PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr TARO-POSACONAZOLE

posaconazole

Delayed-Release Tablets, 100 mg, Oral

Antifungal Agent

Taro Pharmaceuticals Inc.
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RECENT MAJOR LABEL CHANGES

Not applicable	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TARO-POSACONAZOLE (posaconazole) Delayed-Release Tablets is indicated for:

- Prophylaxis of *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections, such as patients with prolonged neutropenia or hematopoietic stem cell transplant (HSCT) recipients.

- Treatment of invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole, or in patients who are intolerant of these medicinal products. Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Limited data on other fungal infections appears in the *Clinical Trials* section of the product monograph.

TARO-POSACONAZOLE Delayed-Release Tablets is indicated in patients 13 years of age and older.

1.1 Pediatrics

Pediatrics (13 - 17 years of age): Safety and effectiveness in pediatric subjects below the age of 13 years have not been studied.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Limited evidence from clinical studies and experience suggests that use in the geriatric population is associated with no overall differences in safety or effectiveness.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph. There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing TARO-POSACONAZOLE to patients with hypersensitivity to other azoles.

- Co-administration of posaconazole and ergot alkaloids. Posaconazole may increase the plasma concentrations of ergot alkaloids, which may lead to ergotism (see 9 DRUG INTERACTIONS).

- Co-administration of posaconazole and certain medicinal products metabolized through the CYP3A4 system: terfenadine, astemizole, cisapride, pimozide and quinidine. Although not studied *in vitro* or *in vivo*, co-administration of these CYP3A4 substrates may result in increased plasma concentrations of those medicinal products, leading to potentially serious and/or life threatening adverse events, such as QT prolongation and rare occurrences of torsade de pointes (see 9 DRUG INTERACTIONS).

- Co-administration of posaconazole and HMG-CoA reductase inhibitors (statins) that are primarily metabolized through CYP3A4, since increased plasma concentration of these drugs can lead to rhabdomyolysis.

- Co-administration of posaconazole and sirolimus. Concomitant administration of posaconazole with sirolimus increases the sirolimus blood concentrations by approximately 9-fold and can result in sirolimus toxicity.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Drug Interactions (see** 2 CONTRAINDICATIONS **section,** 7 WARNINGS AND PRECAUTIONS **and** 9 DRUG INTERACTIONS **of the product monograph)**
- **Cardiovascular effects - QT interval prolongation (see** 7 WARNINGS AND PRECAUTIONS, **Cardiovascular)**
- **Hepatic toxicity (see** 7 WARNINGS AND PRECAUTIONS, **Hepatic)**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The prescriber should follow the specific dosing instructions for each formulation.

- The tablet, oral suspension and intravenous solution are not to be used interchangeably due to the differences in the dosing of each formulation.

- TARO-POSACONAZOLE Delayed-Release Tablets may be taken with or without food.

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

- 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 9 DRUG INTERACTIONS).

- 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.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Table 1 - Dosing for Posaconazole Delayed-Release Tablet

Indication	Dose and Duration of Therapy
Prophylaxis of Invasive Fungal Infections (IFIs)	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Each dose may be taken without regard to food intake. The duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS), prophylaxis with posaconazole should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3.
Treatment of Refractory IFIs / Intolerant Patients with IFIs	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

Dosage Adjustment

Use in Renal Impairment

The pharmacokinetics of posaconazole oral suspension are not significantly affected by renal impairment. Therefore, no dose adjustment is necessary for oral dosing in patients with mild to severe renal impairment. However, due to the variability in exposure with posaconazole oral therapy, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

Use in Hepatic Impairment

There are limited pharmacokinetic data in patients with hepatic insufficiency; therefore, no recommendation for dose adjustment can be made. In the small number of subjects studied who had hepatic insufficiency, there was an increase in half-life with a decrease in hepatic function (see 10 CLINICAL PHARMACOLOGY). Use with caution in patients with severe hepatic impairment (see 10 CLINICAL PHARMACOLOGY).

Use in Pediatrics (13 - 17 years)

A total of 11 patients 13 - 17 years of age were treated with 800 mg/day posaconazole oral suspension in a study for IFIs. Additionally, 12 patients 13 - 17 years of age received 600 mg/day of posaconazole oral suspension for prophylaxis of IFIs (studies C/I98-316 and P01899). The safety profile in these patients < 18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these pediatric patients, the pharmacokinetic profile appears to be similar to patients ≥ 18 years of age (see 10 CLINICAL PHARMACOLOGY).

4.4 Administration

TARO-POSACONAZOLE Delayed-Release Tablet

TARO-POSACONAZOLE delayed-release tablets, the posaconazole oral suspension and posaconazole intravenous solution are NOT interchangeable due to the differences in the dosing of each formulation. Follow the specific dosage recommendations for each of these formulations.

TARO-POSACONAZOLE Delayed-Release Tablets are intended for oral administration only. TARO-

POSACONAZOLE Delayed-Release Tablets are specially designed for release in the small intestine.

They should be swallowed whole, and should not be divided, crushed or chewed.

4.5 Missed Dose

If a dose of this medication is missed, it should be taken as soon as possible. This will help to keep a constant amount of medication in the blood. However, if it is almost time for the next dose, it might be better to skip the missed dose and to go back to the regular dosing schedule.

5 OVERDOSAGE

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

During clinical trials, patients who received posaconazole oral suspension doses up to 1,600 mg/day had no noted adverse reactions different from those reported with patients at the lower doses. In addition, accidental overdose was noted in one patient who took 1,200 mg BID posaconazole oral suspension for 3 days. No adverse reactions were noted by the investigator.

In a trial of patients with severe hemodialysis-dependent renal dysfunction (Cl_{cr} < 20 mL/min), posaconazole was not removed by hemodialysis.

Activated charcoal may be used to remove unabsorbed drug.

For management of a suspected drug overdose, contact your regional poison control centre immediately.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
oral	delayed-release tablets, 100 mg posaconazole	Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and Opadry II Yellow [consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350 (polyethylene glycol 3350), titanium dioxide, talc, and iron oxide yellow].

TARO-POSACONAZOLE Delayed-Release Tablets

TARO-POSACONAZOLE Delayed-Release Tablet is a yellow, capsule-shaped, biconvex, film-coated tablet debossed with "100" on one side and plain on the other side. TARO-POSACONAZOLE is packaged in bottles of 60 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

TARO-POSACONAZOLE delayed release tablets are not interchangeable with the oral suspension or intravenous solution of posaconazole (see 4 DOSAGE AND ADMINISTRATION).

Posaconazole plasma concentrations following administration of posaconazole tablets are generally higher than those obtained with posaconazole oral suspension. Posaconazole plasma concentrations following administration of posaconazole tablets may increase over time in some patients. Safety data at higher exposure levels achieved with posaconazole tablets are limited (see 10 CLINICAL PHARMACOLOGY).

Hypersensitivity: There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing posaconazole to patients with hypersensitivity to other azoles.

No data on the effects of posaconazole on the ability to drive and use machines are available.

Carcinogenesis and Mutagenesis
Carcinogenicity studies did not reveal special hazards for humans. For information on animal data, see the Toxicology section of the product monograph.

Cardiovascular
Posaconazole has been associated with prolongation of the QT interval of the electrocardiogram (ECG) in some patients. Prolongation of the QT interval may increase the risk of arrhythmia.

Due to limited clinical experience, TARO-POSACONAZOLE should be administered with caution to patients with potentially proarrhythmic conditions such as congenital or acquired QT_c prolongation, congestive heart failure, bradycardia, and acute myocardial ischemia. Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during TARO-POSACONAZOLE therapy.

Caution should be exercised if TARO-POSACONAZOLE is used in patients taking other drugs that may prolong the QT interval, such as antipsychotics, tricyclic antidepressants, methadone, erythromycin, Class IA (e.g., procainamide, quinidine) and Class III (e.g., amiodarone, sotalol) antiarrhythmic agents. Drugs metabolized by the hepatic cytochrome P450 isoenzyme CYP3A4 may be affected by posaconazole levels, with possible resulting QT effects. Such drugs include tacrolimus, HIV protease inhibitors and macrolide antibiotics (see 2 CONTRAINDICATIONS, 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY). During clinical development there was a single case of torsade de pointes in a patient taking posaconazole. This report involved a seriously ill patient with multiple confounding risk factors (see 8 ADVERSE REACTIONS, Less Common Clinical Trial Adverse Drug Reactions (< 2%)).

Dependence/Tolerance
There is no known abuse potential for posaconazole.

Hematologic
Rare cases of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura have been reported primarily among patients who had been receiving concomitant cyclosporine or tacrolimus for management of transplant rejection or graft vs. host disease (GVHD).
Hepatic/Biliary/Pancreatic

Hepatic toxicity: In clinical trials, there were infrequent cases of hepatic reactions (e.g., mild to moderate elevations in ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), alkaline phosphatase, total bilirubin, and/or clinical hepatitis) during treatment with posaconazole. The elevations in liver function tests were generally reversible on discontinuation of therapy, and in some instances these tests normalized without drug interruption and rarely required drug discontinuation. Rarely, more severe hepatic reactions including cholestasis or hepatic failure were reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with posaconazole.

Monitoring of hepatic function: Liver function tests should be evaluated at the start of and during the course of TARO-POSACONAZOLE therapy. Patients who develop abnormal liver function tests during TARO-POSACONAZOLE therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of TARO-POSACONAZOLE should be considered if clinical signs and symptoms are consistent with development of worsening liver disease.

Hepatic Impairment: TARO-POSACONAZOLE should be used with caution in patients with severe hepatic impairment. Prolonged elimination half-life may lead to increased exposure.

Immune
Patients Taking Immunosuppressant: Cases of elevated cyclosporine levels resulting in rare serious adverse events, including nephrotoxicity and leukoencephalopathy, and death were reported in clinical efficacy studies. Dose reduction and more frequent clinical monitoring of cyclosporine and tacrolimus should be performed when TARO-POSACONAZOLE therapy is initiated (see 9 DRUG INTERACTIONS).

Neurologic
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 9 DRUG INTERACTIONS).

Other
Venetoclax Toxicity: Concomitant administration of posaconazole with venetoclax (a CYP3A4 substrate) may increase venetoclax toxicities, including the risk of tumor lysis syndrome (TLS) and neutropenia (see 9 DRUG INTERACTIONS). Refer to the venetoclax Product Monograph for detailed guidance.

Renal

Renal impairment: Due to the variability in exposure with posaconazole oral therapy, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

There is insufficient information on the use of posaconazole in pregnant women. The extent of exposure in pregnancy during clinical trials is very limited. There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY). The potential risk to humans is unknown. Women of childbearing potential must always use adequate contraceptive measures while on treatment. TARO-POSACONAZOLE should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.1.2 Breast-feeding

Nursing Women: Posaconazole is excreted into the milk of lactating rats (see 16 NON-CLINICAL TOXICOLOGY). The excretion of posaconazole in human breast milk has not been investigated. Posaconazole should not be used by nursing mothers unless the benefit to the mother clearly outweighs the risk to the infant.

Hepatic Impairment: Posaconazole should be used with caution in patients with severe hepatic impairment. Prolonged elimination half-life may lead to increased exposure.

Patients Taking Immunosuppressant: Cases of elevated cyclosporine levels resulting in rare serious adverse events, including nephrotoxicity and leukoencephalopathy, and death were reported in clinical efficacy studies. Dose reduction and more frequent clinical monitoring of cyclosporine and tacrolimus should be performed when posaconazole therapy is initiated (see 9 DRUG INTERACTIONS).

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 9 DRUG INTERACTIONS).

7.1.3 Pediatrics

Safety and efficacy for POSACONAZOLE in pediatric patients less than 13 years of age have not been established.

7.1.4 Geriatrics

Evidence from clinical studies and experience suggests that safety and effectiveness of posaconazole are similar in geriatric and adult subjects.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Posaconazole Delayed-Release Tablets
The safety of posaconazole delayed-release tablets has been assessed in 230 patients enrolled in the pivotal clinical study. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole delayed-release tablets when given as antifungal prophylaxis. Patients were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. Posaconazole delayed-release tablets therapy was given for a median duration of 28 days. Twenty patients received 200 mg daily dose and 210 patients received 300 mg daily dose (following twice a day (BID) dosing on Day 1 in each cohort).

The posaconazole oral suspension generally achieved lower steady state plasma C_{min} levels of posaconazole than the delayed-release tablet formulation, with a maximum recorded average plasma C_{min} level of 3,650 ng/mL. With the 300 mg tablet formulation, HSCT patients achieved higher average plasma C_{min} levels of posaconazole, with 8% of HSCT subjects (6 patients) achieving average C_{min} values ≥ 3,750 ng/mL and one patient achieving a measured posaconazole plasma level of 9,140 ng/mL. This did not appear to translate into increased safety issues, but the tablet clinical trial database is limited to 210 patients (300 mg once daily dose).The most frequently reported treatment-related adverse reactions with posaconazole delayed-release tablets 300 mg once daily (QD) were diarrhea and nausea.

The most frequently reported adverse reaction leading to discontinuation of posaconazole delayed-release tablets 300 mg QD was nausea.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Clinical Trial Safety Experience with Posaconazole Oral Delayed-Release Tablet

Study P05615
Study P05615 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole delayed-release tablet. Study P05615 was conducted in a similar patient population to that previously studied in the pivotal posaconazole oral suspension clinical program.

Table 3: Treatment-related adverse reactions reported in posaconazole delayed-release tablet subjects treated with 300 mg daily dose reported at an incidence of ≥ 1% for the P05615 Study

Adverse Reactions	Posaconazole delayed-release tablet (300 mg) n=210 (%)
Cardiovascular	
Sinus bradycardia	2 (1)

Adverse Reactions	Posaconazole delayed-release tablet (300 mg) n=210 (%)
Gastrointestinal	
Abdominal discomfort	2 (1)
Abdominal distension	3 (1)
Abdominal pain	9 (4)
Abdominal pain upper	5 (2)
Constipation	3 (1)
Diarrhea	16 (8)
Dry mouth	2 (1)
Dyspepsia	5 (2)
Flatulence	4 (2)
Gastritis	2 (1)
Nausea	23 (11)
Vomiting	9 (4)
General and Administration Site Conditions	
Drug interaction	2 (1)
Pyrexia	2 (1)
Metabolism and Nutrition	
Decreased appetite	2 (1)
Hypocalcemia	3 (1)
Hypokalemia	6 (3)
Hypomagnesemia	3 (1)
Hypophosphatemia	5 (2)
Musculoskeletal and Connective Tissue	
Pain in extremity	2 (1)
Nervous System	
Headache	2 (1)
Skin and Subcutaneous Tissue	
Pruritus	2 (1)
Rash	5 (2)
Rash macular	2 (1)
Rash maculopapular	2 (1)
Rash pruritic	2 (1)
Investigations	
Alanine aminotransferase increased	9 (4)
Aspartate aminotransferase increased	8 (4)
Blood alkaline phosphatase increased	3 (1)
Blood bilirubin increased	3 (1)
Blood creatinine increased	3 (1)
Electrocardiogram QT prolonged	2 (1)
Hepatic enzyme increased	2 (1)
Liver function test abnormal	5 (2)

Clinical Trial Safety Experience with Posaconazole Oral Suspension

Studies P01899 and C/I98-316

Study P01899 was a randomised, evaluator-blinded study that compared posaconazole oral suspension (200 mg three times a day (TID)) with fluconazole suspension (400 mg QD) or itraconazole oral solution (200 mg BID) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS). The mean duration of therapy was comparable between the two treatment groups (29 days, posaconazole; 25 days, fluconazole/itraconazole). In this study, 304 patients were randomly assigned to posaconazole therapy and 240 patients were assigned to fluconazole, and 58 were assigned to itraconazole therapy as the local standard of care.

Study C/I98-316 was a randomised, double-blind trial that compared posaconazole oral suspension (200 mg TID) with fluconazole capsules (400 mg QD) as prophylaxis against IFIs in allogeneic HSCT recipients with GVHD. The mean duration of therapy was comparable between the two treatment groups (80 days, posaconazole; 77 days, fluconazole). In this study, 301 patients were randomly assigned to posaconazole therapy and 299 patients were assigned to fluconazole therapy.

Table 4 - Treatment-related adverse reactions reported in posaconazole oral suspension, fluconazole and itraconazole subjects reported at an incidence of ≥ 1% for the prophylaxis studies C/I98-316 and P01899

Adverse Reactions	posaconazole n=605 (%)	fluconazole n=539 (%)	Itraconazole n=58 (%)
Blood and Lymphatic System			
Anemia	5 (1)	2 (< 1)	0
Thrombocytopenia	4 (1)	3 (1)	0
Cardiovascular			
QT/QT_c prolongation	14 (2)	6 (1)	4 (7)
Hypertension	3 (< 1)	5 (1)	0
Tachycardia	4 (1)	1 (< 1)	0
Bradycardia	1 (< 1)	0	2 (3)
Vasculitis	0	0	1 (2)
Eye			
Vision blurred	3 (< 1)	6 (1)	0
Gastrointestinal			
Nausea	44 (7)	45 (8)	8 (14)
Vomiting	27 (4)	29 (5)	6 (10)
Diarrhea	28 (5)	24 (4)	9 (16)
Abdominal pain	13 (2)	15 (3)	1 (2)
Constipation	4 (1)	12 (2)	0
Dyspepsia	8 (1)	9 (2)	0
Loose stools	1 (< 1)	5 (1)	0
Abdominal distension	4 (1)	2 (< 1)	0
Gastritis	2 (< 1)	3 (1)	0

Adverse Reactions	posaconazole n=605 (%)	fluconazole n=539 (%)	Itraconazole n=58 (%)
Nausea aggravated	2 (< 1)	1 (< 1)	2 (3)
Dry mouth	3 (< 1)	1 (< 1)	1 (2)
Mucositis not otherwise specified	7 (1)	0	0
Stomatitis aphtous	1 (< 1)	0	1 (2)
Gastric disorder	0	0	1 (2)
Rectal pain	0	0	1 (2)
General and Administration Site Conditions			
Fatigue	7 (1)	7 (1)	0
Weakness	3 (< 1)	5 (1)	0
Asthenia	2 (< 1)	3 (1)	0
Fever	2 (< 1)	3 (1)	0
Hepatobiliary			
Bilirubinemia	15 (2)	10 (2)	3 (5)
Hepatic enzymes increased	15 (2)	10 (2)	0
ALT (SGPT) increased	16 (3)	8 (1)	1 (2)
Gamma glutamyl transferase (GGT) increased	14 (2)	8 (1)	1 (2)
AST (SGOT) increased	14 (2)	7 (1)	1 (2)
Hepatic function abnormal	2 (< 1)	5 (1)	0
Jaundice	5 (1)	2 (< 1)	0
Hepatocellular damage	5 (1)	0	0
Immune			
Allergic reaction	3 (< 1)	3 (1)	0
Metabolism and Nutrition			
Hypokalemia	11 (2)	6 (1)	1 (2)
Anorexia	6 (1)	8 (1)	1 (2)
Hypomagnesemia	2 (< 1)	6 (1)	0
Hyperkalemia	2 (< 1)	4 (1)	0
Weight decrease	1 (< 1)	4 (1)	0
Hyperglycemia	2 (< 1)	3 (1)	0
Weight increase	1 (< 1)	0	1 (2)
Musculoskeletal and Connective Tissue			
Myalgia	2 (< 1)	3 (1)	0
Nervous System			
Headache	8 (1)	8 (1)	1 (2)
Dizziness	4 (1)	7 (1)	0
Taste perversion	3 (< 1)	7 (1)	1 (2)
Tremor	4 (1)	6 (1)	0

Adverse Reactions	posaconazole n=605 (%)	fluconazole n=539 (%)	Itraconazole n=58 (%)
Paresthesia	5 (1)	3 (1)	0
Somnolence	2 (< 1)	3 (1)	0
Syncope	2 (< 1)	0	1 (2)
Renal and Urinary System			
Blood creatinine increased	6 (1)	5 (1)	0
Creatinine clearance decreased	2 (< 1)	4 (1)	0
Renal insufficiency	1 (< 1)	4 (1)	0
Renal function abnormal	2 (< 1)	3 (1)	0
Respiratory, Thoracic and Mediastinal			
Coughing	2 (< 1)	2 (< 1)	1 (2)
Skin and Subcutaneous Tissue			
Rash	12 (2)	10 (2)	1 (2)
Pruritus	4 (1)	5 (1)	0
Rash pruritic	3 (< 1)	5 (1)	0
Rash maculopapular	5 (1)	2 (< 1)	0
Sweating increased	1 (< 1)	0	1 (2)
Cellulitis	0	0	1 (2)
Investigations			
Alkaline phosphatase increased	6 (1)	6 (1)	1 (2)
Drug level altered	5 (1)	2 (< 1)	0
LDH increased	5 (1)	0	0

The most common treatment-related serious adverse events (1% each) in the combined prophylaxis studies were bilirubinemia, increased hepatic enzymes, hepatocellular damage, nausea, and vomiting.

Studies P01893 and P00041

Study P01893 was an open-label, randomized, parallel group, study of the safety, tolerability, efficacy, and pharmacokinetic profile of posaconazole in the treatment of immunocompromised patients with rIFI or in febrile neutropenic subjects who required empiric antifungal therapy. Posaconazole oral suspension was given as follows: 200 mg administered 4 times daily (QID), 400 mg QID, 800 mg BID for 2 days followed by 400 mg BID, 600 mg BID, or 800 mg administered every day, respectively, for the remainder of the study. For subjects with rIFIs, daily administration of the study drug was continued for a maximum duration of 6 months. For febrile neutropenic subjects, daily administration of the study drug was continued until after completion of the study or until the recovering absolute neutrophil count reached 500 cells/mm3. In this study, 98 patients were randomized and 93 received posaconazole therapy.

Study P00041 was an open-label, non-comparative study of the safety and efficacy of posaconazole as treatment of IFIs in patients who had disease which was refractory to amphotericin B (including

liposomal formulations) or itraconazole or in patients who were intolerant of these medicinal products. Patients were administered posaconazole oral suspension 800 mg/day in divided doses. In this study, 330 patients received posaconazole therapy. The median duration of posaconazole therapy was 102.5 days (1 – 609 days). The majority of patients were severely immunocompromised with underlying conditions such as hematologic malignancies, including bone marrow transplantation; solid organ transplantation; solid tumors and/or AIDS.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

Benign and Malignant Neoplasms: lipoma, Kaposi's sarcoma.

Blood and Lymphatic System: abnormal blood gases not otherwise specified (NOS), abnormal platelets, anemia aggravated, blood neutrophil count decreased, bone marrow aplasia, coagulation disorder, coagulation time increased, eosinophilia, hematoma, hemoglobin decreased, hemorrhage NOS, leukopenia, lymphadenopathy, neutropenia aggravated, neutrophilia, pancytopenia, platelet count decreased, platelet count increased, prothrombin decreased, prothrombin time prolonged, purpura, splenomegaly, white blood cell count decreased.
In addition, rare cases of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura have been reported primarily among patients who had been receiving concomitant cyclosporine or tacrolimus for management of transplant rejection or GVHD.

Cardiovascular: abnormal ECG, abnormal ECG specific, aortic valve sclerosis, arrhythmia, atherosclerosis, atrial fibrillation, atrial fibrillation aggravated, atrial flutter, AV block, bradycardia, bundle branch block, cardiac failure, cardiomegaly, cardio-respiratory arrest, cerebrovascular accident NOS, deep venous thrombosis NOS, dependent edema, ejection fraction decreased, extrasystoles, flushing, hot flushes, hypotension, hypotension postural, ischemia, mitral valve disease NOS, myocardial infarction, palpitation, premature atrial contractions, premature ventricular contractions, pulmonary embolism, sinus tachycardia, sudden death, supraventricular tachycardia, tachycardia, vascular disorder, ventricular hypertrophy, ventricular tachycardia.

During clinical development there was a single case of torsade de pointes in a patient taking posaconazole. This report involved a seriously ill patient with multiple confounding, potentially contributory risk factors, such as a history of palpitations, recent cardiotoxic chemotherapy, hypokalemia, and hypomagnesemia.

Ear and Labyrinth: earache, hearing impairment, tinnitus, vertigo, vestibular disorder.

Endocrine: adrenal insufficiency, glucocorticoids decreased, gonadotropins decreased.

Eye: conjunctivitis, diplopia, dry eyes, eye irritation, eye pain, periorbital edema, photophobia, scotoma.

Gastrointestinal: abdominal distention, abdominal pain aggravated, abdominal tenderness, ascites, ascites aggravated, bowel motility decreased, cheilitis, diverticulitis aggravated, dysphagia, eructation, esophagitis, esophagus ulceration, feces malodorous, gastritis, gastroenteritis, gastroesophageal reflux, gastrointestinal tract hemorrhage, hiccup, gingivitis, glossitis, hemorrhagic diarrhea, hemorrhagic gastritis, ileus, loose stools, melena, mouth ulceration, odynophagia, pancreatic enzymes NOS increased,

pancreatitis, proctalgia, retching, saliva altered, stomatitis, tenesmus, thirst, tongue discoloration, tongue disorder, tooth discoloration, vomiting aggravated.

General and Administration Site Conditions: appetite increased, death, drug interaction, edema, fall, fatigue aggravated, fistula, generalized edema, influenza-like symptoms, laboratory test abnormality, legs edema, malaise, pain, pallor, peripheral edema, rigors.

Hepatobiliary: asterixis, biliary sludge, bilirubinemia aggravated, cholestasis, hepatic failure, hepatitis, hepatitis aggravated, hepatitis cholestatic, hepatocellular damage, hepatomegaly, hepatosplenomegaly, jaundice, liver tenderness.

Immune System: allergic reaction, allergy, GVHD aggravated, hypersensitivity reaction, non-specific inflammation, sarcoidosis aggravated, Stevens Johnson syndrome.

Infections and Infestations: catheter related infection, non herpetic cold sores, esophageal candidiasis, fungal infection, moniliasis, oral candidiasis, pneumonia, pseudomonas aeruginosa infection, sinusitis, upper respiratory tract infection, urinary tract infection.

Injury and Poisoning: drug toxicity NOS, ecchymoses, overdose NOS, skin trauma.
Metabolism and Nutrition: amylase increased, dehydration, electrolyte abnormality, hypercalcemia, hypercholesterolemia, hypercholesterolemia aggravated, hyperlipemia, hypernatremia, hyperphosphatemia, hyperproteinemia, hypertriglyceridemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hyponatremia, hypophosphatemia, lipase increased, malnutrition, metabolic acidosis, metabolic disorder NOS, NPN increased, renal tubular acidosis, vitamin K deficiency.

Musculoskeletal and Connective Tissue: arthralgia, arthralgia aggravated, back pain, bone pain, chest wall pain, extremities cramps, fasciitis, flank pain, legs cramps, muscle cramps, muscle weakness, musculoskeletal pain, neck stiffness.

Nervous System: abnormal EEG, areflexia, ataxia, central nervous system (CNS) dysfunction, delirium, dysphonia, dystonia, encephalopathy, gait abnormal aggravated, headache aggravated, hemiparesis, hyperkinesia, hyperreflexia, hypoesthesia, hyporeflexia, hypotonia, impaired cognition, impaired concentration, memory impairment, meningism, meningitis, migraine, mononeuritis, neuritis, neuropathy, paraplegia, peripheral neuropathy, restless leg syndrome, sciatica, speech disorder, stupor, twitching.

Psychiatric: abnormal dreaming, altered mental status, amnesia, anxiety, anxiety aggravated, confusion, depression, depression psychotic, emotional lability, libido decreased, nightmare, psychosis, sleep disorder.

Renal and Urinary System: abnormal urine, albuminuria, BUN increased, dysuria, hematuria, micturition disorder, micturition frequency, nephritis interstitial, nocturia, renal calculus, renal failure, renal failure acute, renal insufficiency aggravated, urinary tract obstruction NOS.

Reproductive System and Breast: balanoposthitis, breast pain.

Respiratory, Thoracic and Mediastinal: atelectasis, chest pain, nonproductive cough, dry throat, dyspnea, dyspnea aggravated, epistaxis, epistaxis aggravated, interstitial pneumonia, nasal congestion,

nasal irritation, pharyngitis, pneumonitis, postnasal drip, pulmonary hypertension, pulmonary infiltration, rales, respiratory disorder, rhinitis, rhinorrhea.

Surgical and Medical Procedures: cardioversion.

Skin and Subcutaneous Tissue: acne, alopecia, dermatitis, dry skin, erythema, erythematous rash, face edema, fissures, follicular rash, furunculosis, macular rash, maculopapular rash, night sweats, pruritic rash, rash aggravated, seborrhea, skin disorder, skin nodule, urticaria, vesicular rash.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Clinical Chemistry Findings

In (uncontrolled) trials of patients with IFIs treated with posaconazole oral suspension doses ≥ 800 mg/day, the incidence of clinically significant liver function test abnormalities was: ALT and AST (> 3 X Upper Limit Normal [ULN]) 6% and 5%, respectively; total bilirubin (> 1.5 X ULN) 4%; and alkaline phosphatase (> 3 X ULN) 4%. In healthy volunteers, elevation of hepatic enzymes did not appear to be associated with higher plasma concentrations of posaconazole. In patients, the majority of abnormal liver function tests results showed minor and transient changes and rarely led to discontinuation of therapy. In the comparative trials of hematopoietic stem cell recipients or patients with AML receiving posaconazole oral suspension as prophylaxis at doses up to 600 mg, the incidence of clinically significant liver function test abnormalities was as follows; ALT and AST (> 3 X ULN), 12% and 4%, respectively: total bilirubin (> 1.5 X ULN), 8%; and alkaline phosphatase (> 3 X ULN), 2%.

8.5 Post-Market Adverse Reactions

The following adverse events have been reported during the post-approval use of posaconazole in the US and Europe. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency. A causal relationship to posaconazole could not be excluded for these adverse events, which included:

- **Blood and lymphatic system**: agranulocytosis;
- **Hepatobiliary**: cytolytic hepatitis, toxic hepatitis (including fatality);
- **Endocrine Disorders**: pseudoaldosteronism;
- **Cardiovascular**: QT prolongation, torsades de pointes;
- **Infections and infestations**: *Trichosporon* sepsis.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- **Contraindicated Drugs: ergot alkaloids, terfenadine, astemizole, cisapride, pimozide, quinidine, HMG-CoA reductase inhibitors (statins) and sirolimus (see 2 CONTRAINDICATIONS).**
- **Drugs whose concomitant use should be avoided: cimetidine, rifabutin and phenytoin (see Tables 5 and 6)**
- **Drugs whose concomitant use requires consideration of dose reduction at initiation of concomitant treatment and close therapeutic monitoring of drug levels during treatment: cyclosporine and tacrolimus (see Table 6)**
- **Drugs whose concomitant use requires consideration of dose reduction and close monitoring for adverse events during treatment: vinca alkaloids, midazolam, calcium channel blockers and venetoclax (see Table 5)**

The interactions described in the following subsections apply to posaconazole delayed-release tablets and posaconazole oral suspension unless otherwise specified.

The following information was derived from data with posaconazole oral suspension or an early tablet formulation.

9.2 Drug Interactions Overview

Effects of Other Drugs on Posaconazole Pharmacokinetics
Posaconazole is metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate from p-glycoprotein efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. Posaconazole does not have any major circulating oxidative (CYP450 mediated) metabolites and its concentrations are thus unlikely to be altered by inhibitors of CYP450 enzymes.

Effects of Posaconazole on Pharmacokinetics of Other Drugs
Posaconazole is a strong inhibitor of CYP3A4 and thus the plasma levels of medicinal products that are metabolized through this enzyme pathway may increase when administered with posaconazole.

9.3 Drug-Behavioural Interactions

Not applicable.

9.4 Drug-Drug Interactions

The drugs listed in these tables are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

The majority of drug interaction studies were performed with the posaconazole oral suspension or early tablet formulation, which is 36% less bioavailable than the oral suspension. Although in some drug interaction studies posaconazole exposure levels were lower than observed in the patient population, the drug interactions described below are considered relevant for posaconazole delayed-release tablets at the recommended doses.

Table 5 – Summary of the Effect of Co-administered Drugs on Posaconazole in Healthy Volunteers

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Posaconazole		Recommendations
				Change in Mean C_{max} (ratio estimate[a]; 90% CI of the ratio estimate)	Change in Mean AUC[b] (ratio estimate; 90% CI of the ratio estimate)	
Rifabutin (UDP-G Induction)	clinical trial	300 mg QD[c] x17 days	200 mg (tablets) QD x 10 days	↓ 43% (0.57; 0.43-0.75)	↓ 49% (0.51; 0.37-0.71)	Concomitant use of Posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk.
Phenytoin (UDP-G Induction)	clinical trial	200 mg QD x 10 days	200 mg (tablets) QD x 10 days	↓ 41% (0.59; 0.44-0.79)	↓ 50% (0.50; 0.36-0.71)	Concomitant use of Posaconazole and phenytoin should be avoided unless the benefit to the patient outweighs the risk.
Efavirenz (UDP-G Induction)	clinical trial	400 mg QD × 10 and 20 days	400 mg (oral suspension) BID × 10 and 20 days	↓ 45% (0.55; 0.47-0.66)	↓ 50% (0.50; 0.43-0.60)	Concomitant use of Posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.
Fosamprenavir	clinical trial	700 mg BID x 10 days	200 mg QD on the 1st day, 200 mg BID on the 2nd day, then 400 mg BID x 8 Days	↓ 21% 0.79 (0.71-0.89)	↓ 23% 0.77 (0.68-0.87)	If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended.
Glipizide	clinical trial	10 mg single dose	400 mg BID oral suspension x 10 Days	Glipizide had no clinically significant effect on posaconazole C_{max} and AUC.		No dose adjustments required. Glucose concentrations decreased in some healthy volunteers when glipizide was co-administered with Posaconazole. Glucose concentrations should be monitored in accordance with the current standard of care for patients with diabetes when Posaconazole is co-administered with glipizide.

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Posaconazole		Recommendations
				Change in Mean Cmax (ratio estimate[a]; 90% CI of the ratio estimate)	Change in Mean AUC[b] (ratio estimate; 90% CI of the ratio estimate)	
H2 receptor antagonists, proton pump inhibitors (PPIs) and antacids						
Antacids/H2 receptor antagonists (H2RA)/Proton pump inhibitors (PPI)	clinical trial	Single dose 20 mL of Mylanta[†] ultimate strength liquid; AM dose of 150 mg ranitidine tablet BID; esomeprazole 40 mg once in the morning QAM x 5 days (Day-4 to 1)	400 mg single dose (4x100 mg) delayed release tablets	No clinically relevant effects were observed when posaconazole tablets are concomitantly used with antacids, H2 receptor antagonists and proton pump inhibitors.		No dosage adjustment of Posaconazole Delayed-Release Tablets is required when Posaconazole Delayed-Release Tablets are concomitantly used with antacids, H2 receptor antagonists and proton pump inhibitors.
Cimetidine (Alteration of Gastric pH)	clinical trial	400 mg BID[d] x 10 days	200 mg (tablets) QD x 10 days[e]	↓ 39% (0.61; 0.53-0.70)	↓ 39% (0.61; 0.54-0.69)	Concomitant use of Posaconazole Oral Suspension with H2 receptor antagonists should be avoided if possible.
Esomeprazole (Increase in Gastric pH)	clinical trial	40 mg daily (QAM 5 days, day -4 to 1)	400 mg (oral suspension) single dose	↓ 46% (0.54; 0.43-0.69)	↓ 32% (0.68; 0.57-0.81)	Concomitant use of Posaconazole Oral Suspension with proton pump inhibitors should be avoided if possible.
Gastrointestinal Motility Agents						
Metoclopramide	clinical trial	15 mg QID[f] during 2 days (Day -1 and 1)	400 mg single dose (4x100 mg) delayed release tablets	No clinically meaningful effect on the pharmacokinetics of posaconazole was observed when posaconazole tablets were concomitantly administered with metoclopramide.		No dosage adjustment of Posaconazole Delayed-Release Tablets is required when given concomitantly with metoclopramide.
		10 mg TID[g] × 2 days	400 mg (oral suspension) single dose	Metoclopramide, when given with posaconazole oral suspension, decreases posaconazole plasma concentrations.		If metoclopramide is concomitantly administered with Posaconazole Oral Suspension, it is recommended to closely monitor for breakthrough fungal infections.
Loperamide	clinical trial	4 mg single dose (two 2 mg tablets)	400 mg single dose (oral suspension) administered with a nutritional supplement	Loperamide does not affect posaconazole oral suspension plasma concentrations.		No dosage adjustment of Posaconazole Oral Suspension is required when loperamide and Posaconazole Oral Suspension are used concomitantly.

Table 6 - Summary of the Effect of Posaconazole on Co-administered Drugs in Healthy Volunteers and Patients

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Co-Administered Drugs		Recommendations
				Change in Mean Cmax (ratio estimate[a]; 90% CI of the ratio estimate)	Change in Mean AUC[b] (ratio estimate; 90% CI of the ratio estimate)	
Cyclosporine (inhibition of CYP3A4 by Posaconazole)	clinical trial	Stable maintenance dose in heart transplant recipients	200 mg (tablets) QD[c] x 10 days	↑ cyclosporine whole blood trough concentrations. Cyclosporine dose reductions of up to 29% were required.		When initiating treatment with Posaconazole in patients already receiving cyclosporine, reduction of the cyclosporine dose should be considered (e.g., to about 3/4 of the current dose). Thereafter blood levels of cyclosporine should be monitored carefully during co-administration and upon discontinuation of Posaconazole treatment, the dose of cyclosporine should be adjusted as necessary.
Tacrolimus (inhibition of CYP3A4 by Posaconazole)	clinical trial	0.05 mg/kg single oral dose	400 mg (oral suspension) BID[d] x 7 days	↑ 121% (2.21; 2.01-2.42)	↑ 358% (4.58; 4.03-5.19)	When initiating treatment with Posaconazole in patients already receiving tacrolimus, reduction of the tacrolimus dose should be considered (e.g., to about 1/3 of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during co-administration, and upon discontinuation of Posaconazole, and the dose of tacrolimus should be adjusted as necessary.
Rifabutin (inhibition of CYP3A4 by Posaconazole)	clinical trial	300 mg QD x 17 days	200 mg (tablets) QD x 10 days	↑ 31% (1.31; 1.10-1.57)	↑ 72% (1.72; 1.51-1.95)	Concomitant use of Posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. If the medicinal products are co-administered, careful monitoring of full blood counts and adverse effects related to increased rifabutin levels (e.g., uveitis) is recommended.
Midazolam (inhibition of CYP3A4 by Posaconazole)	clinical trial	0.4-mg single IV[e] dose	200 mg (oral suspension) BID x 7 days	↑ 30% (1.3; 1.13-1.48)	↑ 362% (4.62; 4.02-5.3)	It is recommended that dose adjustments of benzodiazepines, metabolized by CYP3A4, be considered during co-administration with Posaconazole.
		0.4-mg single IV[e] dose	400 mg (oral suspension) BID x 7 days	↑62% (1.62; 1.41-1.86)	↑ 524% (6.24; 5.43-7.16)	
		2-mg single oral dose	200 mg (oral suspension) QD x 7 days	↑ 169% (2.69; 2.46-2.93)	↑ 470% (5.70; 4.82-6.74)	
		2-mg single oral dose	400 mg (oral suspension) BID x 7 days	↑ 138% (2.38; 2.13-2.66)	↑ 397% (4.97; 4.46-5.54)	

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Co-Administered Drugs		Recommendations
				Change in Mean Cmax (ratio estimate[a]; 90% CI of the ratio estimate)	Change in Mean AUC[b] (ratio estimate; 90% CI of the ratio estimate)	
Phenytoin (inhibition of CYP34A by Posaconazole)	clinical trial	200 mg QD PO[f] x 10 days	200 mg (tablets) QD x 10 days	↑ 16% (1.16; 0.85-1.57)	↑ 16% (1.16; 0.84-1.59)	Concomitant use of Posaconazole and phenytoin should be avoided unless the benefit to the patient outweighs the risk. If the medicinal products are co-administered, frequent monitoring of phenytoin concentrations should be performed and dose reduction of phenytoin should be considered.
Ergot alkaloids	theoretical	NA, since theoretical		Posaconazole may ↑ the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism.		Co-administration of Posaconazole and ergot alkaloids is contraindicated (see CONTRAINDICATIONS).
Terfenadine Astemizole Cisapride Pimozide Quinidine	theoretical	NA, since theoretical		Co-administration of posaconazole oral suspension and certain drugs such as cisapride, pimozide, and quinidine, metabolized through the CYP3A4 system may result in ↑ plasma concentrations of these medicinal products, leading to potentially serious and/or life threatening adverse events (QT prolongation and rare occurrences of torsade de pointes).		Co-administration of these drugs with Posaconazole is contraindicated (see CONTRAINDICATIONS).
Sirolimus	clinical trial	2 mg single dose	400 mg (oral suspension) BID x 16 days	↑ 572% (6.72; 5.62-8.03)	↑ 788% (8.88; 7.26-10.9)	Co-administration of Posaconazole and sirolimus is contraindicated (see CONTRAINDICATIONS).
Vinca alkaloids	theoretical	NA, since theoretical		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). Posaconazole may ↑ the plasma concentration of vinca alkaloids (e.g., vincristine and vinblastine), which may lead to 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.
simvastatin (HMG-CoA reductase inhibitor metabolized through CYP3A4)	clinical trial	40 mg single dose	50, 100, and 200 mg (oral suspension) QD x 13 days	↑ Cmax an average of 7.4- to 11.4-fold	↑ AUC an average of 5.7- to 10.6-fold	Increased HMG-CoA reductase inhibitor concentrations in plasma can be associated with rhabdomyolysis. Co-administration of Posaconazole and HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 is contraindicated (see CONTRAINDICATIONS).

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	Posaconazole Dose/Schedule	Effect on Bioavailability of Co-Administered Drugs		Recommendations
				Change in Mean Cmax (ratio estimate[a]; 90% CI of the ratio estimate)	Change in Mean AUC[b] (ratio estimate; 90% CI of the ratio estimate)	
Zidovudine (AZT) Lamivudine (3TC) Indinavir	clinical trial	In HIV infected patients on stable doses of AZT (300 mg BID or 200 mg every 8 hours (h)), 3TC (150 mg BID), and/or indinavir (800 mg every 8 h).	200 mg (tablets) QD[c] x 10 days	Posaconazole had no clinically significant effect on the Cmax and AUC of these medicinal products.		No dose adjustments required.
Atazanavir Atazanavir/ ritonavir boosted regimen	clinical trial	300 mg QD x 14 days 300 mg/100 mg QD x 14 days	400 mg (oral suspension) BID x 7 days 400 mg (oral suspension) BID x 7 days	↑ 155% (2.55; 1.89-3.45) ↑ 53% (1.53; 1.13-2.07)	↑ 268% (3.68; 2.89-4.70) ↑ 146% (2.46; 1.93-3.13)	Frequent monitoring for adverse events and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with Posaconazole.
Calcium channel blockers metabolized through CYP3A4	theoretical	NA, since theoretical		Co-administration of posaconazole with calcium channel blockers metabolized through CYP3A4 may result in significant drug interactions.		Frequent monitoring for adverse effects and toxicity related to calcium channel blockers is recommended during co-administration with Posaconazole. Dose adjustment of calcium channel blockers may be required.
Digoxin	theoretical	NA, since theoretical		Posaconazole may increase plasma concentration of digoxin.		Co-administration of other azoles with digoxin has been associated with increases in digoxin levels. Thus, Posaconazole may increase plasma concentration of digoxin and digoxin levels should be monitored when initiated or discontinuing Posaconazole treatment.
Venetoclax	clinical trial	Refer to venetoclax product monograph.		Concomitant use of venetoclax (a CYP3A4 substrate) with posaconazole increases venetoclax C_{max} and AUC_{0-INF}, which may increase venetoclax toxicities (see 7 WARNINGS AND PRECAUTIONS)		Refer to venetoclax product monograph

a: Ratio Estimate = ratio of co-administered drug plus posaconazole to posaconazole alone for C_{max} or AUC
b: AUC = area under the plasma concentration time curve
c: QD = once daily
d: BID = twice a day e:
IV = intravenous f: PO
= per os

9.5 Drug-Food Interactions

Table 7 – Established or Potential Drug-Food Interactions

Proper name	Ref	Effect	Clinical comment
Caffeine	clinical trial	No clinically significant effect has been noted.	No dose adjustments required.
Food or nutritional supplement	clinical trial	Posaconazole delayed-release tablets when given in the fasted state as a single dose has comparable or greater relative bioavailability as compared to the posaconazole oral suspension given with a high fat meal as a single dose. The AUC of POSACONAZOLE® Delayed-Release Tablets is about 50% greater when administered with a high-fat meal (~ 50 grams fat) relative to the fasted state in healthy subjects.	Posaconazole delayed-release tablets can be taken with or without food. The effect of food is not considered to be clinically meaningful. No dosage adjustment of posaconazole delayed-release tablets is needed (see 10 CLINICAL PHARMACOLOGY).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Posaconazole is an azole antifungal agent. Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane.

10.2 Pharmacodynamics

A correlation between total drug exposure (AUC) and clinical outcome has been observed. For subjects with *Aspergillus* infections, effective drug exposure appears to be higher than that for infections caused by *Candida* species, although the critical AUC/MIC ratio associated with clinical success is uncertain. It is particularly important to try to ensure that maximal plasma levels are achieved in patients infected with *Aspergillus* (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, Pharmacokinetics).

Exposure Response Relationship:
In clinical studies of neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS or HSCT recipients with 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 (C_{avg}) and efficacy outcomes (Table 8). A lower C_{avg} may be associated with an increased risk of treatment failure.

Table 8 – Posaconazole Oral Suspensions Exposure Analysis (C_{avg}) in Clinical Trials

	Treatment of refractory aspergillosis		Prophylaxis in AML/MDS[a]		Prophylaxis in GVHD[b]	
	C_{avg} Range (ng/mL)	Treatment Failure[c] (%)	C_{avg} Range (ng/mL)	Treatment Failure[d] (%)	C_{avg} Range (ng/mL)	Treatment Failure[d] (%)
Quartile 1	55 - 277	76	90 - 322	54.7	22 - 557	44.4
Quartile 2	290 - 544	47	322 - 490	37.0	557 - 915	20.6
Quartile 3	550 - 861	47	490 - 734	46.8	915 – 1,563	17.5
Quartile 4	877 – 2,010	29	734 – 2,200	27.8	1,563 – 3,650	17.5

C_{avg} = the average posaconazole concentration when measured at steady state
a: Neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS
b: HSCT recipients with GVHD
c: Defined as failure to achieve global response at the end of therapy
d: Defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive fungal infections

10.3 Pharmacokinetics

General Pharmacokinetic Characteristics:

Posaconazole Delayed-Release Tablets

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

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

	N	$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	C_{avg}[†] (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max}[‡] (hr)	$t_{½}$ (hr)	CL/F (L/hr)
Healthy Volunteers	12	51618 (25)	2151 (25)	2764 (21)	1785 (29)	4 (3-6)	31 (40)	7.5 (26)
Patients	50	37900 (42)	1580 (42)	2090 (38)	1310 (50)	4 (1.3-8.3)	-	9.39 (45)

CV = coefficient of variation expressed as a percentage (%CV); $AUC_{0\text{-}T}$ = Area under the plasma concentration-time curve from time zero to 24 hr; C_{max} = maximum observed concentration; C_{min} = minimum observed plasma concentration; T_{max} = time of maximum observed concentration; $t_{½}$ = terminal phase half-life; CL/F = Apparent total body clearance

* 300 mg BID on Day 1, then 300 mg QD thereafter

† C_{avg} = time-averaged concentrations (i.e., $AUC_{0\text{-}24\ hr/24\ hr}$)

‡ Median (minimum-maximum)

Absorption:

Posaconazole Delayed-Release Tablets

Posaconazole delayed-release tablets are absorbed with a median t_{max} of 4 to 5 hours and exhibit dose proportional pharmacokinetics after single and multiple dosing up to 300 mg. Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (QD after BID loading dose at Day 1). The absolute availability of the delayed-release tablets is approximately 54% under fasted conditions. The C_{max} and AUC of posaconazole following administration of posaconazole delayed-release tablets is increased 16% and 51%, respectively, when given with a high fat meal compared to a fasted state (see Table 10). However, the effect of food on the absorption of posaconazole delayed-release tablets is not considered clinically meaningful. Food effect was taken into consideration at the time of final dose selection of the 300 mg delayed-release tablet based on data from the pivotal clinical Phase 1b/Phase 3 pharmacokinetic/safety study in which patients took posaconazole delayed-release tablets without regard to food intake. Posaconazole delayed-release tablets can therefore be administered with or without food.

Table 10: Statistical Comparison of Plasma Pharmacokinetics of Posaconazole Following Single Oral Dose Administration of 300 mg Posaconazole Delayed-Release Tablet to Healthy Subjects under Fasting and Fed Conditions

	Fasting Conditions		Fed Conditions (High Fat Meal)*		Fed/Fasting
Pharmacokinetic Parameter	**N**	**GM (95% CI)**	**N**	**GM (95% CI)**	**GMR (90% CI)**
C_{max}† (ng/mL)	14	893 (731, 1,090)	16	1,040 (915, 1,180)	1.16 (0.96, 1.41)
$AUC_{0\text{-}last}$‡ (hr·ng/mL)	14	25600 (21,500, 30,400)	16	38700 (35,000, 42,700)	1.51 (1.33, 1.72)
T_{max}§ (hr)	14	5.00 (3.00, 8.00)	16	6.00 (5.00, 24.00)	N/A

GM = Geometric least-squares mean

GMR = Geometric least-squares mean ratio

CI = Confidence interval

* 48.5 g fat

† C_{max} = maximum observed concentration

‡ $AUC_{0\text{-}last}$ = $AUC_{0\text{-}72hr}$

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

Distribution:

Posaconazole has a mean (CV%) volume of distribution of 287 L (24%) in healthy volunteers.

Posaconazole is highly bound to human 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.

Posaconazoleis primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p- glycoprotein (P-gp) efflux. Inhibitors of inducers of these clearance pathways may affect posaconazole plasma concentrations.
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.

Elimination:
Posaconazole is predominantly eliminated in the feces (77% of the radiolabeled dose) with the major component eliminated as parent drug (66% of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 14% of the radiolabeled dose excreted in urine (< 0.2% of the radiolabeled dose is parent drug).

Posaconazole delayed-release tablet is eliminated with a mean half-life (t½) ranging between 26 and 31 hours and a mean apparent clearance ranging from 7.5 to 11 L/hr.

Special Populations and Conditions

- **Pediatrics:** Use of posaconazole delayed-release tablets in patients 13 to 17 years of age is supported by evidence from adequate and well-controlled studies of posaconazole oral suspension in adults.

  Following administration of 800 mg per day of posaconazole oral suspension as a divided dose for treatment of IFIs, mean trough plasma concentrations from 12 patients 8 – 17 years of age were similar to concentrations from 194 patients 18 – 64 years of age. No pharmacokinetic data are available from pediatric patients less than 8 years of age.

- **Geriatrics:** Of the 230 patients treated with posaconazole delayed-release tablets, 38 (17%) were greater than 65 years of age. The pharmacokinetics of posaconazole delayed-release tablets are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

- **Sex:** The pharmacokinetics of posaconazole are comparable in men and women. No adjustment in the dosage of posaconazole is necessary based on gender.

- **Ethnic Origin:** The pharmacokinetic profile of posaconazole is not significantly affected by race. No adjustment in the dosage of posaconazole is necessary based on race. The AUC and Cmax of posaconazole decreased slightly in Black subjects relative to Caucasian subjects. No other races were studied.
  There is insufficient data among different races with posaconazole delayed-release tablets.

- **Hepatic Insufficiency:** The pharmacokinetic data in subjects with hepatic impairment was not sufficient to determine if dose adjustment is necessary in patients with hepatic dysfunction. It is

recommended that posaconazole oral suspension be used with caution in patients with hepatic impairment (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

Similar recommendations apply to posaconazole delayed-release tablets; however, a specific study has not been conducted with posaconazole delayed-release tablets.

- **Renal Insufficiency:** Following single-dose administration of 400 mg of the oral suspension, there was no significant effect of mild (GFR: 50-80 mL/min/1.73m^2, n=6) and moderate (GFR: 20-49 mL/min/1.73m^2, n=6) renal insufficiency on posaconazole pharmacokinetics; therefore, no dose adjustment is required in patients with mild to moderate renal impairment. In subjects with severe renal insufficiency (GFR: < 20 mL/min/1.73m^2), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (GFR: > 80 mL/min/1.73m^2); however, the range of the AUC estimates was highly variable (CV=96%) in these subjects with severe renal insufficiency as compared to that in the other renal impairment groups (CV < 40%). Due to the variability in exposure with posaconazole oral therapy, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

  Similar recommendations apply to posaconazole delayed-release tablets; however a specific study has not been conducted with posaconazole delayed-release tablets.

- **Obesity**: Pharmacokinetic modeling for posaconazole suggests that patients weighing greater than 120 kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg.

11 STORAGE, STABILITY AND DISPOSAL

Storage

TARO-POSACONAZOLE Delayed-Release Tablets

Store at room temperature (15 to 30°C). Do not use past expiry date on the label.

12 SPECIAL HANDLING INSTRUCTIONS

TARO-POSACONAZOLE Delayed-Release Tablets

No special requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

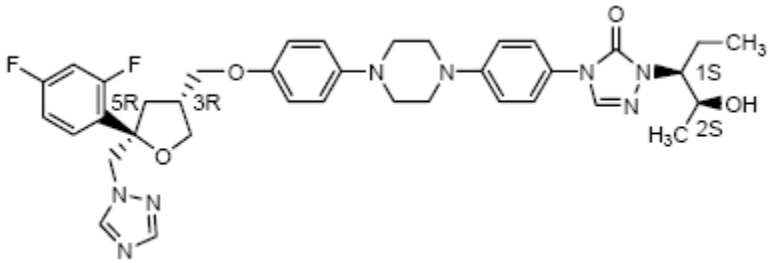
Drug Substance

Proper name: Posaconazole

Chemical name: 4-[4-[4-[4-[[(3*R*,5*R*)-5-(2,4-difluorophenyl)tetrahydro-5-(1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1*S*,2*S*)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one

Molecular formula and molecular mass: $C_{37}H_{42}F_2N_8O_4$ 700.78 g/mol

Structural formula:



Physicochemical properties: Posaconazole is a white powder which is insoluble in hexanes, deionized water, pH 3 buffer, pH 5 buffer, pH 7 buffer and 0.1N NaOH, very slightly soluble in 0.1N HCl, slightly soluble in ethanol, and sparingly soluble in acetonitrile, methanol and acetone.

Product Characteristics:

pH and pKa values:

pH: 5.9 (10 mg/mL aqueous slurry)

Dissociation Constant (potentiometric titration): 3.6 (piperazine)
4.6

(triazole) Melting range: 167.9°C - 169.2°C

14 CLINICAL TRIALS

Pharmacokinetics and Safety of Posaconazole Delayed-Release Tablets in Patients
Study P05615

Study P05615 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole delayed-release tablet. Study P05615 was conducted in a similar patient population to that previously studied in the pivotal posaconazole oral suspension clinical program.

Study P05615 enrolled a total of 230 subjects. Part 1 of the study was designed to select a dose for further study in Part 2, after first evaluating pharmacokinetics, safety, and tolerability in the neutropenic patient population at high risk of a fungal infection. Part 2 of the study was designed to evaluate posaconazole delayed-release tablet in a more diverse patient population, and to confirm the exposure of posaconazole delayed-release tablet in additional subjects at risk of a fungal infection.

Posaconazole delayed-release tablet was administered without regard to food intake in both Part 1 and Part 2 of the study.

The subject population for Part 1 included subjects with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia. Two different dosing groups were evaluated in Part 1: 200 mg BID on Day 1, followed by 200 mg QD thereafter (Part 1A) and 300 mg BID on Day 1, followed by 300 mg QD thereafter (Part 1B).

The subject population in Part 2 included: 1) patients with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia, or 2) patients who had undergone a HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. These types of patients had been previously studied in a pivotal controlled trial of posaconazole oral suspension. Based on the pharmacokinetics and safety results of Part 1, all subjects in Part 2 received 300 mg BID on Day 1, followed by 300 mg QD thereafter.

The total subject population had a mean age of 51 years (range = 19-78 years), 93% were White, the major ethnicity was not Hispanic or Latino (84%), and 62% were male. The study treated 110 (48%) subjects with AML (new diagnosis), 20 (9%) subjects with AML (first relapse), 9 (4%) subjects with MDS, and 91 (40%) subjects with HSCT, as the primary diseases at study entry.

Serial PK samples were collected on Day 1 and at steady-state on Day 8 for all Part 1 subjects and a subset of Part 2 subjects. This serial PK analysis demonstrated that 90% of the subjects treated with the 300 mg QD dose attained steady state C_{avg} between 500 - 2500 ng/mL [C_{avg} was the average concentration of posaconazole at steady state, calculated as AUC/dosing interval (24 hours)]. Subjects with AML/MDS with neutropenia following chemotherapy or HSCT subjects receiving immunosuppressive therapy to prevent or treat GVHD who received 300 mg QD achieved a mean C_{avg} at steady state of 1,580 ng/mL. In addition, 98% of subjects in the serial PK cohort attained a C_{min} at steady-state levels ≥ 500 ng/mL. The PK findings from the pivotal study (Study P05615) support a 300-mg daily dose of posaconazole delayed-release tablet for use in prophylaxis.

14.3 Comparative Bioavailability Studies

Fasting Study

A blinded, single dose, randomized, fully replicated, crossover study between Taro Posaconazole Delayed-Release Tablets, 100 mg (Taro Pharmaceuticals Inc.) and [Pr]POSANOL® Delayed-Release Tablets, 100 mg (Merck Canada Inc.) was conducted in 48 healthy adult Asian male subjects under fasting conditions. A summary of the comparative bioavailability data from the 40 subjects who completed the study is presented in following table:

Posaconazole (1 x 100 mg) Geometric Mean Arithmetic Mean (%CV)				
Pharmacokinetic Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	8507.8 9134.6 (37.1)	8511.9 9178.9 (37.8)	99.8	94.0- 105.9
AUC_I (ng·h/mL)	8826.9 9502.9 (37.9)	8943.9 9657.8 (38.3)	98.8	93.0 - 104.9
C_{max} (ng/mL)	343.9 365.8 (36.5)	330.0 350.2 (35.5)	103.9	95.9 - 112.6
T_{max}[3] (h)	4.5 (1.5 - 8.0)	4.5 (2.5 -7.0)	NA	NA
$t_{½}$[4] (h)	22.3 (24.9)	22.4 (24.7)	NA	NA

[1]Taro-Posaconazole (posaconazole) Delayed-Release Tablets, 100 mg (Taro Pharmaceuticals Inc., Canada)
[2] [PR]POSANOL® (posaconazole) Delayed-Release Tablets, 100 mg (Merck Canada Inc.)
[3]Expressed as the median (range) only
[4]Expressed as the arithmetic mean (%CV) only

Fed Study

A blinded, single dose, randomized, two-way crossover study between Taro Posaconazole Delayed-Release Tablets, 100 mg (Taro Pharmaceuticals Inc.) and PrPOSANOL® Delayed-Release Tablets, 100 mg (Merck Canada Inc.) was conducted in 48 healthy adult Asian male subjects under high-fat, high-calorie fed conditions. A summary of the comparative bioavailability data from the 44 subjects who completed the study is presented in following table:

Posaconazole (1 x 100 mg) Geometric Mean Arithmetic Mean (%CV)				
Pharmacokinetic Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h/mL)	11472.9 11762.8 (22.1)	12387.3 12707.7 (22.2)	92.5	88.7 - 96.5
AUC_I (ng·h/mL)	11797.0 12124.4 (23.3)	12803.5 13175.7 (23.6)	92.0	88.1 - 96.2
C_{max} (ng/mL)	391.3 397.9 (17.9)	442.7 455.4 (23.1)	88.6	84.1 - 93.3
T_{max}[3] (h)	6.0 (2.5-16.0)	5.5 (1.5-12.0)	NA	NA
$t_{½}$[4] (h)	20.9 (22.2)	22.4 (23.7)	NA	NA

[1]Taro-Posaconazole (posaconazole) Delayed-Release Tablets, 100 mg (Taro Pharmaceuticals Inc., Canada)
[2] PRPOSANOL® (posaconazole) Delayed-Release Tablets, 100 mg (Merck Canada Inc.)
[3]Expressed as the median (range) only
[4]Expressed as the arithmetic mean (%CV) only

DETAILED PHARMACOLOGY

Pharmacodynamics

ECG evaluation

No placebo - controlled, randomized, Phase 1 study with a positive control arm for QT prolongation was performed in order to evaluate the effect of posaconazole on the QT interval.
Multiple, time-matched ECGs collected over a 12 h 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 BID with a high-fat meal. In this pooled analysis, the mean QT_c (Fridericia (F)) interval change was -5 msec following administration of the recommended clinical dose. A decrease in the QT_c (F) interval (- 3 msec) was also observed in a small number of subjects (n=16) administered placebo. The placebo-adjusted mean maximum QT_c (F) interval change from baseline was < 0 msec (- 8 msec). No subject administered posaconazole had a QT_c (F) interval of ≥ 500 msec or an increase ≥ 60 msec in their QT_c (F) interval from baseline.

Pharmacokinetics (see 10 CLINICAL PHARMACOLOGY)

The general pharmacokinetic findings across the clinical program in both healthy volunteers and patients were consistent, in that posaconazole was slowly absorbed and slowly eliminated with an extensive volume of distribution.

Exposure following multiple administration of posaconazole delayed-release tablets (200 or 300 mg) QD was 1.3 times higher in healthy volunteers than in patients.

Special Populations and Conditions

Pediatrics

Use of posaconazole delayed-release tablet in patients 13 to 17 years of age is supported by evidence from adequate and well-controlled studies of posaconazole oral suspension in adults.

Following administration of 800 mg per day of posaconazole oral suspension as a divided dose for treatment of IFIs, mean trough plasma concentrations from 12 patients 8 - 17 years of age (776 ng/mL) were similar to concentrations from 194 patients 18 - 64 years of age (817 ng/mL). No pharmacokinetic data are available from pediatric patients less than 8 years of age. Similarly, in the prophylaxis studies, the mean steady-state posaconazole C_{avg} was comparable among 10 adolescents (13 - 17 years of age) to C_{avg} achieved in adults (≥ 18 years of age).

Geriatrics

Of the 230 patients treated with posaconazole delayed-release tablets, 38 (17%) were greater than 65 years of age. The pharmacokinetics of posaconazole delayed-release tablets are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Gender

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

Race
There is insufficient data among different races with posaconazole delayed-release tablets.

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

Hepatic Insufficiency
In a small number of subjects (n=12) studied with hepatic insufficiency (Child-Pugh class A, B or C), C_{max} values generally decreased with the severity of hepatic dysfunction (545, 414 and 347 ng/mL for the mild, moderate, and severe groups, respectively), even though the C_{max} values (mean 508 ng/mL) for the normal subjects were consistent with previous trials in healthy volunteers. In addition, an increase in half-life was also associated with a decrease in hepatic function (26.6, 35.3, and 46.1 h for the mild, moderate, and severe groups, respectively), as all groups had longer half-life values than subjects with normal hepatic function (22.1 h). Due to the limited pharmacokinetic data in patients with hepatic insufficiency, no recommendation for dose adjustment can be made.

Similar recommendations apply to posaconazole delayed-release tablets; however, a specific study has not been conducted with posaconazole delayed-release tablets.

Renal Insufficiency
Following single-dose administration, there was no effect of mild and moderate renal insufficiency (n=18, GFR ≥ 20 mL/min/1.73 m^2) on posaconazole pharmacokinetics, therefore, no dose adjustment is required. In subjects with severe renal insufficiency (n=6, GFR < 20 mL/min/1.73 m^2), the exposure of posaconazole was highly variable (96% CV) compared to the exposure in the other renal groups (< 40% CV). However, as posaconazole is not significantly renally eliminated, an effect of severe renal insufficiency on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended. Posaconazole is not removed by hemodialysis. Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections.

Similar recommendations apply to posaconazole delayed-release tablets; however, a specific study has not been conducted with posaconazole delayed-release tablets.

Animal Pharmacology

Posaconazole Oral Therapy The administration of a single oral dose of 30 mg/kg of posaconazole did not modify cardiovascular, gastrointestinal, behavioral, neurologic, or autonomic function in the rat. A single IV dose of a lipid-containing formulation of posaconazole (bolus) at 30 or 60 mg/kg did not demonstrate changes in respiratory rate, tidal volume, or minute volume, or in behavior, neurologic or autonomic function, compared with vehicle-treated rats. A single dose of 3 or 10 mg/kg did not affect renal function.

In vitro effects of posaconazole on ventricular repolarization were evaluated by measuring both the action potential and the recombinant hERG channel current. In Purkinje fibers isolated from dog heart, exposure to posaconazole at measured concentrations of 25 ng/mL (36 nM), 69 ng/mL (98 nM) and 365 ng/mL (521 nM) induced a small (< 10%) but statistically significant increase in action potential duration at 60% (APD_{60}) and/or 90% (APD_{90}) repolarization. In mouse L-929 cells stably transfected with the human α-subunit (hERG) of the cardiac delayed rectifier, I_{Kr}, a measured concentration of

770 ng/mL (1.1 μM) posaconazole decreased hERG current by 7%. Accounting for protein binding, the drug concentration in the hERG assay was 18-times the free posaconazole Cmax value in healthy volunteers. Changes of the magnitude noted in the recombinant hERG channel and isolated Purkinje fiber systems would be unlikely to elicit QT interval prolongation *in vivo*.

At an oral dose of 90 mg/kg in rats, posaconazole was associated with a minimal increase in systolic (13 to 23 mm Hg) and mean arterial (10 to 19 mm Hg) blood pressures after four weeks of dosing. There were no changes in heart rate. After four weeks of dosing, rats given posaconazole had a decreased intraventricular systolic diameter and increased fractional shortening, which may be indicative of increased cardiac contractility. However, there was no concomitant increase in stroke volume. No other echocardiographic indices of cardiac function were altered by posaconazole.

Cardiovascular parameters in monkeys were assessed in two safety pharmacology studies with the lipid-containing IV formulation of posaconazole. No posaconazole–related effects on heart rate, arterial blood pressure, ECG intervals (RR, PR, QRS, QT, QT_c), or ECG morphology and rhythm were observed following seven days of dosing at doses up to 40 mg/kg. The lowest mean AUC (0-24 hr) was observed on Day 1 and was 141 μg·hr/mL, which is 2.4-fold a human AUC exposure of 59 μg·hr/mL. The absence of QT or QT_c interval changes at 40 mg/kg posaconazole intravenously in conscious monkeys indicates a low potential for posaconazole to produce QT or QT_c interval prolongation.

15 MICROBIOLOGY

Posaconazole is a potent inhibitor of the enzyme lanosterol 14α-demethylase, which catalyses an essential step in ergosterol biosynthesis. Consequently, posaconazole exhibits broad-spectrum antifungal activity against a variety of yeasts and moulds including species of *Candida* (including *C. albicans* isolates resistant to fluconazole, voriconazole and itraconazole, *C. krusei* and *C. glabrata* which are inherently less susceptible to fluconazole, and *C. lusitaniae* which is inherently less susceptible to amphotericin B), *Aspergillus* (including isolates resistant to fluconazole, voriconazole, itraconazole and amphotericin B) and organisms not previously regarded as being susceptible to azoles such as the zygomycetes (e.g., species of *Absidia*, *Mucor*, *Rhizopus* and *Rhizomucor*). *In vitro* posaconazole exhibited fungicidal activity against species of *Aspergillus*, dimorphic fungi (*Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Penicillium marneffei,* and *Coccidioides immitis*) and some species of *Candida*. In animal infection models posaconazole was active against a wide variety of fungal infections caused by moulds or yeasts. However, there was no consistent correlation between minimum inhibitory concentration (MIC) and efficacy.

Posaconazole has been shown *in vitro* and in clinical infections to be active against the following microorganisms (see 1 INDICATIONS): *Aspergillus* species (*A. fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, *A. niger*, *A. ustus*, *A. ochraceus*), *Candida* species (*C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*), *Coccidioides immitis*, *Fonsecaea pedrosoi*, *Pseudallescheria boydii* and species of *Exophiala*, *Fusarium*, *Rhizomucor*, *Mucor*, and *Rhizopus*.

Additionally, the following *in vitro* data are available (see Tables 11 and 12). The results of such studies do not necessarily correlate with clinical outcome. The safety and effectiveness of posaconazole in treating clinical infections due to these microorganisms have not been established in clinical trials.

The posaconazole MIC90 values for mould strains tested are summarized in Table 11.

Table 11 - MIC_{90} Values for Mould Strains Tested

Pathogen	MIC_{90}[a] (µg/mL)	Pathogen	MIC_{90}[a] (µg/mL)	Pathogen	MIC_{90}[a] (µg/mL)
Absidia coerulea	(2.0)[b]	*Curvularia* spp	(0.031 - 0.125)	*Phialophora verrucosa*	(0.5 - 4.0)
Absidia corymbifera	2.0	*Epidermophyton floccosum*	0.125	*Pseudallescheria boydii*	2.0
Absidia glauca	(2.0)	*Exophiala dermatidis*	(0.125)	*Ramichloridium obovoideum*	(0.031 - 0.063)
Absidia pseudocylindrospora	(16.0)	*Exophiala jeanselmei*	0.5	*Rhizomucor miehei*	(0.016)
Absidia repens	(4.0)	*Exophiala moniliae*	(0.016)	*Rhizomucor pusillus*	(0.031 - 0.25)
Absidia spp	(0.031 - 0.5)	*Exserohilum rostratum*	(0.063 - 0.25)	*Rhizomucor* spp	(0.016)
Alternaria alternate	(0.016 - 4.0)	*Fonsecaea pedrosoi*	0.5	*Rhizopus arrhizus*	(0.5 - 32.0)
Alternaria spp	0.25	*Fusarium dimerum*	(1.0 4.0)	*Rhizopus microsporus*	16.0
Apophysomyces spp	(0.031 - 4.0)	*Fusarium moniliforme*	2.0	*Rhizopus microsporus v chinensis*	(16.0)
Aspergillus candidus	(0.031 - 0.063)	*Fusarium oxysporum*	16.0	*Rhizopus microsporus v oligosporus*	(16.0)
Aspergillus flavus	1.0	*Fusarium proliferatum*	(0.5 - 8.0)	*Rhizopus oryzae*	4.0
Aspergillus fumigatus	0.5	*Fusarium solani*	128.0	*Rhizopus schipperae*	(1.0 - 8.0)
Aspergillus glaucus	(0.063-16.0)	*Fusarium* spp	16.0	*Rhizopus* spp	4.0
Aspergillus nidulans	0.25	*Geotrichum candidum*	(0.125)	*Rhizopus stolonifer*	(2.0 - 16.0)
Aspergillus niger	0.5	*Geotrichum spp*	(0.25-32.0)	*Saksenaea vasiformis*	(0.016 - 2.0)
Aspergillus ochraceus	(0.063 - 0.125)	*Histoplasma capsulatum*	0.5	*Scedosporium apiospermum*	2.0
Aspergillus oryzae	(0.25)	*Microsporum audouinii*	(0.25)	*Scedosporium prolificans*	32.0
Aspergillus sydowii	0.5	*Microsporum canis*	0.5	*Schizophyllum commune*	(0.125 - 0.25)
Aspergillus terreus	0.25	*Microsporum fulvum*	(0.5)	*Scopulariopsis brevicaulis*	8.0
Aspergillus ustus	16.0	*Microsporum gypseum*	(0.008 - 0.5)	*Scytalidium dimidiatum*	(0.5)

Aspergillus versicolor	2.0	*Microsporum persicolor*	(0.25)	*Sporothrix schenckii*	2.0
Bipolaris hawaiiensis	(0.016)	*Mucor circinelloides*	16.0	*Trichoderma* spp	(1.0)
Bipolaris spicifera	(0.016 - 0.125)	*Mucor hiemalis*	32.0	*Trichophyton krajdenii*	(0.063)
Bipolaris spp	(0.125 - 1.0)	*Mucor mucedo*	(2.0)	*Trichophyton mentagrophyte* s	0.125
Bjerkandera adusta	0.25	*Mucor racemosus*	(0.008 - 1.0)	*Trichophyton raubitschekii*	(0.25)
Blastomyces dermatitidis	0.5	*Mucor ramosissimus*	(0.125 - 0.5)	*Trichophyton rubrum*	0.25
Cladophialophora bantiana	(0.031 - 0.5)	*Mucor rouxii*	(1.0 - 32.0)	*Trichophyton soudanense*	(0.5)
Cladophialophora carionii	0.5	*Mucor* spp	16.0	*Trichophyton* spp	0.063
Coccidioides immitis	0.5	*Paecilomyces lilacinus*	2.0	*Trichophyton terrestre*	(0.125)
Cunninghamella bertholletiae	(0.5 - 16.0)	*Paecilomyces* spp	0.5	*Trichophyton tonsurans*	0.125
Cunninghamella blakesleeana	(16.0)	*Paecilomyces variotii*	(0.016 - 0.063)	*Trichophyton verrucosum*	(0.5)
Cunninghamella echinulata	(4.0 - 16.0)	*Paracoccidioides brasiliensis*	0.125	*Tritirachium* spp	(1.0 - 16.0)
Cunninghamella elegans	(16.0)	*Penicillium marneffei*	0.016	*Ulocladium* spp	(0.25)
Cunninghamella spp	2.0	*Penicillium* spp	1.0	*Wangiella dermatitidis*	(0.063 - 0.125)
Curvularia lunata	(0.016 - 0.25)	*Phialophora spp*	(0.125 – 32.0)		

a: minimal inhibitory concentration at which 90% of the strains tested are inhibited from growth

b: When the number of strains tested was < 10, the range of MICs is indicated in parentheses.

The posaconazole MIC_{90} values for yeast strains tested are summarized in Table 12.

Table 12 - MIC_{90} Values for Yeast Strains Tested

Pathogen	MIC_{90} [a] (µg/mL)	Pathogen	MIC_{90} [a] (µg/mL)	Pathogen	MIC_{90} (µg/mL)
Blastoschizomyces capitatus	(0.016 - 1.0) [b]	*Candida pseudotropicalis*	(0.002 - 0.063)	*Malassezia pachydermatis*	(0.125)
Candida albicans	0.25	*Candida pulcherrima*	(0.063)	*Malassezia restricta*	(0.031)
Candida beigelii	(0.008 - 1.0)	*Candida rugosa*	0.25	*Malassezia slooffiae*	(0.031)
Candida colluculosa	(0.031 - 1.0)	*Candida sake*	(0.5 - 16.0)	*Malassezia sympodialis*	(0.031 - 0.063)
Candida dubliniensis	0.25	*Candida sphaerica*	(0.25)	*Pichia anomala*	1.0
Candida famata	0.5	*Candida stellatoidea*	(0.004 - 0.25)	*Pichia etchellsii*	(0.125)
Candida glabrata	2.0	*Candida tropicalis*	0.25	*Pichia ohmeri*	(0.016)
Candida guilliermondii	0.5	*Candida utilis*	(2.0)	*Rhodotorula glutinis*	(0.5)
Candida holmii	(0.25)	*Candida zeylanoides*	(0.008 - 0.25)	*Rhodotorula mucilaginosa*	(1.0 - 2.0)

Candida inconspicua	4.0	*Cryptococcus humicolus*	(0.125 - 0.25)	*Rhodotorula rubra*	(0.25 - 128.0)
Candida intermedia	(0.125)	*Cryptococcus laurentii*	(0.008 - 0.5)	*Rhodotorula* spp	8.0
Candida kefyr	0.25	*Cryptococcus luteolus*	(0.063)	*Saccharomyces cerevisiae*	1.0
Candida krusei	1.0	*Cryptococcus neoformans*	0.25	*Trichosporon asahii*	0.5
Candida lambica	(0.016 - 0.25)	*Cryptococcus spp.*	(0.25)	*Trichosporon beigelii*	1.0
Candida lipolytica	1.0	*Dekkera bruxellensis*	(0.25)	*Trichosporon capitatum*	(0.125)
Candida lusitaniae	0.125	*Kluyveromyces marxianus*	(0.063 - 0.25)	*Trichosporon cutaneum*	(0.063 - 0.125)
Candida maris	(0.063 - 0.125)	*Malassezia dermatis*	(0.031 - 0.5)	*Trichosporon inkin*	(0.063 - 0.5)
Candida melibiosica	(0.125)	*Malassezia furfur*	0.063	*Trichosporon mucoides*	16.0
Candida norvegensis	(0.125)	*Malassezia globosa*	0.031	*Trichosporon* spp	(0.5 - 1.0)
Candida parapsilosis	0.125	*Malassezia obtusa*	(0.031)	*Yarrowia lipolytica*	(0.016 - 1.0)
Candida pelliculosa	2.0				

a: minimal inhibitory concentration at which 90% of the strains tested are inhibited from growth

b: When the number of strains tested was < 10, the range of MICs is indicated in parentheses.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Drug Resistance

C. albicans strains resistant to posaconazole could not be generated in the laboratory; spontaneous laboratory *Aspergillus fumigatus* mutants exhibiting a decrease in susceptibility to posaconazole arose at a frequency of $1x10^{-8}$ to $1x10^{-9}$. Clinical isolates of *Candida albicans* and *Aspergillus fumigatus* exhibiting significant decreases in posaconazole susceptibility are rare. In those rare instances where decreased susceptibility was noted, there was no clear correlation between decreased susceptibility and clinical failure. Clinical success has been observed in patients infected with organisms resistant to other azoles; consistent with these observations posaconazole was active *in vitro* against many *Aspergillus* and *Candida* strains that developed resistance to other azoles and/or amphotericin B. Breakpoints for posaconazole have not been established for any fungi.

Antifungal medicinal products combinations

When combinations of posaconazole with either amphotericin B or caspofungin were tested *in vitro* and *in vivo* there was little or no antagonism and in some instances there was an additive effect. The clinical significance of these results is unknown.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity
The maximum non-lethal dose for a single oral dose of posaconazole was greater than 1,500 mg/kg in mice, greater than 4,000 mg/kg in rats and greater than 2,000 mg/kg in dogs.

Long-Term Toxicity
Repeated-dose toxicity studies of posaconazole were conducted in mice for up to three months, in rats for up to six months, and in dogs and monkeys for up to one year.

Posaconazole causes several toxicologic effects that occur with other antifungal substances in the azole class, i.e., hyperplasia of the adrenal glands (mice, rats and dogs), phospholipidosis of lung and lymphoid tissues (all species), disseminated intravascular coagulation (dogs only), bone thinning/fractures (rats only), hepatocellular adenomas (mice only), findings secondary to the interruption of steroidogenesis and fetal toxicity (rats and rabbits). Additional findings not previously reported with other marketed antifungal agents include neuronal phospholipidosis in dogs and increased urinary calcium excretion in dogs and rats.

In a twelve-month study in dogs with doses of posaconazole up to 30 mg/kg, neuronal phospholipidosis occurred after approximately three months of dosing, did not progress in severity over time and was present at the end of a three-month post dose period. There were no neurologic or degenerative changes in affected neurons and no functional changes in affected dogs. There were no posaconazole-related neurotoxicity or neuropathology findings in monkeys when administered daily doses of 180 mg/kg for twelve months.

Local Tolerance
Studies to evaluate local tolerance of posaconazole indicated a low potential for acute dermal toxicity and no potential for irritation or sensitization.

Immunotoxicity Studies
A series of immunotoxicology studies in mice indicate minimal changes in immune function (decreased antibody forming cell response and increased natural killer cell activity) and minimal changes in populations of lymphocytes, NK cells and monocytes in the blood and/or spleen in the 30 and 90 mg/kg groups after one and three months of dosing. The NEL for these changes was 10 mg/kg. The changes in the immune system parameters in the immunotoxicity studies were minimal and reversible, indicating that administration of posaconazole had no permanent effect on the function of the immune system.

Carcinogenicity: No drug-related neoplasms were recorded in rats or mice treated with posaconazole for two years at doses below the maximum tolerated dose. In a two-year carcinogenicity study, rats were given posaconazole orally at doses up to 20 mg/kg (females), or 30 mg/kg (males). These doses are equivalent to 3.9 or 3.5 times the exposure achieved with a 400 mg BID, respectively, based on steady-state AUC in healthy volunteers administered a high fat meal (400 mg BID regimen). In the mouse study, mice were treated at oral doses up to 60 mg/kg/day or 4.8 times the exposure achieved with a 400 mg BID regimen.

Mutagenicity: Posaconazole was evaluated in a bacterial mutagenicity, human peripheral blood lymphocyte, Chinese hamster ovary and mouse micronucleus studies. Posaconazole did not exhibit any genotoxic potential.

Reproductive and Developmental Toxicology: There was no effect on fertility in male rats dosed up to a high-dose of 180 mg/kg. There was no effect on fertility in female rats up to a high-dose of 45 mg/kg.

In a rat embryo-fetal development study, there were no posaconazole-related effects on pregnancy rate and numbers of corpora lutea, implantations and resorptions. At a dose of 27 mg/kg, skeletal variations and malformations occurred. The no-effect dose was 9 mg/kg for maternal and fetal effects in rats.

In a rabbit embryo-fetal development study with doses of 20, 40 and 80 mg/kg, there were no posaconazole-related effects on pregnancy rate, and numbers of corpora lutea and implantations. In the 40 and 80 mg/kg-dosed rabbits, there were increases in resorptions and skeletal variations.
In a perinatal and postnatal development study in rats at doses of 6, 18 or 36 mg/kg, there were no posaconazole-related effects on the various indicators of physical and functional development, as well as behavioral responses, in the F1 pups.

17 SUPPORTING PRODUCT MONOGRAPHS

1. POSANOL® delayed release tablets, 100mg, solution for injection, 300 mg / vial (18 mg / mL), oral suspension, 40 mg / mL, submission control 254862, Product Monograph, Merck Canada Inc. (JAN 04, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr TARO-POSACONAZOLE

Posaconazole, Delayed-Release Tablets

Read this carefully before you start taking **TARO-POSACONAZOLE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TARO-POSACONAZOLE**.

Serious Warnings and Precautions

- **Drug Interactions:** Taking TARO-POSACONAZOLE with other medicines can cause serious side effects. Do **NOT** take TARO-POSACONAZOLE if you are taking any of the following:
  - ergot alkaloids, used to treat migraines
  - cisapride, used to treat stomach problems
  - pimozide, used to treat mental health problems
  - quinidine, used to treat irregular heartbeat
  - terfenadine and astemizole, used to treat allergies
  - certain statin medicines that lower cholesterol, such as atorvastatin, lovastatin, simvastatin
  - sirolimus, used in transplant patients

  Avoid taking TARO-POSACONAZOLE with any of the following:
  - cimetidine, used to treat stomach problems
  - rifabutin, an antibiotic used to treat bacterial infections including tuberculosis
  - phenytoin, used to prevent seizures

  If you are taking TARO-POSACONAZOLE with any of the following your healthcare professional may have to reduce your dose and monitor you closely:
  - cyclosporine or tacrolimus, used in transplant patients
  - vinca alkaloids, including vincristine, used to treat cancer
  - venetoclax, used to treat cancer
  - midazolam, used as a sedative to help you sleep
  - calcium channel blockers, used to treat high blood pressure
- **Heart Problems:** TARO-POSACONAZOLE can cause serious heart problems including problems with your heart rhythm. Tell a healthcare professional immediately if you have any of the following symptoms while you are being treated with TARO-POSACONAZOLE:
  - very slow, fast or irregular heartbeat
  - shortness of breath
  - light-headedness
  - fainting
- **Liver Problems (including Liver Failure):** TARO-POSACONAZOLE can cause serious liver problems including liver failure. Your healthcare professional will do blood tests to see how well your liver is working before you start treatment with TARO-POSACONAZOLE and while you are being treated. Tell a healthcare professional immediately if you have any of the following symptoms while you are being treated with TARO-POSACONAZOLE:
  - dark colored urine
  - pale stools
  - yellowing of the skin and eyes
  - abdominal pain
  - nausea and vomiting

What is TARO-POSACONAZOLE used for?

- Delayed-Release Tablets are used:
  - to prevent fungal infections caused by the fungi Aspergillus and Candida in patients whose immune systems may be weakened due to other medicines or diseases.
  - to treat fungal infections caused by Aspergillus that have not improved during treatment with the anti-fungal medicines amphotericin B or itraconazole or in patients who cannot tolerate these medicines.

- TARO-POSACONAZOLE Delayed-Release Tablets can be used in patients 13 years of age and older.

How does TARO-POSACONAZOLE work?

TARO-POSACONAZOLE belongs to a group of medicines called triazole antifungal agents. Posaconazole works by killing or stopping the growth of some types of fungi that can cause infections in humans.

What are the ingredients in TARO-POSACONAZOLE?

Medicinal ingredients: Posaconazole

Non-medicinal ingredients:
TARO-POSACONAZOLE Delayed-Release Tablets: Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and Opadry II Yellow [consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350 (polyethylene glycol 3350), titanium dioxide, talc, and iron oxide yellow].

TARO-POSACONAZOLE comes in the following dosage forms:

TARO-POSACONAZOLE Delayed-Release Tablets: 100 mg

Do not use TARO-POSACONAZOLE if:

- you are hypersensitive (allergic) to posaconazole or to any of the other ingredients in TARO-POSACONAZOLE (see **What are the ingredients in TARO-POSACONAZOLE?** section).
- you are taking any of the following medicines:
  - ergot alkaloids, used to treat migraines
  - cisapride, used to treat stomach problems
  - pimozide, used to treat mental health problems
  - quinidine, used to treat irregular heartbeat
  - terfenadine and astemizole, used to treat allergies
  - certain statin medicines that lower cholesterol, such as atorvastatin, lovastatin, simvastatin
  - sirolimus, used in transplant patients

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TARO-POSACONAZOLE. Talk about any health conditions or problems you may have, including if you:

- have had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole or voriconazole.
- are taking certain medicines that suppress your immune system such as cyclosporine and tacrolimus. Serious side effects that have been fatal, have happened in patients taking cyclosporine in combination with TARO-POSACONAZOLE. Your healthcare professional may adjust your dose of these immune suppressants and monitor their blood levels if you are taking them with TARO-POSACONAZOLE.
- are taking certain medicines used to treat cancer such as venetoclax and vincristine. Toxicity from vincristine has happened in patients taking it in combination with TARO-POSACONAZOLE. This has caused serious side effects such as:
  - Damage to nervous tissue
  - Seizures
  - Numbness, pain and weakness in hand and feet due to damage to nerves
  - Muscles cramps, nausea, vomiting and confusion due to water retention in body
  - Blockage of the intestine (abdominal pain).

- have or have had liver problems.
- have kidney problems.
- have a history of heart problems, including heart failure, an irregular heartbeat, a slow heartbeat or a genetic condition called "congenital or acquired QT prolongation".
- have problems with your electrolytes (low levels of potassium, magnesium or calcium in your blood).
- suffer from excessive vomiting or diarrhea.
- are breastfeeding. Do not breastfeed while being treated with TARO-POSACONAZOLE unless you have discussed the risks and benefits with your healthcare professional.
- are pregnant or planning on becoming pregnant. Do not use TARO-POSACONAZOLE during pregnancy unless you have discussed the risks and benefits with your healthcare professional. If you are a woman who could become pregnant, you must use effective birth control while you are being treated with TARO-POSACONAZOLE. Tell your healthcare professional immediately if you become pregnant while being treated with TARO-POSACONAZOLE.

Other warnings you should know about:

Blood tests: TARO-POSACONAZOLE can cause abnormal blood test results. Your healthcare professional may ask you to have blood tests while you are being treated with TARO-POSACONAZOLE.

Driving and using machines: Do not drive or operate machinery if you experience sleepiness or blurred vision.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. The following medicines **must not be taken** with TARO-POSACONAZOLE:

- cisapride, used to treat stomach problems
- pimozide, used to treat mental health problems
- quinidine, used to treat irregular heartbeat
- ergot alkaloids, used to treat migraines
- terfenadine and astemizole, used to treat allergies
- certain statin medicines that lower cholesterol, such as atorvastatin, lovastatin, simvastatin
- sirolimus, used in transplant patients

The following may interact with TARO-POSACONAZOLE:

- rifabutin or rifampin, antibiotics used to treat bacterial infections like tuberculosis
- phenytoin, used to prevent seizures
- efavirenz, fosamprenavir, atazanavir and atazanavir/ritonavir, used to treat HIV infection
- vinca alkaloids, including vincristine, used to treat cancer
- venetoclax, used to treat cancer
- cyclosporine and tacroliumus, used in transplant patients
- midazolam, used as a sedative to help you sleep
- statins, used to treat high cholesterol
- calcium channel blockers, used to treat high blood pressure
- digoxin, used to treat heart failure

How to take TARO-POSACONAZOLE:

- TARO-POSACONAZOLE must only be used as directed by your healthcare professional.
- Your healthcare professional will decide how long you are to be treated with TARO-POSACONAZOLE and your dose depending on your condition and how you respond to treatment.
- Do not stop treatment early because your infection may not be fully cured. Even if you feel well, your immune system may still be weakened and you may still need treatment to prevent an infection.
- Do not switch between TARO-POSACONAZOLE Delayed Release Tablets, posaconazole oral suspension, and posaconazole solution for injection without talking to your healthcare professional. The dosing is different for each formulation.
- If you are being treated with TARO-POSACONAZOLE Delayed-Release Tablets:
  - TARO-POSACONAZOLE Delayed-Release Tablets can be taken with or without food.
  - TARO-POSACONAZOLE Delayed-Release Tablets must be swallowed whole. Use plenty of water if you have some difficulty swallowing.
  - Do not crush, chew, break, or dissolve the tablets.

Usual dose:

TARO-POSACONAZOLE Delayed-Release Tablets:

- Take 300 mg (three 100 mg tablets) twice on the first day.
- After the first day take 300 mg (three 100 mg tablets) once a day.

Overdose:

Take your bottle of TARO-POSACONAZOLE with you.

If you think you, or a person you are caring for, have taken too much TARO-POSACONAZOLE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss taking a dose of TARO-POSACONAZOLE, take it as soon as possible. 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 forgotten dose.

What are possible side effects from using TARO-POSACONAZOLE?

These are not all the possible side effects you may have when taking TARO-POSACONAZOLE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- diarrhea
- gas
- nausea, vomiting
- stomach pain
- loss of appetite
- abnormal taste in the mouth
- dry mouth
- swelling in the mouth
- headache
- dizziness
- numbness or tingling
- sleepiness, tiredness
- weakness
- rash
- cough, shortness of breath

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Anemia (low red blood cells): shortness of breath, feeling very tired, pale skin, fast heartbeat, loss of energy, or weakness.		✓	
Neutropenia (low white blood cells): infections (fever, chills, sore throat, mouth sores), weakness, fatigue, aches and pains, and flu-like symptoms.		✓	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness, nosebleeds, tiny red spots on the skin.		✓	
Electrolyte imbalance (low levels of potassium, magnesium or calcium in your blood): weakness, fatigue, muscle cramps.		✓	
Edema: swelling of the hands or feet.	✓		
UNCOMMON			
Heart problems: very slow, fast or irregular heartbeat, shortness of breath, light-headedness, fainting.			✓
RARE			
Allergic reaction: severe skin blistering, peeling, rash, swollen lips, mouth and throat, difficulty in breathing.			✓
Liver problems (including liver failure): dark colored urine, pale stools, yellowing of the skin and eyes, abdominal pain, nausea, vomiting.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
TARO-POSACONAZOLE Delayed-Release Tablets:
Store at room temperature (15 to 30°C).

Keep out of the reach and sight of children. Do not use this product after the expiry date stated on the label.

If you want more information about TARO-POSACONAZOLE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.taro.ca, or by calling 1-800-268-1975.

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