

PRODUCT MONOGRAPH

Pr APO-POSACONAZOLE

Posaconazole Delayed-Release Tablets

100 mg posaconazole

Antifungal Agent

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION	2
SUMMARY PRODUCT INFORMATION	2
INDICATIONS AND CLINICAL USE	2
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS	3
ADVERSE REACTIONS	6
DRUG INTERACTIONS	13
DOSAGE AND ADMINISTRATION	19
OVERDOSAGE	21
ACTION AND CLINICAL PHARMACOLOGY	21
STORAGE AND STABILITY	25
SPECIAL HANDLING INSTRUCTIONS	25
DOSAGE FORMS, COMPOSITION AND PACKAGING	25
PART II: SCIENTIFIC INFORMATION	26
PHARMACEUTICAL INFORMATION	26
CLINICAL TRIALS	27
DETAILED PHARMACOLOGY	29
MICROBIOLOGY	32
TOXICOLOGY	34
REFERENCES	36
PART III: CONSUMER INFORMATION	37

PrAPO-POSACONAZOLE
Posaconazole delayed-release tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	delayed-release tablets, 100 mg posaconazole	Colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, hydroxypropyl cellulose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, Polyethylene glycol, Polyvinyl Alcohol, talc and titanium dioxide.

INDICATIONS AND CLINICAL USE

APO-POSACONAZOLE (posaconazole) delayed-release tablets are 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.

APO-POSACONAZOLE delayed-release tablets are indicated in patients 13 years of age and older.

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.

Pediatrics (13 - 17 years of age):

Safety and effectiveness in pediatric subjects below the age of 13 years have not been studied.

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 APO-POSACONAZOLE to patients with hypersensitivity to other azoles.
- Co-administration of APO-POSACONAZOLE and ergot alkaloids. Posaconazole may increase the plasma concentrations of ergot alkaloids, which may lead to ergotism (see DRUG INTERACTIONS).
- Co-administration of APO-POSACONAZOLE and certain medicinal products metabolized through the CYP3A4 system: terfenadine*, astemizole*, cisapride*, pimozone, 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 DRUG INTERACTIONS).
* No longer marketed in Canada
- Co-administration of APO-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 APO-POSACONAZOLE and sirolimus. Concomitant administration of posaconazole with sirolimus increases the sirolimus blood concentrations by approximately 9-fold and can result in sirolimus toxicity.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Drug Interactions (see the Contraindications section and the Drug Interactions section of the product monograph)**
- **Cardiovascular effects - QT interval prolongation (see the Cardiovascular section below)**
- **Hepatic toxicity (see the Hepatic section below)**

General

Oral Formulations: APO-POSACONAZOLE delayed-release tablets and posaconazole oral solution are not interchangeable (see **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 **ACTION AND CLINICAL PHARMACOLOGY**).

Hypersensitivity: There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing APO-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, 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 APO-POSACONAZOLE therapy.

Caution should be exercised if APO-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 CONTRAINDICATIONS, DRUG INTERACTIONS and ACTION AND 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 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 APO-POSACONAZOLE therapy. Patients who develop abnormal liver function tests during APO-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 APO-POSACONAZOLE should be considered if clinical signs and symptoms are consistent with development of worsening liver disease.

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 **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Special Populations

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 **TOXICOLOGY**). The potential risk to humans is unknown. Women of childbearing potential must always use adequate contraceptive measures while on treatment. APO-POSACONAZOLE should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Hepatic Impairment: APO-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 APO-POSACONAZOLE therapy is initiated (see **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 **DRUG INTERACTIONS**).

ADVERSE REACTIONS

Adverse Drug 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 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 formulation generally achieved lower steady state plasma C_{min} levels of posaconazole than the 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 $\geq 3,750$ 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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 2: Treatment-related adverse reactions reported in Posaconazole delayed-release tablet subjects treated with 300 mg daily dose reported at an incidence of $\geq 1\%$ for the P05615 Study

Adverse Reactions	Posaconazole delayed-release tablet (300 mg) n=210 (%)
Cardiovascular	
Sinus bradycardia	2 (1)
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 3 - Treatment-related adverse reactions reported in Posaconazole Oral Suspension, fluconazole and itraconazole subjects reported at an incidence of $\geq 1\%$ 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/QTc 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
Nausea aggravated	2 (< 1)	1 (< 1)	2 (3)
Dry mouth	3 (< 1)	1 (< 1)	1 (2)
Mucositis not otherwise specified	7 (1)	0	0

Adverse Reactions	Posaconazole n=605 (%)	Fluconazole n=539 (%)	Itraconazole n=58 (%)
Stomatitis aphthous	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
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

Adverse Reactions	Posaconazole n=605 (%)	Fluconazole n=539 (%)	Itraconazole n=58 (%)
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 to 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.

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.

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 ($> 3 \times$ Upper Limit Normal [ULN]) 6% and 5%, respectively; total bilirubin ($> 1.5 \times$ ULN) 4%; and alkaline phosphatase ($> 3 \times$ 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 ($> 3 \times$ ULN), 12 % and 4

%, respectively: total bilirubin (> 1.5 X ULN), 8 %; and alkaline phosphatase (> 3 X ULN), 2%.

Post-Market Adverse Drug 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.

DRUG INTERACTIONS

Serious Drug Interactions
Contraindicated Drugs: ergot alkaloids, terfenadine*, astemizole*, cisapride*, pimozone, quinidine, HMG-CoA reductase inhibitors (statins) and sirolimus (see CONTRAINDICATIONS)
* No longer marketed in Canada
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 (see Table 5)

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

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

Overview

Effect of Other Drugs on Posaconazole Pharmacokinetics

Posaconazole is metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for 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.

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 x 17 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 (posaconazole) 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 1 st day, 200 mg BID on the 2 nd 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 posaconazole 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.
H₂ receptor antagonists, proton pump inhibitors (PPIs) and antacids						

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)	
Antacids/H ₂ receptor antagonists (H ₂ RA)/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, H ₂ 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, H ₂ 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 H ₂ 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 (posaconazole) 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 x 2 days	400 mg (posaconazole) 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 (posaconazole) 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.

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

f: QID = four times a day

g: TID = three times a day

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 C _{max} (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	<p>↑ cyclosporine whole blood trough concentrations.</p> <p>Cyclosporine dose reductions of up to 29% were required.</p>		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 C _{max} (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 CYP3A4 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 * No longer marketed in Canada	theoretical	NA, since theoretical		Co-administration of posaconazole 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	↑ C _{max} 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 C _{max} (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 C _{max} 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 (posaconazole) 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.

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

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.

Proper name	Ref	Effect	Clinical comment
Food or nutritional supplement	clinical trial	<p>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.</p> <p>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.</p>	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 ACTION AND CLINICAL PHARMACOLOGY).

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The prescriber should follow the specific dosing instructions for each formulation.
- The tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation.
- APO-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 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.

Recommended Dose and Dosage Adjustment

Recommended Dose

Table 9 - 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 WARNINGS AND PRECAUTIONS and ACTION AND 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 ACTION AND CLINICAL PHARMACOLOGY). Use with caution in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY).

Use in Pediatrics (13 - 17 years)

A total of 11 patients 13 to 17 years of age were treated with 800 mg/day posaconazole oral suspension in a study for IFIs. Additionally, 12 patients 13 to 17 years of age received 600 mg/day of posaconazole oral suspension for prophylaxis of IFIs (studies C/198-316 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 ACTION AND CLINICAL PHARMACOLOGY).

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.

Administration

APO-POSACONAZOLE Delayed-Release Tablet

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

APO-POSACONAZOLE delayed-release tablets are intended for oral administration only.

APO-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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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 DOSAGE AND ADMINISTRATION and ACTION AND 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 11). A lower C_{avg} may be associated with an increased risk of treatment failure.

Table 11: Posaconazole 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

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 14.

Table 14: Arithmetic Mean (%CV) of Steady State PK Parameters in Healthy Volunteers and Patients Following Administration of Posaconazole Delayed-Release Tablets (300 mg)*

	N	AUC _{0-24 hr} (ng·hr/mL)	C _{avg} [†] (ng/mL)	C _{max} (ng/mL)	C _{min} (ng/mL)	T _{max} [‡] (hr)	t _{1/2} (hr)	CL/F (L/hr)
Healthy Volunteers	12	51618 (25)	2151 (25)	2764 (21)	1785 (29)	4 (3-6)	31 (40)	7.5 (26)
Patients	50	37900 (42)	1580 (42)	2090 (38)	1310 (50)	4 (1.3-8.3)	-	9.39 (45)

CV = coefficient of variation expressed as a percentage (%CV); AUC_{0-τ} = 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_{1/2} = 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_{0-24 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 17). 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 tablet can therefore be administered with or without food.

Table 17: 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

Pharmacokinetic Parameter	Fasting Conditions		Fed Conditions (High Fat Meal)*		Fed/Fasting
	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-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-last} = AUC_{0-72hr}

§ 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.

Posaconazole is 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.

Excretion:

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 ($t_{1/2}$) 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 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 to 17 years of age were similar to concentrations from 194 patients 18 to 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.

Gender:

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

Race:

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 C_{max} 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.

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:

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 **WARNINGS AND PRECAUTIONS** and **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 to 80 mL/min/1.73m², n=6) and moderate (GFR: 20 to 49 mL/min/1.73m², 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/1.73m²), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (GFR: > 80 mL/min/1.73m²); 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 WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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

STORAGE AND STABILITY

Storage

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

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-POSACONAZOLE Delayed-Release Tablets

APO-POSACONAZOLE delayed-release tablet is a yellow, oval, biconvex, coated tablet. Engraved “POS100” on one side, “APO” on the other side. Each tablet contains 100 mg of posaconazole and the following inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, hydroxypropyl cellulose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

Available in bottles of 60 with child-resistant closure.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

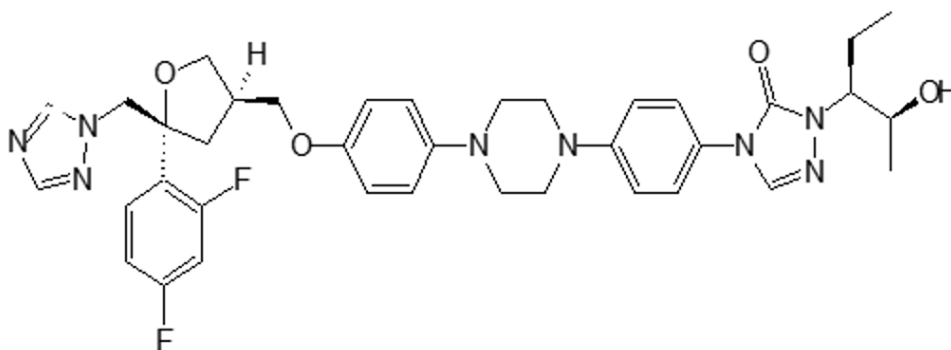
Common name: posaconazole

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:

C₃₇H₄₂F₂N₈O₄ 700.78 g/mol

Structural formula:



Physicochemical properties:

Posaconazole is a white to off-white solid which is freely soluble in dichloromethane, and sparingly soluble in methanol and acetone.

pH and pKa values:

pH: N/A due to water solubility

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

Melting range:

167.9°C to 169.2°C

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male and female volunteers. The results obtained from 29 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of posaconazole was measured and compared following a single oral dose (1 x 100 mg tablet) of Apo-Posaconazole (posaconazole) 100 mg Delayed-Release Tablets (Apotex Inc.) and ^{Pr}POSANOL[®] (posaconazole) 100 mg delayed-release tablets (Merck Canada Inc.).

Posaconazole (1 x 100 mg) From Measured Data Geometric Mean [#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference [†]	Ratio of Geometric Means (%)	90% Confidence Interval
AUC ₀₋₇₂ (ng•h/mL)	6959.28 7267.55 (31.43)	7219.50 7450.66 (25.67)	96.4	88.7 - 104.7
C _{max} (ng/mL)	286.31 301.50 (32.24)	292.58 308.71 (31.63)	97.9	85.8 - 111.7
T _{max} [§] (h)	5.00 (3.00 - 10.00)	5.00 (3.00 - 10.00)		
<p>* Apo-Posaconazole (posaconazole) 100 mg Delayed-Release Tablets (Apotex Inc.) [†] ^{Pr}POSANOL[®] (posaconazole) 100 mg delayed-release tablets (Merck Canada Inc.) was purchased in Canada. [#]Based on Geometric Least Squares Means. [§] Expressed as median (range) only</p> <p>Due to the long elimination half-life of posaconazole, AUC₁ and T_{1/2} could not be accurately calculated from the data obtained in the study.</p>				

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fed conditions, was performed on healthy male and female volunteers. The results obtained from 29 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of posaconazole was measured and compared following a single oral dose (1 x 100 mg tablet) of Apo-Posaconazole (posaconazole) 100 mg Delayed-Release Tablets (Apotex Inc.) and ^{Pr}POSANOL[®] (posaconazole) 100 mg delayed-release tablets (Merck Canada Inc.).

Posaconazole (1 x 100 mg) From Measured Data Geometric Mean [#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference [†]	Ratio of Geometric Means (%)	90% Confidence Interval
AUC ₀₋₇₂ (ng•h/mL)	9499.35 9710.98 (20.31)	9683.65 9926.75 (22.13)	98.1	95.1 - 101.2
C _{max} (ng/mL)	385.10 398.14 (26.35)	402.09 415.92 (27.51)	95.8	90.1 - 101.8
T _{max} [§] (h)	6.00 (3.00 - 18.00)	6.00 (2.00 - 12.00)		

* Apo-Posaconazole (posaconazole) 100 mg Delayed-Release Tablets (Apotex Inc.)
[†] ^{Pr}POSANOL[®] (posaconazole) 100 mg delayed-release tablets (Merck Canada Inc.) was purchased in Canada.
[#]Based on Geometric Least Squares Means.
[§] Expressed as median (range) only

Due to the long elimination half-life of posaconazole, AUC₁ and T_{1/2} could not be accurately calculated from the data obtained in the study.

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 \geq 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.

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 ACTION AND 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 to 17 years of age (776 ng/mL) were similar to concentrations from 194 patients 18 to 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 to 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. Results from a multiple dose study in healthy volunteers (n=56) indicated that there was only a slight decrease (16%) in the AUC and C_{max} of posaconazole oral suspension in Black subjects relative to Caucasian subjects, therefore, no dose adjustment for race is required.

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 \geq 20 mL/min/1.73 m²) on posaconazole pharmacokinetics, therefore, no dose adjustment is required. In subjects with severe renal insufficiency (n=6, GFR < 20 mL/min/1.73 m²), 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% (APD₆₀) and/or 90% (APD₉₀) 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 μ M) posaconazole decreased hERG current by 7%. Accounting for protein binding, the drug concentration in the hERG assay was 18-times the free posaconazole C_{max} 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 mcg·hr/mL, which is 2.4-fold a human AUC exposure of 59 mcg·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.

MICROBIOLOGY

Posaconazole is a potent inhibitor of the enzyme lanosterol 14 α -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 INDICATIONS AND CLINICAL USE): *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 23 and 24). 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 28.

Table 28 - MIC₉₀ Values for Mould Strains Tested

Pathogen	MIC ₉₀ ^a (mcg/mL)	Pathogen	MIC ₉₀ ^a (mcg/mL)	Pathogen	MIC ₉₀ ^a (mcg/mL)
<i>Absidia coerulea</i>	(2.0) ^b	<i>Curvularia</i> spp	(0.031 - 0.125)	<i>Phialophora verrucosa</i>	(0.5 - 4.0)
<i>Absidia corymbifera</i>	2.0	<i>Epidermophyton floccosum</i>	0.125	<i>Pseudallescheria boydii</i>	2.0
<i>Absidia glauca</i>	(2.0)	<i>Exophiala dermatidis</i>	(0.125)	<i>Ramichloridium obovoideum</i>	(0.031 - 0.063)
<i>Absidia pseudocylindrospora</i>	(16.0)	<i>Exophiala jeanselmei</i>	0.5	<i>Rhizomucor miehei</i>	(0.016)
<i>Absidia repens</i>	(4.0)	<i>Exophiala moniliae</i>	(0.016)	<i>Rhizomucor pusillus</i>	(0.031 - 0.25)
<i>Absidia</i> spp	(0.031 - 0.5)	<i>Exserohilum rostratum</i>	(0.063 - 0.25)	<i>Rhizomucor</i> spp	(0.016)
<i>Alternaria alternata</i>	(0.016 - 4.0)	<i>Fonsecaea pedrosoi</i>	0.5	<i>Rhizopus arrhizus</i>	(0.5 - 32.0)
<i>Alternaria</i> spp	0.25	<i>Fusarium dimerum</i>	(1.0 - 4.0)	<i>Rhizopus microsporus</i>	16.0
<i>Apophysomyces</i> spp	(0.031 - 4.0)	<i>Fusarium moniliforme</i>	2.0	<i>Rhizopus microsporus v chinensis</i>	(16.0)
<i>Aspergillus candidus</i>	(0.031 - 0.063)	<i>Fusarium oxysporum</i>	16.0	<i>Rhizopus microsporus v oligosporus</i>	(16.0)
<i>Aspergillus flavus</i>	1.0	<i>Fusarium proliferatum</i>	(0.5 - 8.0)	<i>Rhizopus oryzae</i>	4.0

Pathogen	MIC ₉₀ ^a (mcg/mL)	Pathogen	MIC ₉₀ ^a (mcg/mL)	Pathogen	MIC ₉₀ ^a (mcg/mL)
<i>Aspergillus fumigatus</i>	0.5	<i>Fusarium solani</i>	128.0	<i>Rhizopus schipperae</i>	(1.0 - 8.0)
<i>Aspergillus glaucus</i>	(0.063-16.0)	<i>Fusarium spp</i>	16.0	<i>Rhizopus spp</i>	4.0
<i>Aspergillus nidulans</i>	0.25	<i>Geotrichum candidum</i>	(0.125)	<i>Rhizopus stolonifer</i>	(2.0 - 16.0)
<i>Aspergillus niger</i>	0.5	<i>Geotrichum spp</i>	(0.25-32.0)	<i>Saksenaia vasiformis</i>	(0.016 - 2.0)
<i>Aspergillus ochraceus</i>	(0.063 - 0.125)	<i>Histoplasma capsulatum</i>	0.5	<i>Scedosporium apiospermum</i>	2.0
<i>Aspergillus oryzae</i>	(0.25)	<i>Microsporium audouinii</i>	(0.25)	<i>Scedosporium prolificans</i>	32.0
<i>Aspergillus sydowii</i>	0.5	<i>Microsporium canis</i>	0.5	<i>Schizophyllum commune</i>	(0.125 - 0.25)
<i>Aspergillus terreus</i>	0.25	<i>Microsporium fulvum</i>	(0.5)	<i>Scopulariopsis brevicaulis</i>	8.0
<i>Aspergillus ustus</i>	16.0	<i>Microsporium gypseum</i>	(0.008 - 0.5)	<i>Scytalidium dimidiatum</i>	(0.5)
<i>Aspergillus versicolor</i>	2.0	<i>Microsporium persicolor</i>	(0.25)	<i>Sporothrix schenckii</i>	2.0
<i>Bipolaris hawaiiensis</i>	(0.016)	<i>Mucor circinelloides</i>	16.0	<i>Trichoderma spp</i>	(1.0)
<i>Bipolaris spicifera</i>	(0.016 - 0.125)	<i>Mucor hiemalis</i>	32.0	<i>Trichophyton krajenii</i>	(0.063)
<i>Bipolaris spp</i>	(0.125 - 1.0)	<i>Mucor mucedo</i>	(2.0)	<i>Trichophyton mentagrophytes</i>	0.125
<i>Bjerkandera adusta</i>	0.25	<i>Mucor racemosus</i>	(0.008 - 1.0)	<i>Trichophyton raubitschekii</i>	(0.25)
<i>Blastomyces dermatitidis</i>	0.5	<i>Mucor ramosissimus</i>	(0.125 - 0.5)	<i>Trichophyton rubrum</i>	0.25
<i>Cladophialophora bantiana</i>	(0.031 - 0.5)	<i>Mucor rouxii</i>	(1.0 - 32.0)	<i>Trichophyton sudanense</i>	(0.5)
<i>Cladophialophora carionii</i>	0.5	<i>Mucor spp</i>	16.0	<i>Trichophyton spp</i>	0.063
<i>Coccidioides immitis</i>	0.5	<i>Paecilomyces lilacinus</i>	2.0	<i>Trichophyton terrestre</i>	(0.125)
<i>Cunninghamella bertholletiae</i>	(0.5 - 16.0)	<i>Paecilomyces spp</i>	0.5	<i>Trichophyton tonsurans</i>	0.125
<i>Cunninghamella blakesleeana</i>	(16.0)	<i>Paecilomyces variotii</i>	(0.016 - 0.063)	<i>Trichophyton verrucosum</i>	(0.5)
<i>Cunninghamella echinulata</i>	(4.0 - 16.0)	<i>Paracoccidioides brasiliensis</i>	0.125	<i>Tritirachium spp</i>	(1.0 - 16.0)
<i>Cunninghamella elegans</i>	(16.0)	<i>Penicillium marneffeii</i>	0.016	<i>Ulocladium spp</i>	(0.25)
<i>Cunninghamella spp</i>	2.0	<i>Penicillium spp</i>	1.0	<i>Wangiella dermatitidis</i>	(0.063 - 0.125)
<i>Curvularia lunata</i>	(0.016 - 0.25)	<i>Phialophora spp</i>	(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 MIC₉₀ values for yeast strains tested are summarized in Table 29.

Table 29 - MIC₉₀ Values for Yeast Strains Tested

Pathogen	MIC ₉₀ ^a (mcg/mL)	Pathogen	MIC ₉₀ ^a (mcg/mL)	Pathogen	MIC ₉₀ ^a (mcg/mL)
<i>Blastoschizomyces capitatus</i>	(0.016 - 1.0) b	<i>Candida pseudotropicalis</i>	(0.002 - 0.063)	<i>Malassezia pachydermatis</i>	(0.125)
<i>Candida albicans</i>	0.25	<i>Candida pulcherrima</i>	(0.063)	<i>Malassezia restricta</i>	(0.031)
<i>Candida beigelii</i>	(0.008 - 1.0)	<i>Candida rugosa</i>	0.25	<i>Malassezia slooffiae</i>	(0.031)
<i>Candida colluculosa</i>	(0.031 - 1.0)	<i>Candida sake</i>	(0.5 - 16.0)	<i>Malassezia sympodialis</i>	(0.031 - 0.063)
<i>Candida dubliniensis</i>	0.25	<i>Candida sphaerica</i>	(0.25)	<i>Pichia anomala</i>	1.0
<i>Candida famata</i>	0.5	<i>Candida stellatoidea</i>	(0.004 - 0.25)	<i>Pichia etchellsii</i>	(0.125)
<i>Candida glabrata</i>	2.0	<i>Candida tropicalis</i>	0.25	<i>Pichia ohmeri</i>	(0.016)
<i>Candida guilliermondii</i>	0.5	<i>Candida utilis</i>	(2.0)	<i>Rhodotorula glutinis</i>	(0.5)
<i>Candida holmii</i>	(0.25)	<i>Candida zeylanoides</i>	(0.008 - 0.25)	<i>Rhodotorula mucilaginosa</i>	(1.0 - 2.0)
<i>Candida inconspicua</i>	4.0	<i>Cryptococcus humicolus</i>	(0.125 - 0.25)	<i>Rhodotorula rubra</i>	(0.25 - 128.0)
<i>Candida intermedia</i>	(0.125)	<i>Cryptococcus laurentii</i>	(0.008 - 0.5)	<i>Rhodotorula spp</i>	8.0
<i>Candida kefyr</i>	0.25	<i>Cryptococcus luteolus</i>	(0.063)	<i>Saccharomyces cerevisiae</i>	1.0
<i>Candida krusei</i>	1.0	<i>Cryptococcus neoformans</i>	0.25	<i>Trichosporon asahii</i>	0.5
<i>Candida lambica</i>	(0.016 - 0.25)	<i>Cryptococcus spp.</i>	(0.25)	<i>Trichosporon beigelii</i>	1.0
<i>Candida lipolytica</i>	1.0	<i>Dekkera bruxellensis</i>	(0.25)	<i>Trichosporon capitatum</i>	(0.125)
<i>Candida lusitaniae</i>	0.125	<i>Kluyveromyces marxianus</i>	(0.063 - 0.25)	<i>Trichosporon cutaneum</i>	(0.063 - 0.125)
<i>Candida maris</i>	(0.063 - 0.125)	<i>Malassezia dermatis</i>	(0.031 - 0.5)	<i>Trichosporon inkin</i>	(0.063 - 0.5)
<i>Candida melibiosica</i>	(0.125)	<i>Malassezia furfur</i>	0.063	<i>Trichosporon mucoides</i>	16.0

Pathogen	MIC ₉₀ ^a (mcg/mL)	Pathogen	MIC ₉₀ ^a (mcg/mL)	Pathogen	MIC ₉₀ ^a (mcg/mL)
<i>Candida norvegensis</i>	(0.125)	<i>Malassezia globosa</i>	0.031	<i>Trichosporon spp</i>	(0.5 - 1.0)
<i>Candida parapsilosis</i>	0.125	<i>Malassezia obtusa</i>	(0.031)	<i>Yarrowia lipolytica</i>	(0.016 - 1.0)
<i>Candida pelliculosa</i>	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 1×10^{-8} to 1×10^{-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.

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.

Reproductive Toxicity

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.

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.

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.

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.

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PART III: CONSUMER INFORMATION

Pr APO-POSACONAZOLE

Posaconazole Delayed-Release Tablets

This leaflet is part III of a three-part "Product Monograph" published when APO-POSACONAZOLE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-POSACONAZOLE. Contact your doctor or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you start taking this medicine. Keep this leaflet; you may need to read it again. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

What the medication is used for:

- APO-POSACONAZOLE Delayed-Release Tablets can be used to prevent invasive fungal infections caused by *Aspergillus* and *Candida* in patients whose immune systems may be weakened due to other medicines or diseases.
- APO-POSACONAZOLE Delayed-Release Tablets can be used to treat the following types of fungal infections:
 - Infections caused by fungi of the *Aspergillus* family that have not improved during treatment with the anti-fungal medicines amphotericin B or itraconazole or when these medicines have had to be stopped.

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

What it does:

APO-POSACONAZOLE belongs to a group of medicines called triazole antifungal agents. These medicines are used to treat a wide variety of fungal infections. APO-POSACONAZOLE works by killing or stopping the growth of some types of fungi that can cause infections in humans.

When it should not be used:

- If you are hypersensitive (allergic) to posaconazole or to any of the excipients (see *What the important nonmedicinal ingredients are* section).
- If you are taking the following medicines, as they may interact with APO-POSACONAZOLE:
 - ergot alkaloids
 - cisapride*
 - pimozone
 - quinidine
 - terfenadine*

- astemizole*
 - certain statin medicines that lower cholesterol (atorvastatin, lovastatin, simvastatin)
 - sirolimus (used in transplant patients)
- *No longer marketed in Canada

What the medicinal ingredient is:

Posaconazole

What the nonmedicinal ingredients are:

Colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, hydroxypropyl cellulose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

What dosage forms it comes in:

APO-POSACONAZOLE Delayed-Release Tablets:

- Are yellow, oval, biconvex coated tablet. Engraved "POS 100" on one side, "APO" on the other side.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Drug Interactions (See the *When it should not be used* section and the *Interactions With This Medication* section)**
- **Heart Effects (See the *Warnings and Precautions* section and the *Side Effects and What To Do About Them* section)**
- **Liver Problems (See the *Warnings and Precautions* section and the *Side Effects and What To Do About Them* section)**

BEFORE you use APO-POSACONAZOLE talk to your doctor or pharmacist if:

- You have had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole or voriconazole.
- You are taking certain drugs that suppress your immune system like cyclosporine and tacrolimus. Serious and rare fatal toxicity from cyclosporine has occurred when taken in combination with APO-POSACONAZOLE. Therefore the doctor may adjust the dosage of these immune suppressants and monitor their blood levels when taken with APO-POSACONAZOLE.
- You are taking vincristine (a medicine used to treat cancer). Toxicity from vincristine has occurred when taken in combination with APO-POSACONAZOLE and serious adverse events have occurred 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 can occur due to water retention in body
Obstruction of the intestine (abdominal pain).

- You have or have had liver problems.
- You are taking or have taken any other medicines, even those that are obtained without a prescription. Some medicines may affect the way APO-POSACONAZOLE works or APO-POSACONAZOLE may affect the way they work. Please see the section “Interactions with this medication” for medicines which may interact with APO-POSACONAZOLE.
- You have any of the following conditions: history of heart disease, or an irregular beat.
- You are a nursing mother. Do not breast feed while being treated with APO-POSACONAZOLE unless you are told by your doctor.
- You are pregnant or planning on becoming pregnant. Do not use APO-POSACONAZOLE during pregnancy unless you are told by your doctor. Use effective contraception if you are a woman who could become pregnant. Contact your doctor immediately if you become pregnant while being treated with APO-POSACONAZOLE.

Your doctor may ask you to have your blood tested during treatment with APO-POSACONAZOLE.

Do not drive or operate machinery if you experience sleepiness or blurred vision.

Contact your doctor if you develop severe diarrhea or vomiting, as these conditions may limit the effectiveness of APO-POSACONAZOLE.

INTERACTIONS WITH THIS MEDICATION

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

The following list of medicines **must not be taken** (contraindicated) during your course of APO-POSACONAZOLE treatment:

- vincristine (a medicine used to treat cancer)
- cisapride* (a medicine for stomach problems)
- pimozide (a medicine for treating mental illness)
- quinidine (a medicine for treating irregular heart beat)
- ergot alkaloids (a medicine to treat migraines along with other indications)
- terfenadine* (a medicine to treat allergies)
- astemizole* (a medicine to treat allergies)
- certain statin medicines that lower cholesterol (atorvastatin, lovastatin, simvastatin)
- sirolimus (used in transplant patients)

*No longer marketed in Canada

Certain medications may affect the levels of APO-POSACONAZOLE and these combinations should be avoided if possible. Tell your doctor if you are taking or if you plan to stop taking any of the following:

- rifabutin or rifampin (a medicine to treat bacterial infections like tuberculosis)
- phenytoin (a medicine to treat seizures)
- efavirenz (a medicine to treat HIV infection)

APO-POSACONAZOLE may cause changes in the blood levels of certain medications you may be using. Tell your doctor if you are taking or plan to stop taking any of the following medicines before starting treatment with APO-POSACONAZOLE, as dose adjustment or monitoring may be needed:

- vinca alkaloids (used to treat cancer)
- cyclosporine (used in transplant patients)
- tacrolimus (used in transplant patients)
- rifabutin (a medicine to treat bacterial infections)
- midazolam (used as a sedative to help sleep)
- statins (used to treat high cholesterol)
- calcium channel blockers (used to treat high blood pressure)
- digoxin (used to treat heart failure)

PROPER USE OF THIS MEDICATION

APO-POSACONAZOLE must only be used as directed by your doctor.

Your doctor will monitor your response and condition to determine what APO-POSACONAZOLE dose is needed.

Do not switch between APO-POSACONAZOLE Delayed-Release Tablets and posaconazole oral suspension without talking to your doctor first, as the dosing is different for the 2 formulations.

APO-POSACONAZOLE delayed-release tablets:

- Take APO-POSACONAZOLE Delayed-Release Tablets exactly as prescribed by your doctor.
- Take APO-POSACONAZOLE Delayed-Release Tablets for as long as your doctor tells you.
- Take APO-POSACONAZOLE Delayed-Release Tablets by mouth, with or without food.
- APO-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:

APO-POSACONAZOLE Delayed-Release Tablets:

Indication	Dose
Prevention of Certain Serious Fungal Infections	Take 300 mg (three 100 mg tablets) twice a day on the first day. After the first day, take 300 mg (three 100 mg tablets) once a day.

Treatment of Certain Refractory (not successfully treated by other therapies) Fungal Infections	Take 300 mg (three 100 mg tablets) twice a day on the first day. After the first day, take 300 mg (three 100 mg tablets) once a day thereafter.
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Your doctor will determine how long the duration of your treatment will be and may change your dose depending on your condition. Do not stop treatment early because your infection may not be fully cured. If you are given APO-POSACONAZOLE for preventing infections, take the full course as prescribed by your doctor, as your immune system may still be weakened and you may need treatment to prevent an infection from occurring even if you feel well.

Overdose:

Take your bottle of APO-POSACONAZOLE with you.

If you think you have taken too much APO-POSACONAZOLE, contact your 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 APO-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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, APO-POSACONAZOLE can have side effects. If side effects do occur, most are likely to be minor and temporary. Please tell your doctor or healthcare professional if you experience any reaction that is continuous, bothersome or you think is serious.

APO-POSACONAZOLE delayed-release tablets:

The most commonly reported side effects for posaconazole delayed-release tablets were diarrhea, fever, and nausea.

Common side effects (occurring in at least 1 in 100 patients) are:

Headache; dizziness; numbness or tingling; sleepiness; feeling or being sick; loss of appetite; stomach pain; diarrhea; upset stomach; nausea; vomiting; flatulence (excessive gas in the digestive tract); dry mouth; abnormal liver function tests; rash; weakness; tiredness; a decrease in white blood cells (that can increase the risk of infections); fever; abnormal amounts of salts in the blood.

Other reported side effects include infrequent cases of liver reactions (e.g., mild to moderate elevations in liver tests called ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis). The elevations in liver function tests were generally reversible when posaconazole was stopped, and in some instances these tests went back to normal without stopping posaconazole. These effects rarely required stopping posaconazole. Rarely, more severe liver reactions including cholestasis (back-up of bile in the liver) or liver failure were

reported in patients with serious underlying medical conditions (e.g., leukemia or other blood cancers) during treatment with posaconazole. As posaconazole has been known to affect the liver in patients who already have liver problems, your doctor may wish to monitor the function of your liver by doing blood tests. Some of the symptoms of liver problems include yellowing of the eyes or skin, “flu-like” feeling or feeling more tired than usual, stomach pains, light colored stools, nausea or vomiting. Please let your doctor know if you have any of these symptoms.

Uncommon and rare treatment related serious or medically significant adverse events reported during clinical trials with posaconazole have included poor functioning of the adrenal gland; heart problems including very fast heartbeat, very slow heartbeat, irregular heartbeat including Torsade de Pointes; abnormal findings on heart tests (like ECGs that show heart rhythm), severe allergic reactions, including widespread blistering rash and skin peeling. There have been rare cases of hemolytic uremic syndrome (a serious problem with the blood vessels causing low red blood cell counts and kidney failure) and thrombotic thrombocytopenic purpura (a serious blood problem causing bruising, confusion, fever, and low blood clotting cell counts), which have been reported primarily among patients who had been receiving concomitant cyclosporine or tacrolimus for management of transplant rejection or graft vs. host disease.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	Blood problems , including decreased white blood cells, and other blood cell types, with symptoms such as increased infection, fever, bleeding, bruising.		✓	
Infrequent	Liver problems , including liver failure, with symptoms such as dark colored urine, pale stools, yellowing of the skin and eyes, abdominal pain, nausea, vomiting.			✓
Uncommon	Heart problems such as very slow, fast or irregular heartbeat.			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	Severe allergic reaction with symptoms such as severe skin blistering, peeling, rash, swollen lips, mouth and throat, difficulty in breathing.			✓

This is not a complete list of side effects. For any unexpected effects while taking APO-POSACONAZOLE, contact your doctor or pharmacist.

HOW TO STORE IT

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

Store at room temperature 15°C to 30°C. Protect from moisture.

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.

MORE INFORMATION

If you want more information about APO-POSACONAZOLE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>). Find the Consumer Information on the manufacturer's website <http://www.apotex.ca/products> or by calling 1-800-667-4708.

To report an adverse event related to APO-POSACONAZOLE, please contact 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9

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