POSACONAZOLE - posaconazole injection
Eugia US LLC

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

POSACONAZOLE injection, for intravenous use
Initial U.S. Approval: 2006

INDICATIONS AND USAGE

Posaconazole injection is an azole antifungal indicated as follows:

- **Posaconazole injection** 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)
  - **Posaconazole injection:** adults

DOSAGE AND ADMINISTRATION

- **Posaconazole injection** must be administered through an in-line filter.
- Administer **posaconazole injection** by intravenous infusion over approximately 90 minutes via a central venous line. (2.1)
- Do NOT administer **posaconazole injection** as an intravenous bolus injection. (2.1)

Table 1: Recommended Dosage in Adult Patients

Indication	Dosage Form, Dose, and Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	**Posaconazole Injection:** Loading dose: 300 mg posaconazole injection intravenously twice a day on the first day. Maintenance dose: 300 mg posaconazole injection intravenously once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.2)

DOSAGE FORMS AND STRENGTHS

- Posaconazole injection: 300 mg per vial (18 mg per mL) in a single-dose vial (3)

CONTRAINDICATIONS

- Known hypersensitivity to posaconazole or other azole antifungal agents. (4.1)
- Coadministration of posaconazole with the following drugs is contraindicated; posaconazole increases concentrations and toxicities of:
  - Sirolimus (4.2, 5.1, 7.1)
  - 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, 7.3)
  - Ergot alkaloids (4.5, 7.4)
  - Venetoclax: in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) at initiation and during the ramp up phase (4.6, 5.10, 7.16)

WARNINGS AND PRECAUTIONS

- Calcineurin-Inhibitor Toxicity: Posaconazole increases concentrations of cyclosporine or tacrolimus; reduce dose of cyclosporine and tacrolimus and monitor concentrations frequently. (5.1)
- Arrhythmias and QTc Prolongation: Posaconazole 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)

- Electrolyte Disturbances: Monitor and correct, especially those involving potassium (K^+), magnesium (Mg^{++}), and calcium (Ca^{++}), before and during posaconazole therapy. (5.3)
- Hepatic Toxicity: Elevations in liver tests may occur. Discontinuation should be considered in patients who develop abnormal liver tests or monitor liver tests during treatment. (5.4)
- Renal Impairment: Posaconazole injection should be avoided in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of posaconazole injection. (5.5, 8.6)
- Concomitant Use with Midazolam: Posaconazole can prolong hypnotic/sedative effects. Monitor patients and benzodiazepine receptor antagonists should be available. (5.6, 7.5)
- Vincristine Toxicity: Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions; reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options. (5.7, 7.10)
- Venetoclax Toxicity: Concomitant administration of posaconazole 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, 5.10, 7.16)

ADVERSE REACTIONS

- Common adverse reactions in studies with posaconazole are diarrhea, nausea, fever, vomiting, headache, coughing, and hypokalemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eugia US LLC at 1-866-850-2876 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

DRUG INTERACTIONS

Interaction Drug	***Interaction***
Rifabutin, phenytoin, efavirenz, cimetidine	*Avoid coadministration unless the benefit outweighs the risks (7.6, 7.7, 7.8)*
Other drugs metabolized by CYP3A4	*Consider dosage adjustment and monitor for adverse effects and toxicity (7.1, 7.10, 7.11)*
Digoxin	*Monitor digoxin plasma concentrations (7.12)*
Fosamprenavir	*Monitor for breakthrough fungal infections (7.6)*

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)

Pediatric Use information is approved for Merck Sharp & Dohme Corp.'s NOXAFIL (posaconazole) injection. However, due to Merck Sharp & Dohme Corp.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Posaconazole injection 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 *[see Clinical Studies (14.1)]* as follows:

- **Posaconazole injection:** adults

Pediatric Use information is approved for Merck Sharp & Dohme Corp.'s NOXAFIL (posaconazole) injection. However, due to Merck Sharp & Dohme Corp.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Posaconazole 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 (2.4)].*

● If a central venous catheter is not available, posaconazole injection may be administered through a peripheral venous catheter by slow intravenous infusion over 30 minutes only as a single-dose in advance of central venous line placement or to bridge the period during which a central venous line is replaced or is in use for other intravenous treatment.

● When multiple dosing is required, the infusion should be done via a central venous line.
● Do **NOT** administer posaconazole injection as an intravenous bolus injection.

2.2 Dosing Regimen in Adult Patients

Table 1: Dosing Regimens in Adult Patients

Indication	Dose and Frequency	Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	**Posaconazole Injection:** Loading dose: 300 mg posaconazole injection intravenously twice a day on the first day. Maintenance dose: 300 mg posaconazole injection intravenously once a day thereafter.	Loading dose: 1 day Maintenance dose: Duration of therapy is based on recovery from neutropenia or immunosuppression.

2.4 Preparation, Intravenous Line Compatibility, and Administration of Posaconazole Injection

Preparation:

- Equilibrate the refrigerated vial of posaconazole injection to room temperature.
- To prepare the required dose, aseptically transfer one vial (16.7 mL) of posaconazole injection (containing 300 mg of posaconazole in solution) to an intravenous bag (or bottle) of a compatible admixture diluent (as described in **Table 5**), to achieve a final concentration of posaconazole that is between 1 mg/mL and 2 mg/mL. Use of other diluents is not recommended because they may result in particulate formation.
- Posaconazole injection is a single-dose sterile solution without preservatives. Discard any unused portion from the vial.
- Once admixed, the diluted solution of posaconazole injection in the intravenous bag (or bottle) should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2 to 8°C (36 to 46°F). Discard any unused portion.
- Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit. Once admixed, the solution of posaconazole injection ranges from colorless to yellow. Variations of color within this range do not affect the quality of the product.

Intravenous Line Compatibility:

A study was conducted to evaluate physical compatibility of posaconazole injection with injectable drug products and commonly used intravenous diluents during simulated Y-site infusion. Compatibility was determined through visual observations, measurement of particulate matter and turbidity. Compatible diluents and drug products are listed in **Tables 5 and 6** below. Any diluents or drug products not listed in the tables below should not be co-administered through the same intravenous line (or cannula).

- Posaconazole injection can be infused at the same time through the same intravenous line (or cannula) with the following compatible diluents:

Table 5: Compatible Diluents

0.45% sodium chloride
0.9% sodium chloride
5% dextrose in water
5% dextrose and 0.45% sodium chloride
5% dextrose and 0.9% sodium chloride
5% dextrose and 20 mEq potassium chloride

- Posaconazole injection can be infused at the same time through the same intravenous line (or cannula) with the following drug products prepared in 5% dextrose in water or sodium chloride 0.9%. Co-administration of drug products prepared in other diluents may result in particulate formation.

Table 6: Compatible Drugs

Amikacin sulfate
Caspofungin
Ciprofloxacin
Daptomycin
Dobutamine hydrochloride
Famotidine
Filgrastim
Gentamicin sulfate
Hydromorphone hydrochloride
Levofloxacin
Lorazepam
Meropenem
Micafungin
Morphine sulfate
Norepinephrine bitartrate
Potassium chloride
Vancomycin hydrochloride

Incompatible Diluents:

Posaconazole injection must not be diluted with the following diluents:

Lactated Ringer’s solution

5% dextrose with Lactated Ringer’s solution

4.2% sodium bicarbonate

Administration:

- Posaconazole injection must be administered through a 0.22-micron polyethersulfone (PES) or polyvinylidene difluoride (PVDF) filter.
- Administer via a central venous line, including a central venous catheter or PICC by slow infusion over approximately 90 minutes. Posaconazole injection is not for bolus administration.
- If a central venous catheter is not available, posaconazole injection may be administered through a peripheral venous catheter only as a single-dose in advance of central venous line placement or to bridge the period during which a central venous line is replaced or is in use for other treatment.
- When multiple dosing is required, the infusion should be done via a central venous line. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes. Note: In clinical trials, multiple peripheral infusions given through the same vein resulted in infusion site reactions *[see Adverse Reactions (6.1)]*.

2.9 Dosage Adjustments in Patients with Renal Impairment

- Posaconazole injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of posaconazole injection.
- In patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <50 mL/min), receiving the posaconazole injection, accumulation of the intravenous vehicle, Betadex Sulfobutyl Ether Sodium (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.

3 DOSAGE FORMS AND STRENGTHS

Posaconazole Injection

Posaconazole injection (300 mg per vial) is available as a clear, colorless to yellow sterile liquid in a single-dose vial.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

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

4.2 Use with Sirolimus

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

4.3 QT Prolongation with Concomitant Use with CYP3A4 Substrates

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

4.4 HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 (e.g., atorvastatin, lovastatin, and simvastatin) is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

4.5 Use with Ergot Alkaloids

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

4.6 Use with Venetoclax

Coadministration of posaconazole 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 (5.10) and Drug Interactions (7.16)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Calcineurin-Inhibitor Toxicity

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

5.2 Arrhythmias and QT Prolongation

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

Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval. Multiple, time-matched ECGs collected over a 12-hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18 to 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 posaconazole had a QTc(F) interval ≥500 msec or an increase ≥60 msec in their QTc(F) interval from baseline.

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

5.3 Electrolyte Disturbances

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

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

5.5 Renal Impairment

Posaconazole injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of posaconazole injection. In patients with moderate or severe renal impairment (eGFR <50 mL/min), receiving the posaconazole 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 (2.9) and Use in Specific Populations (8.6)]*.

5.6 Midazolam Toxicity

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

5.7 Vincristine Toxicity

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

5.10 Venetoclax Toxicity

Concomitant administration of posaconazole, 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 posaconazole during initiation and the ramp-up phase of venetoclax is contraindicated *[see Contraindications (4.6)]*. Refer to the venetoclax labeling for safety monitoring and dose reduction in the steady daily dosing phase in CLL/SLL patients.

For patients with acute myeloid leukemia (AML), dose reduction and safety monitoring are recommended across all dosing phases when coadministering posaconazole with venetoclax *[see Drug Interactions (7.16)]*. 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:

- Hypersensitivity *[see Contraindications (4.1)]*
- Arrhythmias and QT Prolongation *[see Warnings and Precautions (5.2)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

Clinical Trial Experience in Adults

Clinical Trial Experience with Posaconazole Injection for Prophylaxis

Multiple doses of posaconazole injection administered via a peripheral venous catheter were associated with thrombophlebitis (60% incidence). Therefore, in subsequent studies, posaconazole injection was administered via central venous catheter.

The safety of posaconazole injection has been assessed in 268 patients in a clinical trial. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole injection when given as antifungal prophylaxis (Posaconazole 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 to 82 years, 19% of patients were ≥65 years of age), and were 95% white and 8% Hispanic. Ten patients received a single-dose of 200 mg posaconazole injection, 21 patients received 200 mg daily dose for a median of 14 days, and 237 patients received 300 mg daily dose for a median of 9 days.

Table 8 presents adverse reactions observed in patients treated with posaconazole injection 300 mg daily dose in the Posaconazole Injection Study. Each patient received a loading dose, 300 mg twice on Day 1. Following posaconazole intravenous therapy, patients received Noxafil oral suspension to complete 28 days of total posaconazole therapy.

Table 8: Posaconazole Injection Study: Adverse Reactions in at Least 10% of Subjects Treated with Posaconazole Injection 300 mg Daily Dose

Body System	**Posaconazole Injection Treatment Phase n=237 (%)***		**Posaconazole Injection Treatment Phase or Subsequent Noxafil Oral Suspension Treatment Phase n=237 (%)†**	
Subjects Reporting any Adverse Reaction	220	(93)	235	(99)
Blood and Lymphatic System Disorder				
Anemia	16	(7)	23	(10)
Thrombocytopenia	17	(7)	25	(11)
Gastrointestinal Disorders				
Abdominal Pain Upper	15	(6)	25	(11)
Abdominal Pain	30	(13)	41	(17)
Constipation	18	(8)	31	(13)
Diarrhea	75	(32)	93	(39)
Nausea	46	(19)	70	(30)
Vomiting	29	(12)	45	(19)
General Disorders and Administration Site Conditions				
Fatigue	19	(8)	24	(10)
Chills	28	(12)	38	(16)
Edema Peripheral	28	(12)	35	(15)
Pyrexia	49	(21)	73	(31)
Metabolism and Nutrition Disorders				
Decreased appetite	23	(10)	29	(12)
Hypokalemia	51	(22)	67	(28)
Hypomagnesemia	25	(11)	30	(13)
Nervous System Disorders				

Headache	33	(14)	49	(21)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	21	(9)	31	(13)
Dyspnea	16	(7)	24	(10)
Epistaxis	34	(14)	40	(17)
Skin and Subcutaneous Tissue Disorders				
Petechiae	20	(8)	24	(10)
Rash	35	(15)	56	(24)
Vascular Disorders				
Hypertension	20	(8)	26	(11)

* Adverse reactions reported in patients with an onset during the posaconazole 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 posaconazole therapy.

The most frequently reported adverse reactions with an onset during the posaconazole intravenous 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.

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6.2 Postmarketing Experience

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

Endocrine Disorders: Pseudoaldosteronism

7 DRUG INTERACTIONS

Posaconazole is primarily metabolized via UDP glucuronosyltransferase and is a substrate of p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. Coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections.

Posaconazole is also a strong inhibitor of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole *[see Clinical Pharmacology (12.3)]*.

The following information was derived from data with Noxafil oral suspension or early tablet formulation unless otherwise noted. All drug interactions with Noxafil oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility), are considered relevant to posaconazole injection as well.

7.1 Immunosuppressants Metabolized by CYP3A4

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

Tacrolimus: Posaconazole has been shown to significantly increase the C_{max} and AUC of tacrolimus. At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

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

7.2 CYP3A4 Substrates

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

7.3 HMG-CoA Reductase Inhibitors (Statins) Primarily Metabolized Through CYP3A4

Concomitant administration of posaconazole with simvastatin increases the simvastatin plasma concentrations by approximately 10-fold. Therefore, posaconazole is contraindicated with HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 *[see Contraindications (4.4) and Clinical Pharmacology (12.3)]*.

7.4 Ergot Alkaloids

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

7.5 Benzodiazepines Metabolized by CYP3A4

Concomitant administration of posaconazole with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant use of posaconazole and other benzodiazepines metabolized by CYP3A4 (e.g., alprazolam, triazolam) could result in increased plasma concentrations of these

benzodiazepines. Patients must be monitored closely for adverse effects associated with high plasma concentrations of benzodiazepines metabolized by CYP3A4 and benzodiazepine receptor antagonists must be available to reverse these effects *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)].*

7.6 Anti-HIV Drugs

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

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

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

7.7 Rifabutin

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

7.8 Phenytoin

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

7.10 Vinca Alkaloids

Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions *[see Warnings and Precautions (5.7)].* Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including

vincristine, who have no alternative antifungal treatment options.

7.11 Calcium Channel Blockers Metabolized by CYP3A4

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

7.12 Digoxin

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

7.14 Glipizide

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

7.16 Venetoclax

Concomitant use of venetoclax (a CYP3A4 substrate) with posaconazole increases venetoclax C_{max} and $AUC_{0\text{-}INF}$, which may increase venetoclax toxicities *[see Contraindications (4.6), Warnings and Precautions (5.10)]*. Refer to the venetoclax prescribing information for more information on the dosing instructions and the extent of increase in venetoclax exposure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal data, posaconazole may cause fetal harm when administered to pregnant women. Available data for use of posaconazole in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, skeletal malformations (cranial malformations and missing ribs) and maternal toxicity (reduced food consumption and reduced body weight gain) were observed when posaconazole was dosed orally to pregnant rats during organogenesis at doses ≥1.4 times the 400 mg twice daily oral suspension regimen based on steady-state plasma concentrations of posaconazole in healthy volunteers. In pregnant rabbits dosed orally during organogenesis, increased resorptions, reduced litter size, and reduced body weight gain of females were seen at doses 5 times the exposure achieved with the 400 mg twice daily oral suspension regimen. Doses of ≥ 3 times the clinical exposure caused an increase in resorptions in these rabbits *(see Data)*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically 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 posaconazole and any potential adverse effects on the breastfed child from posaconazole or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of posaconazole have not been established in pediatric patients younger than 2 years of age.

Pediatric Use information is approved for Merck Sharp & Dohme Corp.'s NOXAFIL (posaconazole) injection. However, due to Merck Sharp & Dohme Corp.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

8.5 Geriatric Use

No overall differences in the safety of **posaconazole injection** were observed between geriatric patients and younger adult patients in the clinical trials; therefore, no dosage adjustment is recommended for any formulation of posaconazole in geriatric patients. No clinically meaningful differences in the pharmacokinetics of posaconazole were

observed in geriatric patients compared to younger adult patients during clinical trials *[see Clinical Pharmacology (12.3)]*.

Of the 279 patients treated with **posaconazole injection** in the Posaconazole Injection Study, 52 (19%) were greater than 65 years of age. Of the 288 patients randomized to posaconazole injection in the Aspergillosis Treatment Study, 85 (29%) were ≥65 years of age.

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

8.6 Renal Impairment

Posaconazole injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of posaconazole injection. In patients with moderate or severe renal impairment (eGFR <50 mL/min), receiving the posaconazole 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 (2.9) and Warnings and Precautions (5.5)]*.

8.7 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 Cmax was 1% higher, 40% higher, and 34% lower in subjects with mild, moderate, or severe hepatic impairment, respectively. The mean apparent oral clearance (CL/F) was reduced by 18%, 36%, and 28% in subjects with mild, moderate, or severe hepatic impairment, respectively, compared to subjects with normal hepatic function. The elimination half-life (t½) was 27 hours, 39 hours, 27 hours, and 43 hours in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment, respectively.

It is recommended that no dose adjustment of Noxafil oral suspension, Noxafil delayed-release tablets, Noxafil PowderMix for delayed-release oral suspension, and posaconazole injection is needed in patients with mild to severe hepatic impairment (Child-Pugh Class A, B, or C) *[see Dosage and Administration (2)* and *Warnings and Precautions (5.4)]*. However, a specific study has not been conducted with, Noxafil delayed-release tablets, Noxafil PowderMix for delayed-release oral suspension, and posaconazole injection.

8.8 Gender

The pharmacokinetics of posaconazole are comparable in males and females. No adjustment in the dosage of posaconazole is necessary based on gender.

8.9 Race

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

8.10 Weight

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

10 OVERDOSAGE

There is no experience with overdosage of posaconazole injection.

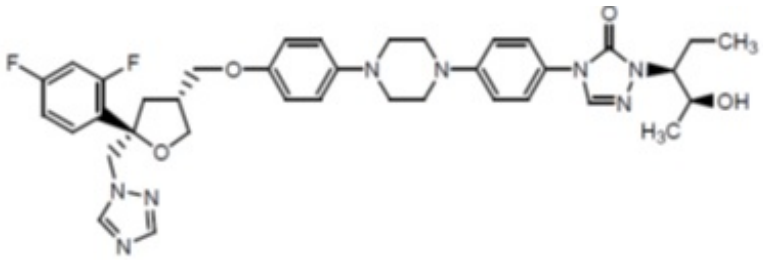
During the clinical trials, some patients received Noxafil oral suspension up to 1,600 mg/day with no adverse reactions noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1,200 mg twice daily Noxafil oral suspension for 3 days. No related adverse reactions were noted by the investigator.

Posaconazole is not removed by hemodialysis.

11 DESCRIPTION

Posaconazole injection is an azole antifungal agent available as concentrated solution to be diluted before intravenous administration.

Posaconazole is designated chemically as 4-[4-[4-[4-[[(3*R*,5*R*)-5- (2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1*S*,2*S*)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one with an molecular formula of $C_{37}H_{42}F_2N_8O_4$ and a molecular weight of 700.78. The chemical structure is:



Posaconazole is a white to off-white crystalline powder with a low aqueous solubility.

Posaconazole Injection

Posaconazole injection is available as a clear colorless to yellow, 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

General Pharmacokinetic Characteristics

Posaconazole Injection

Posaconazole 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 posaconazole injection in healthy volunteers and patients are shown in **Table 18**.

Table 18: 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 Posaconazole 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	35,400 (50)	8,840 (20)	2,250 (29)	23.6 (23)	6.5 (32)
	300	9	46,400 (26)	13,000 (13)	2,840 (30)	24.6 (20)	6.9 (27)
Patients	200	30	N/D	5,570 (32)	954 (44)	N/D	N/D
	300	22	N/D	8,240 (26)	1,590 (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; $t_{1/2}$ = terminal phase half-life; CL = total body clearance; N/D = Not Determined

Table 19 displays the pharmacokinetic parameters of posaconazole in patients following administration of posaconazole injection 300 mg taken once a day for 10 or 14 days following twice daily dosing on Day 1.

Table 19: Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Patients Following Dosing of Posaconazole Injection (300 mg)*

Day	N	C_{max}	$T_{max}^{\dagger}$	AUC_{0-24}	Cav	C_{min}

Day	N	(ng/mL)	(hr)	(ng*hr/mL)	(ng/mL)	(ng/mL)
10/14	49	3,280 (74)	1.5 (0.98 to 4)	36,100 (35)	1,500 (35)	1,090 (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)

Distribution:

The mean volume of distribution of posaconazole after intravenous solution administration was 261 L and ranged from 226 to 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 primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. A summary of drugs studied clinically with the oral suspension or an early tablet formulation, which affect posaconazole concentrations, is provided in **Table 27.**

Table 27: Summary of the Effect of Coadministered Drugs on Posaconazole in Healthy Volunteers

Coadministered Drug (Postulated Mechanism of Interaction)	Coadministered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Posaconazole	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)
Efavirenz (UDP-G	400 mg once daily × 10 and 20	400 mg (oral suspension) twice	↓ 45%	↓ 50% (0.50; 0.43-

Induction)	daily × 10 and 20 days	daily × 10 and 20 days	(0.55; 0.47-0.66)	(0.50; 0.43-0.60)
Fosamprenavir (unknown mechanism)	700 mg twice daily x 10 days	200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days	↓ 21% 0.79 (0.71-0.89)	↓ 23% 0.77 (0.68-0.87)
Rifabutin (UDP-G Induction)	300 mg once daily x 17 days	200 mg (tablets) once daily × 10 days†	↓ 43% (0.57; 0.43-0.75)	↓ 49% (0.51; 0.37-0.71)
Phenytoin (UDP-G Induction)	200 mg once daily x 10 days	200 mg (tablets) once daily × 10 days†	↓ 41% (0.59; 0.44-0.79)	↓ 50% (0.50; 0.36-0.71)

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

In vitro studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4. A clinical study in healthy volunteers also indicates that posaconazole is a strong CYP3A4 inhibitor as evidenced by a >5-fold increase in midazolam AUC. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole. A summary of the drugs studied clinically, for which plasma concentrations were affected by posaconazole, is provided in **Table 28** *[see Contraindications (4)* and *Drug Interactions (7.1) including recommendations]*.

Table 28: Summary of the Effect of Posaconazole 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**	**Posaconazole Dose/Schedule**	**Effect on Bioavailability of Coadministered Drugs**	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	**Change in Mean AUC** (ratio estimate*; 90% CI of the ratio estimate)
Sirolimus	2-mg single oral dose	400 mg (oral suspension) 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	↑ 121% (2.21; 2.01-	↑ 358% (4.58; 4.03-

		daily × 7 days	2.42)	5.19)
Simvastatin	40-mg single oral dose	100 mg (oral suspension) once daily x 13 days	Simvastatin ↑ 841% (9.41, 7.13-12.44)	Simvastatin ↑ 931% (10.31, 8.40-12.67)
			Simvastatin Acid ↑ 817% (9.17, 7.36-11.43)	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 ↑ 960% (10.60, 8.63-13.02)
			Simvastatin Acid ↑ 851% (9.51, 8.15-11.10)	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 × 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)
Ritonavir	100 mg once daily x 14 days	400 mg (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 posaconazole to coadministered drug alone for C_{max} or AUC.

† The tablet refers to a non-commercial tablet formulation without polymer.

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

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

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).

Posaconazole 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 to 66 hours).

Specific Populations

No clinically significant differences in the pharmacokinetics of posaconazole were observed based on age, sex, renal impairment, and indication (prophylaxis or treatment).

Race/Ethnicity:

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

Patients Weighing More Than 120 kg:

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

Pediatric Use information is approved for Merck Sharp & Dohme Corp.'s NOXAFIL (posaconazole) injection. However, due to Merck Sharp & Dohme Corp.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

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).

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.2 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 32** contains the results from Noxafil Oral Suspension Study 1.

Table 32: 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 Proven/probable fungal infection prior to death	22 (7%) 2 (<1%)	24 (8%) 6 (2%)
SAF†	27 (9%)	25 (8%)
Through 16 weeks		
Clinical Failure*,‡	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(Aspergillus)	7 (2%)	21 (7%)
(Candida)	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths Proven/probable fungal infection prior to death	58 (19%) 10 (3%)	59 (20%) 16 (5%)
SAF†	26 (9%)	30 (10%)
Event free lost to follow-up§	24 (8%)	30 (10%)

* Patients may have met more 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 postrandomization. The mean duration of therapy was comparable between the 2 treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole).

Table 33 contains the results from Noxafil Oral Suspension Study 2.

Table 33: 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 Proven/probable fungal infection prior to death	17 (6%) 1 (<1%)	25 (8%) 2 (1%)
SAF‡	67 (22%)	98 (33%)
Through 100 days postrandomization		
Clinical Failure†	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(Aspergillus)	2 (1%)	26 (9%)
(Candida)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths Proven/probable fungal infection prior to death	44 (14%) 2 (1%)	64 (21%) 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 (**Tables 32 and 33**), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Noxafil Oral Suspension Study 1 (**Table 32**), 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 33**) 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 posaconazole-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 posaconazole prophylaxis when compared to patients receiving fluconazole or itraconazole.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Posaconazole Injection

Posaconazole injection is available as a clear, colorless to yellow sterile liquid in single-dose Type I glass vials closed with bromobutyl rubber stopper and aluminum seal and is supplied as follows.

300 mg per 16.7 mL (18 mg/mL):

16.7 mL Single-Dose Vial

Packaged Individually NDC 55150-388-01

16.2 Storage and Handling

Posaconazole Injection

Posaconazole injection vial should be stored refrigerated at 2 to 8°C (36 to 46°F). Storage conditions for the diluted solution are presented in another section of the prescribing information *[see Dosage and Administration (2.4)].*

The vial stopper is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

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

Important Administration Instructions

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.

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

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Manufactured by:
Eugia Pharma Specialities Limited
Hyderabad - 500032
India

Patient Information

Posaconazole (POE-sa-KON-a-zole)
Injection

What is posaconazole injection?

Posaconazole injection is prescription medicine used in adults to help prevent fungal infections that can spread throughout your body (invasive fungal infections). These infections are caused by fungi called *Aspergillus* or *Candida*. Posaconazole injection is used in people who have an increased chance of getting these infections due to a weak immune system. These include people who have had a hematopoietic stem cell transplantation (bone marrow transplant) with graft versus host disease or those with a low white blood cell count due to chemotherapy for blood cancers (hematologic malignancy)

Posaconazole injection is used for
- prevention of fungal infections in adults.

It is not known if posaconazole injection is safe and effective in children under 2 years of

age.

Who should not take posaconazole injection?

Do not take posaconazole injection if you:
• are allergic to posaconazole, any of the ingredients in posaconazole injection, or other azole antifungal medicines. See the end of this leaflet for a complete list of ingredients in posaconazole injection.
• are taking any of the following medicines:
  o sirolimus
  o pimozide
  o quinidine
  o certain statin medicines that lower cholesterol (atorvastatin, lovastatin, simvastatin)
  o ergot alkaloids (ergotamine, dihydroergotamine)
• have chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) and you have just started taking venetoclax or your venetoclax dose is being slowly increased.

Ask your healthcare provider or pharmacist if you are not sure if you are taking any of these medicines.
Do not start taking a new medicine without talking to your healthcare provider or pharmacist.

What should I tell my healthcare provider before taking posaconazole injection?

Before you take posaconazole injection, tell your healthcare provider if you:
• are taking certain medicines that lower your immune system like cyclosporine or tacrolimus.
• are taking certain drugs for HIV infection, such as ritonavir, atazanavir, efavirenz, or fosamprenavir. Efavirenz and fosamprenavir can cause a decrease in the posaconazole levels in your body. Efavirenz and fosamprenavir should not be taken with posaconazole injection.
• are taking midazolam, a hypnotic and sedative medicine.
• are taking vincristine, vinblastine and other “vinca alkaloids” (medicines used to treat cancer).
• are taking venetoclax, a medicine used to treat cancer.
• have or had liver problems.
• have or had kidney problems.
• have or had an abnormal heart rate or rhythm, heart problems, or blood circulation problems.
• are pregnant or plan to become pregnant. It is not known if posaconazole injection will harm your unborn baby.
• are breastfeeding or plan to breastfeed. It is not known if posaconazole passes into your breast milk. You and your healthcare provider should decide if you will take posaconazole injection 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. Posaconazole injection can affect the way other medicines work, and other medicines can affect the way posaconazole injection work, and can cause serious side effects.

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 will I take posaconazole injection?
• Take posaconazole injection exactly as your healthcare provider tells you to take it.
• Your healthcare provider will tell you how much posaconazole injection to take and when to take it.
• Take posaconazole injection for as long as your healthcare provider tells you to take it.
• If you take too much posaconazole, call your healthcare provider or go to the nearest hospital emergency room right away.
• Posaconazole injection is usually given over 30 to 90 minutes through a plastic tube placed in your vein.

What are the possible side effects of posaconazole injection?

Posaconazole injection may cause serious side effects, including:

• **drug interactions with cyclosporine or tacrolimus.** If you take posaconazole injection with cyclosporine or tacrolimus, your blood levels of cyclosporine or tacrolimus may increase. Serious side effects can happen in your kidney or brain if you have high levels of cyclosporine or tacrolimus in your blood. Your healthcare provider should do blood tests to check your levels of cyclosporine or tacrolimus if you are taking these medicines while taking posaconazole injection. Tell your healthcare provider right away if you have swelling in your arm or leg or shortness of breath.

• **problems with the electrical system of your heart (arrhythmias and QTc prolongation)**. Certain medicines used to treat fungus called azoles, including posaconazole, the active ingredient in posaconazole, may cause heart rhythm problems. People who have certain heart problems or who take certain medicines have a higher chance for this problem. Tell your healthcare provider right away if your heartbeat becomes fast or irregular.

• **changes in body salt (electrolytes) levels in your blood.** Your healthcare provider should check your electrolytes while you are taking posaconazole.

• **liver problems.** Some people who also have other serious medical problems may have severe liver problems that may lead to death, especially if you take certain doses of posaconazole injection. Your healthcare provider should do blood tests to check your liver while you are taking posaconazole injection. Call your healthcare provider right away if you have any of the following symptoms of liver problems:

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

• **increased amounts of midazolam in your blood.** If you take posaconazole injection with midazolam, posaconazole injection increases the amount of midazolam in your blood. This can make your sleepiness last longer. Your healthcare provider should check you closely for side effects if you take midazolam with posaconazole injection.
The most common side effects of posaconazole injection include:
- diarrhea
- headache

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

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

These are not all the possible side effects of posaconazole injection. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store posaconazole injection?
Posaconazole injection
- Store posaconazole injection refrigerated at 36°F to 46°F (2°C to 8°C).

Safely throw away medicine that is out of date or no longer needed.

Keep posaconazole injection and all medicines out of the reach of children.
General information about the safe and effective use of posaconazole injection.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use posaconazole injection for a condition for which it was not prescribed. Do not give posaconazole injection to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about posaconazole injection that is written for health professionals.

What are the ingredients in posaconazole injection?

Active ingredient: posaconazole

Inactive ingredients:

Posaconazole injection: Betadex Sulfobutyl Ether Sodium (SBECD), edetate disodium, hydrochloric acid, sodium hydroxide, and water for injection.

Pediatric Use information is approved for Merck Sharp & Dohme Corp.'s NOXAFIL (posaconazole) injection. However, due to Merck Sharp & Dohme Corp.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

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Manufactured by:
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Hyderabad - 500032
India

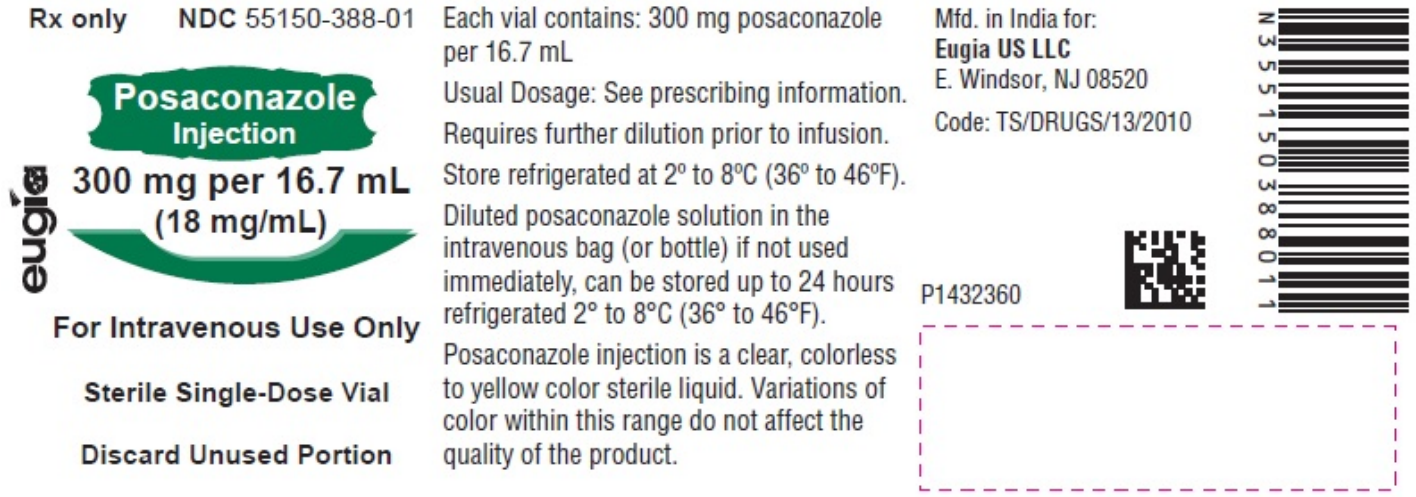
For more information, go to eugiaus.com or call 1-888-238-7880.

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

Revised: February 2023

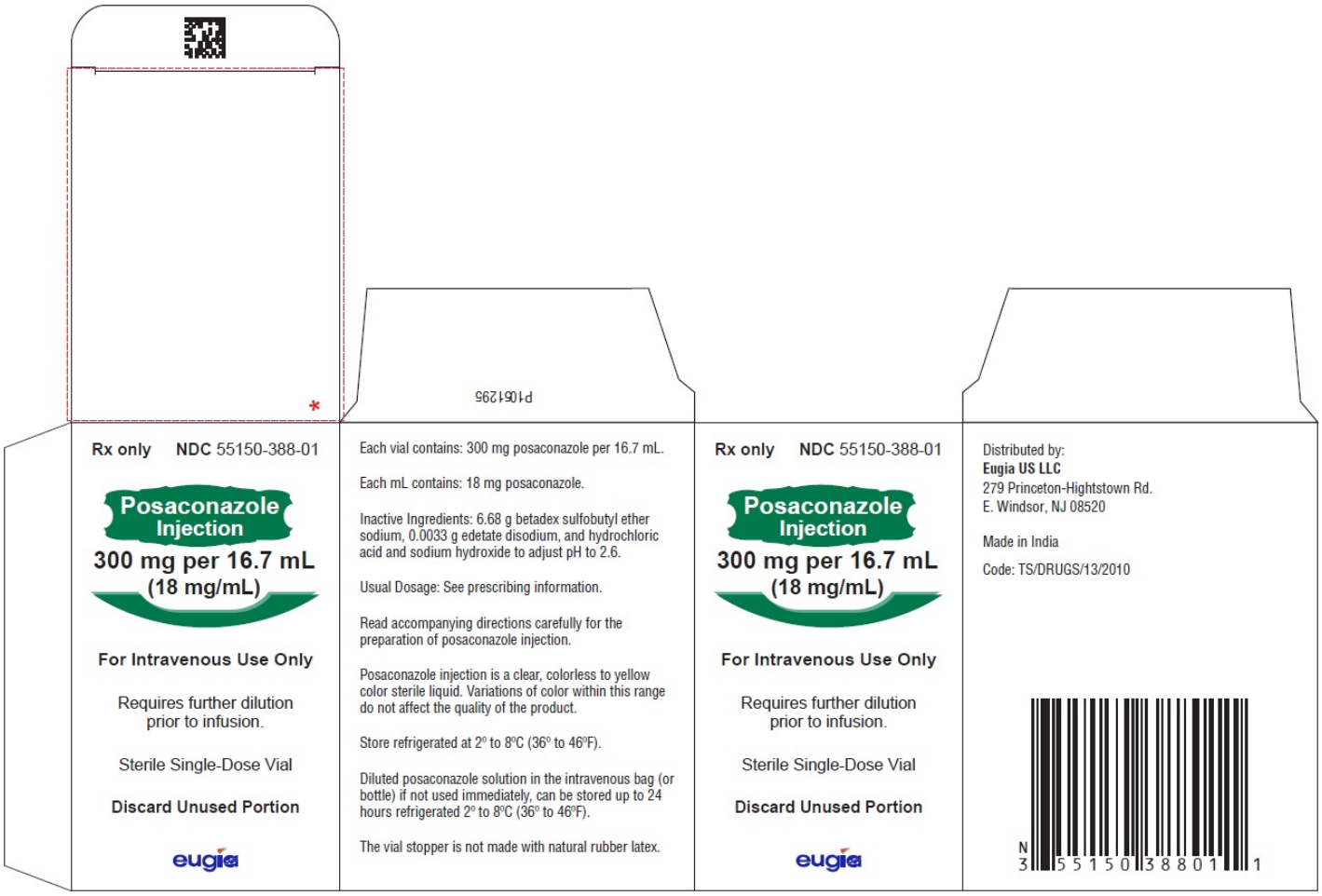
PACKAGE LABEL-PRINCIPAL DISPLAY PANEL-300 mg per 16.7 mL (18 mg/mL)-Container Label

Rx only **NDC** 55150-388-01
Posaconazole
Injection
300 mg per 16.7 mL
(18 mg/mL)
For Intravenous Use Only
Sterile Single-Dose Vial
Discard Unused Portion



PACKAGE LABEL-PRINCIPAL DISPLAY PANEL-300 mg per 16.7 mL (18 mg/mL) – Container-Carton Label

Rx only **NDC** 55150-388-01
Posaconazole
Injection
300 mg per 16.7 mL
(18 mg/mL)
For Intravenous Use Only
Requires further dilution
prior to infusion.
Sterile Single-Dose Vial
Discard Unused Portion
eugia



POSACONAZOLE

posaconazole injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:55150-388
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:55150-388-01	1 in 1 CARTON	12/26/2023	
1		16.7 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA214842	12/26/2023	

Labeler - Eugia US LLC (968961354)

Establishment

Name	Address	ID/FEI	Business Operations
Eugia Pharma Specialities Limited		650498244	ANALYSIS(55150-388) , MANUFACTURE(55150-388) , PACK(55150-388)

Revised: 12/2023 Eugia US LLC