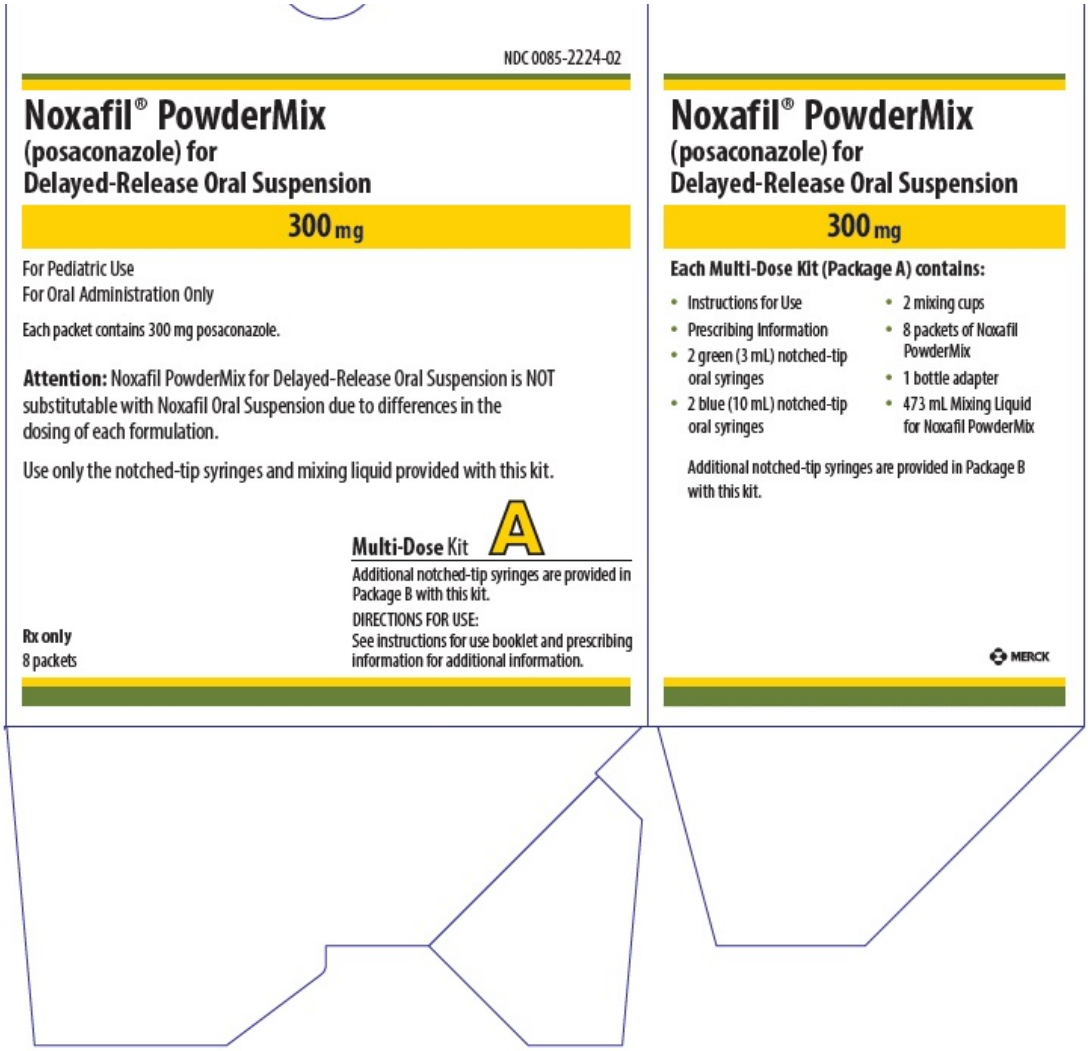
3 0085-2224-02 0
7010290700
Noxafil® PowderMix
(posaconazole) for
Delayed-Release Oral Suspension
300 mg
PHARMACY LABEL



NOXAFIL

posaconazole suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0085-1328
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
posaconazole (UNII: 6TK1G07BHZ) (posaconazole - UNII:6TK1G07BHZ)	posaconazole	40 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
polysorbate 80 (UNII: 6OZP39ZG8H)	
sodium benzoate (UNII: OJ245FE5EU)	
trisodium citrate dihydrate (UNII: B22547B95K)	
citric acid monohydrate (UNII: 2968PHW8QP)	

glycerin (UNII: PDC6A3C0OX)	
xanthan gum (UNII: TTV12P4NEE)	
anhydrous dextrose (UNII: 5SL0G7R0OK)	
titanium dioxide (UNII: 15FIX9V2JP)	
water (UNII: 059QF0KO0R)	

Product Characteristics			
Color		**Score**	
Shape		**Size**	
Flavor	CHERRY	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0085-1328-01	1 in 1 CARTON	09/15/2006	
1		105 mL in 1 BOTTLE, GLASS; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022003	09/15/2006	

NOXAFIL

posaconazole tablet, coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0085-4324
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
posaconazole (UNII: 6TK1G07BHZ) (posaconazole - UNII:6TK1G07BHZ)	posaconazole	100 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSE ACETATE SUCCINATE 06081224 (3 MM2/S) (UNII: 6N003M473W)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)	

SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TALC (UNII: 7SEV7J4R1U)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics

Color	YELLOW	**Score**	no score
Shape	OVAL (oblong)	**Size**	17mm
Flavor		**Imprint Code**	100
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0085-4324-02	60 in 1 BOTTLE; Type 0: Not a Combination Product	11/25/2013	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA205053	11/25/2013	

NOXAFIL

posaconazole solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0085-4331
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
posaconazole (UNII: 6TK1G07BHZ) (posaconazole - UNII:6TK1G07BHZ)	posaconazole	18 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BETADEX SULFOBUTYL ETHER SODIUM (UNII: 2PP9364507)	
EDETATE DISODIUM (UNII: 7FLD91C86K)	

HYDROCHLORIC ACID (UNII: QTT17582CB)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0085-4331-01	1 in 1 CARTON	03/13/2014	
1		16.7 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA205596	03/13/2014	

NOXAFIL

posaconazole powder, for suspension

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0085-2224
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
POSACONAZOLE (UNII: 6TK1G07BHZ) (POSACONAZOLE - UNII:6TK1G07BHZ)	POSACONAZOLE	300 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSE ACETATE SUCCINATE 06081224 (3 MM2/S) (UNII: 6N003M473W)	
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	
DIMETHICONE (UNII: 92RU3N3Y1O)	
CARBOXYMETHYLCELLULOSE SODIUM, UNSPECIFIED (UNII: K679OBS311)	
CARRAGEENAN (UNII: 5C69YCD2YJ)	
GLYCERIN (UNII: PDC6A3C0OX)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POTASSIUM SORBATE (UNII: 1VPU26JZZ4)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	
WATER (UNII: 059QF0KO0R)	
SODIUM CITRATE, UNSPECIFIED FORM (UNII: 1Q73Q2JULR)	
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE (UNII: 593YOG76RN)	

SACCHARIN SODIUM (UNII: SB8ZUX40TY)	
SORBITOL SOLUTION (UNII: 8KW3E207O2)	
XANTHAN GUM (UNII: TTV12P4NEE)	
CALCIUM SULFATE, UNSPECIFIED FORM (UNII: WAT0DDB505)	
SODIUM PHOSPHATE, TRIBASIC, ANHYDROUS (UNII: SX01TZO3QZ)	

Product Characteristics

Color	WHITE	**Score**	
Shape		**Size**	
Flavor	BERRY (berry citrus sweet flavor)	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0085-2224-02	8 in 1 CARTON	06/08/2021	
1	NDC:0085-2224-01	1 in 1 PACKET; Type 1: Convenience Kit of Co-Package		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA214770	06/08/2021	

Labeler - Merck Sharp & Dohme LLC (118446553)

Revised: 1/2026 Merck Sharp & Dohme LLC