POSACONAZOLE- posaconazole suspension
Hikma Pharmaceuticals USA Inc.

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

POSACONAZOLE oral suspension
Initial U.S. Approval: 2006

RECENT MAJOR CHANGES

Warnings and Precautions, Pseudoaldosteronism (5.4) 10/2024

INDICATIONS AND USAGE

Posaconazole is an azole antifungal indicated as follows:

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

DOSAGE AND ADMINISTRATION

- **Posaconazole oral suspension** is not substitutable with **posaconazole delayed-release tablets** or **posaconazole powder 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)
- Administer **posaconazole oral suspension** with a full meal. (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 Oral Suspension:** 200 mg (5 mL) three times a day. Duration of therapy is based on recovery from neutropenia or immunosuppression. (2.2, 2.3)
Oropharyngeal Candidiasis (OPC)	**Posaconazole Oral Suspension:** Loading Dose: 100 mg (2.5 mL) twice a day on the first day. Maintenance Dose: 100 mg (2.5 mL) once a day for 13 days. (2.2, 2.3)
OPC Refractory (rOPC) to Itraconazole and/or Fluconazole	**Posaconazole Oral Suspension:** 400 mg (10 mL) twice a day. Duration of therapy is based on the severity of the patient's underlying disease and clinical response. (2.2, 2.3)

- For pediatric patients, see the Full Prescribing Information for dosing recommendations for **posaconazole oral suspension** based on the age and indication associated with the dosage form. (1.2, 1.3, 2.1, 2.3)

DOSAGE FORMS AND STRENGTHS

Posaconazole oral suspension: 40 mg per mL (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, 5.11, 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)
- 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)
- Concomitant Use with Midazolam: Posaconazole can prolong hypnotic/sedative effects. Monitor patients and benzodiazepine receptor antagonists should be available. (5.7, 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. (5.8, 7.10)
- Breakthrough Fungal Infections: Monitor patients with severe diarrhea or vomiting when receiving posaconazole oral suspension. (5.10)
- 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, 5.11, 7.16)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-800-962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Interaction Drug	**Interaction**
Rifabutin, phenytoin, efavirenz, cimetidine, esomeprazole	*Avoid coadministration unless the benefit outweighs the risks (7.6, 7.7, 7.8, 7.9)*
Other drugs metabolized by CYP3A4	*Consider dosage adjustment and monitor for adverse effects and toxicity (7.1, 7.10, 7.11)*
Digoxin	*Monitor digoxin plasma concentrations (7.12)*
Fosamprenavir, metoclopramide	*Monitor for breakthrough fungal infections (7.6, 7.13)*

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Pediatrics: Safety and effectiveness in patients younger than 13 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: 12/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Posaconazole 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 (14.2)]*

as follows:

- **Posaconazole oral suspension:** adults and pediatric patients 13 years of age and older

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

Posaconazole 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

Non-substitutable:

Posaconazole oral suspension is not substitutable with **posaconazole delayed-release tablets** or **posaconazole powder for delayed-release oral suspension** due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations *[see Dosage and Administration (2.2, 2.3)]*.

Posaconazole 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 (2.6)].*
- Co-administration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections *[see Drug Interactions (7.6, 7.7, 7.8, 7.9, 7.13)].*

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 Oral Suspension:** 200 mg (5 mL) three times a day.	Duration of therapy is based on recovery from neutropenia or immunosuppression.
Oropharyngeal Candidiasis (OPC)	**Posaconazole Oral Suspension:** Loading dose: 100 mg (2.5 mL) twice a day on the first day. Maintenance dose: 100 mg (2.5 mL) once a day thereafter.	Loading dose: 1 day Maintenance dose: 13 days
OPC Refractory	**Posaconazole Oral Suspension:** 400 mg (10	Duration of therapy is

(rOPC) to Itraconazole and/or Fluconazole	mL) twice a day.	based on the severity of the patient's underlying disease and clinical response.

2.3 Dosing Regimen in Pediatric Patients (ages 13 to less than 18 years of age)

The recommended dosing regimen of posaconazole oral suspension for pediatric patients ages 13 to less than 18 years of age is shown in **Table 3***[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)]*.

Table 3: Posaconazole Oral Suspension Dosing Regimens for Pediatric Patients (ages 13 to less than 18 years of age)

Indication	Loading Dose (volume) and frequency	Maintenance Dose (volume) and frequency	Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	200 mg (5 mL) three times a day	200 mg (5 mL) three times a day	Duration of therapy is based on recovery from neutropenia or immunosuppression.
Oropharyngeal Candidiasis (OPC)	100 mg (2.5 mL) twice daily on the first day.	100 mg (2.5 mL) once daily	13 days
OPC Refractory (rOPC) to Itraconazole and/or Fluconazole	400 mg (10 mL) twice daily	400 mg (10 mL) twice daily	Duration of therapy is based on the severity of the patient's underlying disease and clinical response.

2.6 Administration Instructions for Posaconazole Oral Suspension

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

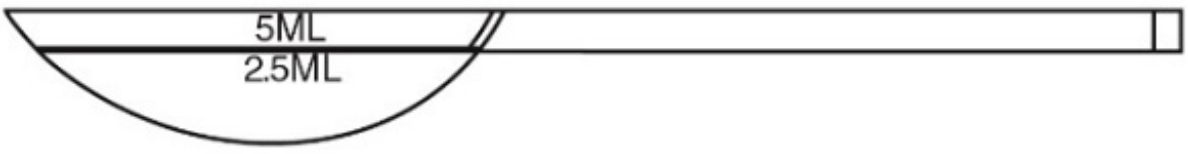


Figure 1: A measured dosing spoon is provided, marked for doses of 2.5 mL and 5 mL.

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

2.7 Non-substitutability between Posaconazole Oral Suspension and Other Formulations

Posaconazole oral suspension is not substitutable with posaconazole delayed-release tablets or posaconazole powder 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)]*.

2.9 Dosage Adjustments in Patients with Renal Impairment

The pharmacokinetics of posaconazole oral suspension are not significantly affected by renal impairment. Therefore, no adjustment is necessary for oral dosing in patients with mild to severe renal impairment.

3 DOSAGE FORMS AND STRENGTHS

Posaconazole oral suspension is available as a white to off-white, cherry brandy flavored suspension in 4-ounce (120 mL) amber glass bottles with child-resistant closures containing 105 mL of suspension (40 mg of posaconazole per mL).

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 (5.11) 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 posaconazole 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 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 posaconazole, 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 posaconazole. These severe hepatic reactions were seen primarily in subjects receiving the posaconazole 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.

5.6 Renal Impairment

Due to the variability in exposure with posaconazole oral suspension, patients with severe renal impairment should be monitored closely for breakthrough fungal infections *[see Dosage and Administration (2.9) and Use in Specific Populations (8.6)].*

5.7 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)]*.

5.8 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 Breakthrough Fungal Infections

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

5.11 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 (5.5)]*

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 Safety Experience with Posaconazole Oral Suspension:

The safety of posaconazole oral suspension has been assessed in 1,844 patients. This includes 605 patients in the active-controlled prophylaxis studies, 557 patients in the active-controlled OPC studies, 239 patients in refractory OPC studies, and 443 patients from other indications. This represents a heterogeneous population, including immunocompromised patients, e.g., patients with hematological malignancy, neutropenia post-chemotherapy, GVHD post HSCT, and HIV infection, as well as non-neutropenic patients. This patient population was 71% male, had a mean age of 42 years (range 8 to 84 years, 6% of patients were ≥65 years of age and 1% was <18 years of age), and were 64% white, 16% Hispanic, and 36% non-white (including 14% black). Posaconazole therapy was given to 171 patients for ≥6 months, with 58 patients receiving posaconazole therapy for ≥12 months. **Table 10** presents adverse reactions observed at an incidence of >10% in posaconazole prophylaxis studies. **Table 11** presents adverse reactions observed at an incidence of at least 10% in the OPC/rOPC studies.

Prophylaxis of *Aspergillus* and *Candida*: In the 2 randomized, comparative prophylaxis studies (Posaconazole Oral Suspension Study 1 and 2), the safety of posaconazole oral suspension 200 mg three times a day was compared to fluconazole 400 mg once daily or itraconazole 200 mg twice a day in severely immunocompromised patients.

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

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

Table 10: Posaconazole Oral Suspension Study 1 and Study 2. Adverse Reactions in at Least 10% of the Posaconazole Oral Suspension or Fluconazole Treatment Groups (Pooled Prophylaxis Safety Analysis)

Body System	**Posaconazole Oral Suspension n=605 (%)**		**Fluconazole n=539 (%)**		**Itraconazole n=58 (%)**	
Subjects Reporting any Adverse Reaction	595	(98)	531	(99)	58	(100)
Body as a Whole - General Disorders						
Fever	274	(45)	254	(47)	32	(55)
Headache	171	(28)	141	(26)	23	(40)
Rigors	122	(20)	87	(16)	17	(29)
Fatigue	101	(17)	98	(18)	5	(9)
Edema Legs	93	(15)	67	(12)	11	(19)
Anorexia	92	(15)	94	(17)	16	(28)
Dizziness	64	(11)	56	(10)	5	(9)
Edema	54	(9)	68	(13)	8	(14)

Weakness	51	(8)	52	(10)	2	(3)
Cardiovascular Disorders, General						
Hypertension	106	(18)	88	(16)	3	(5)
Hypotension	83	(14)	79	(15)	10	(17)
Disorders of Blood and Lymphatic System						
Anemia	149	(25)	124	(23)	16	(28)
Neutropenia	141	(23)	122	(23)	23	(40)
Disorders of the Reproductive System and Breast						
Vaginal Hemorrhage*	24	(10)	20	(9)	3	(12)
Gastrointestinal System Disorders						
Diarrhea	256	(42)	212	(39)	35	(60)
Nausea	232	(38)	198	(37)	30	(52)
Vomiting	174	(29)	173	(32)	24	(41)
Abdominal Pain	161	(27)	147	(27)	21	(36)
Constipation	126	(21)	94	(17)	10	(17)
Dyspepsia	61	(10)	50	(9)	6	(10)
Heart Rate and Rhythm Disorders						
Tachycardia	72	(12)	75	(14)	3	(5)
Infection and Infestations						
Pharyngitis	71	(12)	60	(11)	12	(21)
Liver and Biliary System Disorders						
Bilirubinemia	59	(10)	51	(9)	11	(19)
Metabolic and Nutritional Disorders						
Hypokalemia	181	(30)	142	(26)	30	(52)
Hypomagnesemia	110	(18)	84	(16)	11	(19)
Hyperglycemia	68	(11)	76	(14)	2	(3)
Hypocalcemia	56	(9)	55	(10)	5	(9)
Musculoskeletal System Disorders						
Musculoskeletal Pain	95	(16)	82	(15)	9	(16)
Arthralgia	69	(11)	67	(12)	5	(9)
Back Pain	63	(10)	66	(12)	4	(7)
Platelet, Bleeding and Clotting Disorders						
Thrombocytopenia	175	(29)	146	(27)	20	(34)
Petechiae	64	(11)	54	(10)	9	(16)
Psychiatric Disorders						
Insomnia	103	(17)	92	(17)	11	(19)
Respiratory System Disorders						
Coughing	146	(24)	130	(24)	14	(24)
Dyspnea	121	(20)	116	(22)	15	(26)
Epistaxis	82	(14)	73	(14)	12	(21)
Skin and Subcutaneous Tissue Disorders						
Rash	113	(19)	96	(18)	25	(43)
Pruritus	69	(11)	62	(12)	11	(19)

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

HIV Infected Subjects with OPC: In 2 randomized comparative studies in OPC, the safety of posaconazole oral suspension at a dose of less than or equal to 400 mg once daily in 557 HIV-infected patients was compared to the safety of fluconazole in 262 HIV-infected patients at a dose of 100 mg once daily.

An additional 239 HIV-infected patients with refractory OPC received posaconazole oral suspension in 2 non-comparative trials for refractory OPC (rOPC). Of these subjects, 149 received the 800 mg/day dose and the remainder received the less than or equal to 400 mg once daily dose.

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

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

Table 11: Adverse Reactions in at Least 10% of the Treated Population in OPC Studies with Posaconazole Oral Suspension

Body System	**Number (%) of Subjects**		
	Controlled OPC Pool		**Refractory OPC Pool**
	Posaconazole Oral Suspension	**Fluconazole**	**Posaconazole Oral Suspension**
	n=557	**n=262**	**n=239**
Subjects Reporting any Adverse Reaction*	356 (64)	175 (67)	221 (92)
Body as a Whole – General Disorders			
Fever	34 (6)	22 (8)	82 (34)
Headache	44 (8)	23 (9)	47 (20)
Anorexia	10 (2)	4 (2)	46 (19)
Fatigue	18 (3)	12 (5)	31 (13)
Asthenia	9 (2)	5 (2)	31 (13)
Rigors	2 (<1)	4 (2)	29 (12)
Pain	4 (1)	2 (1)	27 (11)
Disorders of Blood and Lymphatic System			
Neutropenia	21 (4)	8 (3)	39 (16)
Anemia	11 (2)	5 (2)	34 (14)
Gastrointestinal System Disorders			
Diarrhea	58 (10)	34 (13)	70 (29)
Nausea	48 (9)	30 (11)	70 (29)
Vomiting	37 (7)	18 (7)	67 (28)
Abdominal Pain	27 (5)	17 (6)	43 (18)
Infection and Infestations			
Candidiasis,	3 (1)	1 (<1)	28 (12)

Oral			
Herpes Simplex	16 (3)	8 (3)	26 (11)
Pneumonia	17 (3)	6 (2)	25 (10)
Metabolic and Nutritional Disorders			
Weight Decrease	4 (1)	2 (1)	33 (14)
Dehydration	4 (1)	7 (3)	27 (11)
Psychiatric Disorders			
Insomnia	8 (1)	3 (1)	39 (16)
Respiratory System Disorders			
Coughing	18 (3)	11 (4)	60 (25)
Dyspnea	8 (1)	8 (3)	28 (12)
Skin and Subcutaneous Tissue Disorders			
Rash	15 (3)	10 (4)	36 (15)
Sweating Increased	13 (2)	5 (2)	23 (10)

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

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

Other clinically significant adverse reactions reported in less than 5% of patients in clinical trials of posaconazole 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

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

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

Table 12: Posaconazole Oral Suspension Study 1 and Study 2. Changes in Liver Test Results from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4

Number (%) of Patients with Change*		
Posaconazole Oral Suspension Study 1		
Laboratory Parameter	Posaconazole 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)
Posaconazole Oral Suspension Study 2		
Laboratory Parameter	Posaconazole 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)
*Change from Grade 0 to 2 at baseline to Grade 3 or 4 during the study. These data are presented in the form X/Y, where X represents the number of patients who met the criterion as indicated, and Y represents the number of patients who had a baseline observation and at least one post-baseline observation. CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase.		

The number of patients treated for OPC with clinically significant liver 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: Posaconazole Oral Suspension Studies: Clinically Significant Laboratory Test Abnormalities without Regard to Baseline Value

Laboratory Test	**Controlled**		**Refractory**
	Posaconazole Oral Suspension	**Fluconazole**	**Posaconazole Oral Suspension**
	n=557(%)	**n=262(%)**	**n=239(%)**
ALT > 3.0 × ULN	16/537 (3)	13/254 (5)	25/226 (11)
AST > 3.0 × ULN	33/537 (6)	26/254 (10)	39/223 (17)
Total Bilirubin > 1.5 × ULN	15/536 (3)	5/254 (2)	9/197 (5)
Alkaline Phosphatase > 3.0 × ULN	17/535 (3)	15/253 (6)	24/190 (13)
ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase.			

The number 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%), AST (13%), and bilirubin (13%).

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

Number (%) of Patients with Change*		
Laboratory Parameter	**Posaconazole 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)
*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. N=Number of subjects 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.		

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 posaconazole oral suspension or early tablet formulation unless otherwise noted. All drug interactions with posaconazole oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility), are considered relevant to posaconazole injection, posaconazole delayed-release tablet, and posaconazole powder for delayed-release oral suspension as well *[see Drug Interactions (7.9) and (7.13)]*.

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 (5.7) and Clinical Pharmacology (12.3)].

7.6 Anti-HIV Drugs

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

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

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

7.7 Rifabutin

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

7.8 Phenytoin

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

7.9 Gastric Acid Suppressors/Neutralizers

Cimetidine (an H_2-receptor antagonist) and esomeprazole (a proton pump inhibitor) when given with posaconazole oral suspension results in decreased posaconazole plasma concentrations *[see Clinical Pharmacology (12.3)]*. It is recommended to avoid concomitant use of cimetidine and esomeprazole with posaconazole oral suspension unless the benefit outweighs the risks. However, if concomitant administration is required, close monitoring for breakthrough fungal infections is recommended.

No clinically relevant effects were observed when posaconazole oral suspension is concomitantly used with antacids and H_2-receptor antagonists other than cimetidine. No

dosage adjustment of posaconazole oral suspension is required when posaconazole oral suspension is concomitantly used with antacids and H_2-receptor antagonists other than cimetidine.

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 (5.8)].* 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.

7.13 Gastrointestinal Motility Agents

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

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

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 (5.11)]*. 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 oral suspension for the prophylaxis of invasive *Aspergillus* and *Candida* infections have been established in pediatric patients aged 13 and older who are at high risk of developing these infections due to being severely immunocompromised, such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

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

Use of posaconazole in these age groups is supported by evidence from adequate and well-controlled studies of posaconazole in adult and pediatric patients *[see Clinical Pharmacology (12.3) and Clinical Studies (14)].*

The safety and effectiveness of posaconazole oral suspension have not been established in pediatric patients younger than 13 years of age.

8.5 Geriatric Use

No overall differences in the safety of posaconazole oral suspension were observed between geriatric patients and younger adult patients in the clinical trials; therefore, no dosage adjustment is recommended for posaconazole oral suspension 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 605 patients randomized to posaconazole oral suspension in the Posaconazole Oral Suspension Study 1 and Study 2, 63 (10%) were ≥65 years of age. In addition, 48 patients treated with greater than or equal to 800-mg/day posaconazole oral suspension in another indication were ≥65 years of age.

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

8.6 Renal Impairment

Following single-dose administration of 400 mg of the posaconazole oral suspension, there was no significant effect of mild (eGFR: 50 to 80 mL/min/1.73 m^2, n=6) or moderate (eGFR: 20 to 49 mL/min/1.73 m^2, n=6) renal impairment on posaconazole pharmacokinetics; therefore, no dose adjustment is required in patients with mild to moderate renal impairment. In subjects with severe renal impairment (eGFR: <20 mL/min/1.73 m^2), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (eGFR: >80 mL/min/1.73 m^2); however, the range of the AUC estimates was highly variable (CV=96%) in these subjects with severe renal impairment as compared to that in the other renal impairment groups (CV<40%). Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections *[see Dosage and Administration (2)].*

8.7 Hepatic Impairment

After a single oral dose of posaconazole oral suspension 400 mg, the mean AUC was 43%, 27%, and 21% higher in subjects with mild (Child-Pugh Class A, N=6), moderate (Child-Pugh Class B, N=6), or severe (Child-Pugh Class C, N=6) hepatic impairment, respectively, compared to subjects with normal hepatic function (N=18). Compared to subjects with normal hepatic function, the mean C_{max} was 1% higher, 40% higher, and 34% lower in subjects with mild, moderate, or severe hepatic impairment, respectively. The mean apparent oral clearance (CL/F) was reduced by 18%, 36%, and 28% in subjects with mild, moderate, or severe hepatic impairment, respectively, compared to subjects with normal hepatic function. The elimination half-life ($t_{½}$) was 27 hours, 39 hours, 27 hours, and 43 hours in subjects with normal hepatic function and mild, moderate, or severe hepatic impairment, respectively.

It is recommended that no dose adjustment of posaconazole oral suspension 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 (5.5)]*.

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 *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

During the clinical trials, some patients received posaconazole 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 posaconazole oral suspension for 3 days. No related adverse reactions were noted by the investigator.

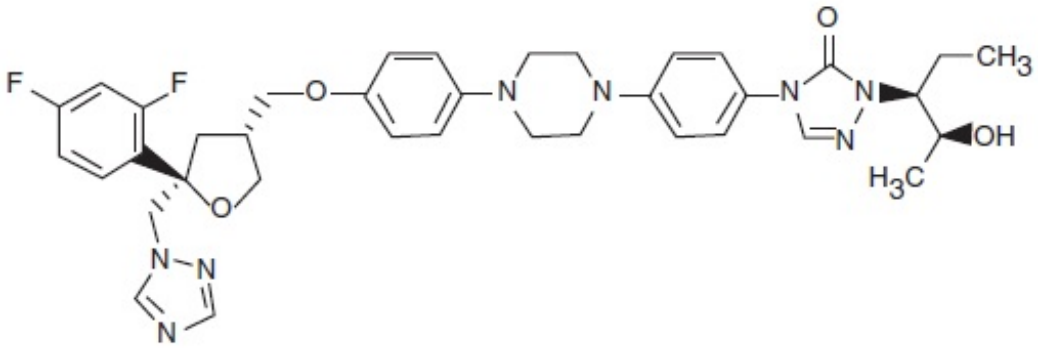
Posaconazole is not removed by hemodialysis.

11 DESCRIPTION

Posaconazole is an azole antifungal agent available as an injection solution to be diluted before intravenous administration, delayed-release tablet, oral suspension, and powder for delayed-release oral suspension intended for oral administration.

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

one with an empirical formula of $C_{37}H_{42}F_2N_8O_4$ and a molecular weight of 700.8. The chemical structure is:



Posaconazole is a white to off-white powder that is practically insoluble in water.

Posaconazole oral suspension is a white to off-white, cherry-brandy flavored immediate-release suspension containing 40 mg of posaconazole per mL and the following inactive ingredients: cherry-brandy flavor, citric acid monohydrate, hydroxyethyl cellulose, glycerin, polyoxyl 35 castor oil, simethicone emulsion, sodium benzoate, sodium citrate, sorbitol solution, titanium dioxide, and water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Exposure Response Relationship Prophylaxis: In clinical studies of neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) or hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD), a wide range of plasma exposures to posaconazole was noted following administration of posaconazole oral suspension. A pharmacokinetic-pharmacodynamic analysis of patient data revealed an apparent association between average posaconazole concentrations (Cavg) and prophylactic efficacy (**Table 17**). 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 17: Posaconazole 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 to 322	54.7	22 to 557	44.4
Quartile 2	322 to 490	37.0	557 to 915	20.6

Quartile 3	490 to 734	46.8	915 to 1,563	17.5
Quartile 4	734 to 2,200	27.8	1,563 to 3,650	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

12.3 Pharmacokinetics

General Pharmacokinetic Characteristics:

Dose-proportional increases in plasma exposure (AUC) to posaconazole oral suspension were observed following single oral doses from 50 mg to 800 mg and following multiple-dose administration from 50 mg 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] posaconazole 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 21.**

Table 21: The Mean (%CV) [min-max] Posaconazole Steady-State Pharmacokinetic Parameters in Patients Following Oral Administration of Posaconazole 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)	1,103 (67) [21.5 to 3650]	ND§	ND§	ND§	ND§
200 mg three times a day¶ (n=215)	583 (65) [89.7 to 2,200]	15,900 (62) [4100 to 56,100]	51.2 (54) [10.7 to 146]	2425 (39) [828 to 5,702]	37.2 (39) [19.1 to 148]
400 mg twice daily# (n=23)	723 (86) [6.70 to 2,256]	9093 (80) [1,564 to 26,794]	76.1 (78) [14.9 to 256]	3088 (84) [407 to 13,140]	31.7 (42) [12.4 to 67.3]

Cavg = the average posaconazole concentration when measured at steady state

* Oral suspension administration
† AUC (0 to 24 hr) for 200 mg three times a day and AUC (0 to 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
The variability in average plasma posaconazole concentrations in patients was relatively higher than that in healthy subjects.

Absorption:

Posaconazole oral suspension is absorbed with a median T_{max} of ~3 to 5 hours. Steady-state plasma concentrations are attained at 7 to 10 days following multiple-dose administration.

Following single-dose administration of 200 mg, the mean AUC and C_{max} of posaconazole are approximately 3-times higher when the oral suspension is administered with a nonfat meal and approximately 4-times higher when administered with a high-fat meal (~50 gm fat) relative to the fasted state. Following single-dose administration of posaconazole oral suspension 400 mg, the mean AUC and C_{max} of posaconazole are approximately 3-times higher when administered with a liquid nutritional supplement (14 gm fat) relative to the fasted state (see **Table 24**). In addition, the effects of varying gastric administration conditions on the C_{max} and AUC of posaconazole oral suspension in healthy volunteers have been investigated and are shown in **Table 25**.

In order to assure attainment of adequate plasma concentrations, it is recommended to administer posaconazole oral suspension during or immediately following a full meal. In patients who cannot eat a full meal, posaconazole 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 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 to 267]	3.50 [1.5 to 36‡]	4179 (31) [2,705 to 7,269]	51 (25) [28 to 74]	23.5 (25) [15.3 to 33.7]
200 mg nonfat (n=20)†	378 (43) [131 to 834]	4 [3 to 5]	10,753 (35) [4,579 to 17,092]	21 (39) [12 to 44]	22.2 (18) [17.4 to 28.7]
200 mg high fat (54 gm fat) (n=20)†	512 (34) [241 to 1,016]	5 [4 to 5]	15,059 (26) [10,341 to 24,476]	14 (24) [8.2 to 19]	23.0 (19) [17.2 to 33.4]
400 mg fasted (n=23)§	121 (75) [27 to 366]	4 [2 to 12]	5258 (48) [2,834 to 9,567]	91 (40) [42 to 141]	27.3 (26) [16.8 to 38.9]
400 mg with liquid nutritional supplement (14 gm fat) (n=23)§	355 (43) [145 to 720]	5 [4 to 8]	11,295 (40) [3,865 to 20,592]	43 (56) [19 to 103]	26.0 (19) [18.2 to 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 Posaconazole Oral Suspension in Healthy Volunteers*

Study Description	Administration Arms	Change in C_{max} (ratio estimate†; 90% CI of the ratio estimate)	Change in AUC (ratio estimate†; 90% CI of the ratio estimate)
400 mg single dose with a high-fat meal relative to fasted state (n=12)	5 minutes before high-fat meal	↑96% (1.96; 1.48 to 2.59)	↑111% (2.11; 1.60 to 2.78)
	During high-fat meal	↑339% (4.39; 3.32 to 5.80)	↑382% (4.82; 3.66 to 6.35)
	20 minutes after high-fat meal	↑333% (4.33; 3.28 to 5.73)	↑387% (4.87; 3.70 to 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 to 2.11)	↑66% (1.66; 1.30 to 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 to 3.02)	↑161% (2.61; 2.04 to 3.35)
	With BOOST	↑137% (2.37; 1.86 to 3.04)	↑157% (2.57; 2.00 to 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 to 2.44)	↑70% (1.70; 1.43 to 2.03)
	Esomeprazole	↓32% (0.68; 0.53 to 0.86)	↓30% (0.70; 0.59 to 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 to 0.87)	↓19% (0.81; 0.72 to 0.91)
	With loperamide + BOOST	↓3% (0.97; 0.88 to 1.07)	↑11% (1.11; 0.99 to 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 to 0.91)	↓23% (0.77; 0.69 to 0.86)

* In 5 subjects, the C_{max} and AUC decreased substantially (range: -27% to -53% and -33% to -51%, respectively) when posaconazole was administered via an NG tube compared to when

posaconazole was administered orally. It is recommended to closely monitor patients for breakthrough fungal infections when posaconazole 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 posaconazole to coadministered drug alone for C_{max} or AUC.

‡ NG = nasogastric

Concomitant administration of posaconazole oral suspension with drugs affecting gastric pH or gastric motility results in lower posaconazole exposure. (See **Table 26).**

Table 26: The Effect of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Posaconazole Oral Suspension in Healthy Volunteers

Coadministered Drug (Postulated Mechanism of Interaction)	Coadministered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Posaconazole	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)
Cimetidine (Alteration of gastric pH)	400 mg twice daily × 10 days	200 mg (tablets) once daily × 10 days†	↓ 39% (0.61; 0.53 to 0.70)	↓ 39% (0.61; 0.54 to 0.69)
Esomeprazole (Increase in gastric pH)‡	40 mg every morning × 3 days	400 mg (oral suspension) single dose	↓ 46% (0.54; 0.43 to 0.69)	↓ 32% (0.68; 0.57 to 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 to 0.87)	↓ 19% (0.81; 0.72 to 0.91)

* 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 drug interactions associated with the oral suspension are also relevant for the delayed-release tablet with the exception of Esomeprazole and Metoclopramide.

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 Induction)	400 mg once daily × 10 and 20 days	400 mg (oral suspension) twice daily × 10 and 20 days	↓45% (0.55; 0.47 to 0.66)	↓ 50% (0.50; 0.43 to 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 to 0.89)	↓23% 0.77 (0.68 to 0.87)
Rifabutin (UDP-G Induction)	300 mg once daily × 17 days	200 mg (tablets) once daily × 10 days†	↓ 43% (0.57; 0.43 to 0.75)	↓ 49% (0.51; 0.37 to 0.71)
Phenytoin (UDP-G Induction)	200 mg once daily × 10 days	200 mg (tablets) once daily × 10 days†	↓ 41% (0.59; 0.44 to 0.79)	↓ 50% (0.50; 0.36 to 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 × 16 days	↑ 572% (6.72; 5.62 to 8.03)	↑ 788% (8.88; 7.26 to 10.9)
Cyclosporine	Stable maintenance dose in heart transplant recipients	200 mg (tablets) once daily × 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 × 7 days	↑ 121% (2.21; 2.01 to 2.42)	↑ 358% (4.58; 4.03 to 5.19)
Simvastatin	40 mg single oral dose	100 mg (oral suspension) once daily × 13 days	Simvastatin ↑ 841% (9.41, 7.13 to 12.44) Simvastatin Acid ↑ 817% (9.17, 7.36 to 11.43)	Simvastatin ↑ 931% (10.31, 8.40 to 12.67) Simvastatin Acid ↑634% (7.34, 5.82 to 9.25)
		200 mg (oral suspension) once daily × 13 days	Simvastatin ↑ 1041% (11.41, 7.99 to 16.29) Simvastatin Acid ↑851% (9.51, 8.15 to 11.10)	Simvastatin ↑ 960% (10.60, 8.63 to 13.02) Simvastatin Acid ↑748% (8.48, 7.04 to 10.23)
Midazolam	0.4 mg single intravenous dose‡	200 mg (oral suspension) twice daily × 7 days	↑ 30% (1.3; 1.13 to 1.48)	↑ 362% (4.62; 4.02 to 5.3)

	0.4 mg single intravenous dose‡	400 mg (oral suspension) twice daily × 7 days	↑62% (1.62; 1.41 to 1.86)	↑524% (6.24; 5.43 to 7.16)
	2 mg single oral dose‡	200 mg (oral suspension) once daily × 7 days	↑ 169% (2.69; 2.46 to 2.93)	↑ 470% (5.70; 4.82 to 6.74)
	2 mg single oral dose‡	400 mg (oral suspension) twice daily × 7 days	↑ 138% (2.38; 2.13 to 2.66)	↑ 397% (4.97; 4.46 to 5.54)
Rifabutin	300 mg once daily × 17 days	200 mg (tablets) once daily × 10 days	↑ 31% (1.31; 1.10 to 1.57)	↑ 72% (1.72;1.51 to 1.95)
Phenytoin	200 mg once daily PO × 10 days	200 mg (tablets) once daily × 10 days	↑ 16% (1.16; 0.85 to 1.57)	↑ 16% (1.16; 0.84 to 1.59)
Ritonavir	100 mg once daily × 14 days	400 mg (oral suspension) twice daily × 7 days	↑ 49% (1.49; 1.04 to 2.15)	↑ 80% (1.8;1.39 to 2.31)
Atazanavir	300 mg once daily × 14 days	400 mg (oral suspension) twice daily × 7 days	↑ 155% (2.55; 1.89 to 3.45)	↑ 268% (3.68; 2.89 to 4.70)
Atazanavir/ ritonavir boosted regimen	300 mg/100 mg once daily × 14 days	400 mg (oral suspension) twice daily × 7 days	↑ 53% (1.53; 1.13 to 2.07)	↑ 146% (2.46; 1.93 to 3.13)

* The 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 posaconazole 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 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 Cavg 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 Patients:

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

A total of 12 patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) of posaconazole oral suspension for prophylaxis of invasive fungal infections. 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 posaconazole 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.

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 × 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 × 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 Posaconazole Oral Suspension

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

The first study (Posaconazole Oral Suspension Study 1) was a randomized, double-blind

trial that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD). Efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (patients may have met more than one of these criteria). This assessed all patients while on study therapy plus 7 days and at 16 weeks post-randomization. The mean duration of therapy was comparable between the 2 treatment groups (80 days, posaconazole oral suspension; 77 days, fluconazole). **Table 32** contains the results from Posaconazole 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): Posaconazole 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 (Posaconazole Oral Suspension Study 2) was a randomized, open-label study that compared posaconazole oral suspension (200 mg 3 times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS. As in Posaconazole 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 Posaconazole 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: Posaconazole 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 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	44 (14%)	64 (21%)
Proven/probable fungal infection prior to death	2 (1%)	16 (5%)
SAF[‡]	98 (32%)	125 (42%)
Event free lost to follow-up[§]	34 (11%)	24 (8%)

* 95% confidence interval (posaconazole-fluconazole/itraconazole) = (-22.9%, -7.8%).

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

In summary, 2 clinical studies of prophylaxis were conducted with the posaconazole oral suspension. As seen in the accompanying tables (**Tables 32 and 33**), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Posaconazole 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 Posaconazole 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 Posaconazole 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 Posaconazole Oral Suspension Study 2 [POS 44/304 (14%) vs. FLU/ITZ 64/298 (21%)]. Both studies demonstrated substantially fewer breakthrough infections caused by *Aspergillus* species in patients receiving posaconazole prophylaxis when compared to patients receiving fluconazole or itraconazole.

14.3 Treatment of Oropharyngeal Candidiasis with Posaconazole Oral Suspension

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

Clinical and mycological outcomes were assessed after 14 days of treatment and at 4 weeks after the end of treatment. Patients who received at least 1 dose of study medication and had a positive oral swish culture of *Candida* species at baseline were included in the analyses (see **Table 34**). 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 34**).

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 34**).

Table 34: Posaconazole Oral Suspension Clinical Success, Mycological Eradication, and Relapse Rates in Oropharyngeal Candidiasis

	Posaconazole	**Fluconazole**

Clinical Success at End of Therapy (Day 14)	155/169 (91.7%)	148/160 (92.5%)
Clinical Relapse (4 Weeks after End of Therapy)	45/155 (29.0%)	52/148 (35.1%)
Mycological Eradication (Absence of CFU) at End of Therapy (Day 14)	88/169 (52.1%)	80/160 (50.0%)
Mycological Relapse (4 Weeks after End of Treatment)	49/88 (55.6%)	51/80 (63.7%)

Mycologic response rates, using a criterion for success as a posttreatment quantitative culture with ≤20 colony forming units (CFU/mL) were also similar between the two groups (posaconazole 68.0%, fluconazole 68.1%). The clinical significance of this finding is unknown.

14.4 Posaconazole Oral Suspension Treatment of Oropharyngeal Candidiasis Refractory to Treatment with Fluconazole or Itraconazole

Posaconazole Oral Suspension Study 4 was a noncomparative study of posaconazole oral suspension in HIV-infected subjects with OPC that was refractory to treatment with fluconazole or itraconazole. An episode of OPC was considered refractory if there was failure to improve or worsening of OPC after a standard course of therapy with fluconazole greater than or equal to 100 mg/day for at least 10 consecutive days or itraconazole 200 mg/day for at least 10 consecutive days and treatment with either fluconazole or itraconazole had not been discontinued for more than 14 days prior to treatment with posaconazole. Of the 199 subjects enrolled in this study, 89 subjects met these strict criteria for refractory infection.

Forty-five subjects with refractory OPC were treated with posaconazole oral suspension 400 mg 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 posaconazole was assessed by the clinical success (cure or improvement) rate after 4 weeks of treatment. The clinical success rate was 74.2% (66/89). The clinical success rates for both the original and the amended dosing regimens were similar (73.3% and 75.0%, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Posaconazole Oral Suspension

Posaconazole oral suspension is available as a white to off-white, cherry brandy flavored suspension in 4-ounce (120 mL) amber glass bottles with child-resistant closures containing 105 mL of suspension (40 mg of posaconazole per mL).

NDC 0054-0449-49: Bottle of 105 mL

Supplied with each oral suspension bottle is a plastic dosing spoon calibrated for measuring 2.5-mL and 5-mL doses.

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F); [See USP Controlled Room Temperature.]

DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

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

Important Administration Instructions

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

Instruct patients that if they miss a dose, they should take it as soon as they remember. However, if it is almost time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

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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Patient Information

Posaconazole Oral Suspension

(poe’ sa kon’ a zole)

Rx only

What is posaconazole oral suspension?

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

Posaconazole oral suspension is used for:

- prevention of fungal infections in adults and children 13 years of age and older.

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

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

Who should not take posaconazole oral suspension?

Do not take posaconazole if you:

- are allergic to posaconazole, any of the ingredients in posaconazole, or other azole antifungal medicines. See the end of this leaflet for a complete list of ingredients in posaconazole.
- are taking any of the following medicines:
  - sirolimus
  - pimozide
  - 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.

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 oral suspension?

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

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

Ask your healthcare provider or pharmacist for a list of these medicines if 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 oral suspension?

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

- Take posaconazole for as long as your healthcare provider tells you to take it.
- If you take too much posaconazole, call your healthcare provider or go to the nearest hospital emergency room right away.
- **Posaconazole oral suspension:**
  - Shake posaconazole oral suspension well before use.
  - Take each dose of posaconazole oral suspension during or within 20 minutes after a full meal. If you cannot eat a full meal, take each dose of posaconazole oral suspension with a liquid nutritional supplement or an acidic carbonated beverage, like ginger ale.
  - A measured dosing spoon comes with your posaconazole oral suspension and is marked for doses of **2.5 mL** and **5 mL**. **See Figure A and B.**

Figure A

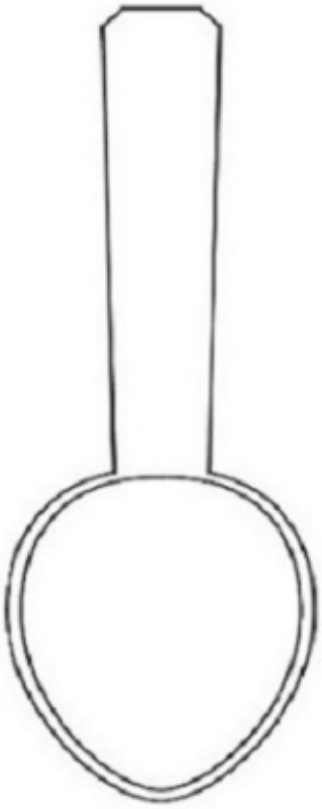
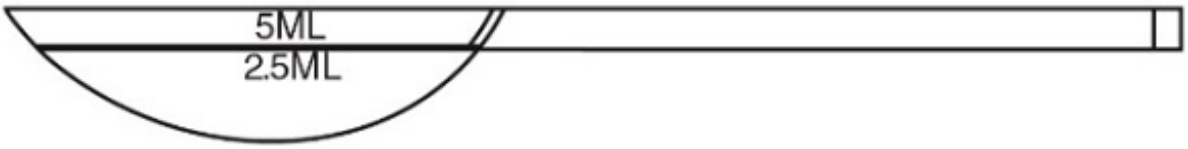


Figure B



- Rinse the spoon with water after each dose of posaconazole 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.

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

What are the possible side effects of posaconazole oral suspension?

Posaconazole may cause serious side effects, including:

- **drug interactions with cyclosporine or tacrolimus.** If you take posaconazole with cyclosporine or tacrolimus, your blood levels of cyclosporine or tacrolimus may increase. Serious side effects can happen in your kidney or brain if you have high levels of cyclosporine or tacrolimus in your blood. Your healthcare provider should do blood tests to check your levels of cyclosporine or tacrolimus if you are taking these medicines while taking posaconazole. Tell your healthcare provider right away if you have swelling in your arm or leg or shortness of breath.
- **problems with the electrical system of your heart (arrhythmias and QTc prolongation).** Certain medicines used to treat fungus called azoles, including posaconazole, the active ingredient in posaconazole oral suspension, 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.
- **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 posaconazole. Your healthcare provider should do blood tests to check your liver while you are taking posaconazole. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - 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 posaconazole with midazolam, posaconazole increases the amount of midazolam in your blood. This can make your sleepiness last longer. Your healthcare provider should check you closely for side effects if you take midazolam with posaconazole.

The most common side effects of posaconazole include:

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

If you take posaconazole 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 posaconazole. For more information, ask your healthcare provider or pharmacist.

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

How should I store posaconazole oral suspension?

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

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

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

General information about the safe and effective use of posaconazole.

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

What are the ingredients in posaconazole oral suspension?

Active ingredient: posaconazole
Inactive ingredients: cherry-brandy flavor, citric acid monohydrate, hydroxyethyl cellulose, glycerin, polyoxyl 35 castor oil, simethicone emulsion, sodium benzoate, sodium citrate, sorbitol solution, titanium dioxide, and water.

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

Distributed by:
Hikma Pharmaceuticals USA Inc.
Berkeley Heights, NJ 07922

C50000256/06
Revised December 2024

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 105 mL Bottle Carton

NDC 0054-**0449**-49
105 mL

Posaconazole
Oral Suspension

200 mg/5 mL
Each mL contains 40 mg posaconazole.

Rx Only

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 105 mL Bottle Label

NDC 0054-**0449**-49
105 mL

Posaconazole
Oral Suspension

200 mg/5 mL
Each mL contains 40 mg posaconazole.

Rx Only

POSACONAZOLE
posaconazole suspension

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0054-0449
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**
POLYOXYL 35 CASTOR OIL (UNII: 6D4M1DAL6O)	

SODIUM BENZOATE (UNII: OJ245FE5EU)	
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
GLYCERIN (UNII: PDC6A3C0OX)	
SORBITOL (UNII: 506T60A25R)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
WATER (UNII: 059QF0KO0R)	
HYDROXYETHYL CELLULOSE (2000 MPA.S AT 1%) (UNII: S38J6RZN16)	
DIMETHICONE, UNSPECIFIED (UNII: 92RU3N3Y1O)	

Product Characteristics

Color		**Score**	
Shape		**Size**	
Flavor	CHERRY (CHERRY BRANDY)	**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-0449-49	1 in 1 CARTON	03/29/2023	
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
ANDA	ANDA208773	03/29/2023	

Labeler - Hikma Pharmaceuticals USA Inc. (080189610)

Establishment

Name	Address	ID/FEI	Business Operations
West-Ward Columbus Inc.		058839929	MANUFACTURE(0054-0449) , PACK(0054-0449)

Establishment

Name	Address	ID/FEI	Business Operations
Zhejiang Ausun Pharmaceutical Co., Ltd.		421277322	API MANUFACTURE(0054-0449)