PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

POSANOL®

posaconazole

Solution for Injection, 300 mg/vial (18 mg/mL), Intravenous

Delayed-Release Tablets, 100 mg, Oral

Suspension, 40 mg/mL, Oral

Antifungal Agent

Merck Canada Inc.
16750 route Transcanadienne
Kirkland QC Canada H9H 4M7
www.merck.ca

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	12/2021
9 DRUG INTERACTIONS, 9.4 Drug-Drug Interaction	12/2021

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

POSANOL® (posaconazole) Solution for Injection, Delayed-Release Tablets and Oral Suspension 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.

POSANOL® Solution for Injection is indicated in patients 18 years of age and older.

POSANOL® Delayed-Release Tablets and Oral Suspension is indicated in patients 13 years of age and older.

POSANOL® Oral Suspension is also indicated for:
- Treatment of oropharyngeal candidiasis (OPC).

1.1 Pediatrics

Pediatrics (13 - 17 years of age): Safety and effectiveness in pediatric subjects below the age of 13 years have not been studied. A limited number of subjects between the ages of 13 and 17 have received POSANOL® Oral Suspension including 11 patients in the refractory invasive fungal infection (rIFI) studies and 12 patients in the prophylaxis studies. The safety profile in these patients < 18 years appears similar to the safety profile observed in adults.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

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

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

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

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

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

- POSANOL® Solution for Injection should be administered via a central venous line, including a central venous catheter or PICC, by slow IV infusion over approximately 90 minutes. If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter by slow IV infusion over 30 minutes (see 7 WARNINGS AND PRECAUTIONS, General). POSANOL® Solution for Injection is not for IV bolus administration.

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

- POSANOL® Delayed-Release Tablets may be taken with or without food.

- Each dose of POSANOL® Oral Suspension should be administered with a meal, or with a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption. For patients who cannot eat a full meal or tolerate an oral nutritional supplement and who do not have the option of taking POSANOL® Delayed-Release Tablets, an alternative antifungal therapy should be considered or patients should be monitored closely for breakthrough fungal infections.

- 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 POSANOL® should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections (see 9 DRUG INTERACTIONS).

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

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Table 1 - Recommended POSANOL® Solution for Injection Dose According to Indication

Indication	Dose and Duration of Therapy
Prophylaxis of Invasive Fungal Infections (IFIs)	Loading dose of 300 mg (300 mg Solution for Injection) twice a day on the first day, then 300 mg (300 mg Solution for Injection) once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS), prophylaxis with POSANOL® 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 (300 mg Solution for Injection) twice a day on the first day, then 300 mg (300 mg Solution for Injection) once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

Table 2 - Dosing for POSANOL® 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 POSANOL® 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.

Table 3 - Dosing for POSANOL® Oral Suspension

Indication	Dose and Duration of therapy
Prophylaxis of Invasive Fungal Infections (IFIs)	200 mg (5 mL) three times a day. 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 POSANOL® 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	400 mg (10 mL) twice a day[a] In patients who cannot tolerate a meal or a nutritional supplement, POSANOL® should be administered at a dose of 200 mg (5 mL) four times a day. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Treatment of Oropharyngeal Candidiasis (OPC)	Loading dose of 100 mg (2.5 mL) BID on the first day, then 100 mg (2.5 mL) once a day for 13 days.

a: Increasing the total daily dose of oral suspension above 800 mg does not further enhance the exposure to POSANOL®.

Dosage Adjustment

Use in Renal Impairment

The pharmacokinetics of POSANOL® 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 POSANOL® oral therapy, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

In patients with moderate or severe renal impairment (eGFR <50 mL/min), receiving the POSANOL® Solution for Injection, accumulation of the IV vehicle, SBECD, is expected to occur. POSANOL® Solution for Injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of POSANOL® Solution for Injection. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to POSANOL® Oral Suspension therapy (see 7 WARNINGS AND PRECAUTIONS).

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

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

4.3 Reconstitution
Parenteral Products:
See Administration section below under ***POSANOL® Solution for Injection.***

4.4 Administration

POSANOL® Solution for Injection

Reconstitution:

- Equilibrate the refrigerated vial of POSANOL® Solution for Injection to room temperature.
- Aseptically transfer 16.7 mL (300 mg) of POSANOL® Solution for Injection to an IV bag (or bottle) containing a compatible admixture diluent to achieve a final concentration not less than 1 mg/mL and not greater than 2 mg/mL. Use of other diluents is not recommended because they may result in particulate formation.
- POSANOL® Solution for Injection must be diluted with one of the following diluents: 5% dextrose in water, 0.9% sodium chloride, 0.45% sodium chloride, 5% dextrose and 0.45% sodium chloride, 5% dextrose and 0.9% sodium chloride or 5% dextrose and 20 mEq KCl. POSANOL® Solution for Injection must not be diluted with: Lactated Ringer's solution, 5% dextrose with Lactated Ringer's solution or 4.2% sodium bicarbonate. (see below).

Compatible Diluents	Non-Compatible Diluents
5% dextrose in water	Lactated Ringer’s solution
0.9% sodium chloride	5% dextrose with Lactated Ringer’s solution
0.45% sodium chloride	4.2% sodium bicarbonate
5% dextrose and 0.45% sodium chloride	
5% dextrose and 0.9% sodium chloride	
5% dextrose and 20 mEq KCl	

- Administer via a central venous line, including a central venous catheter or PICC by slow IV infusion over approximately 90 minutes. POSANOL® Solution for Injection is not for IV bolus administration.

- If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes. **Note: In clinical trials, multiple peripheral infusions given through the same vein were not well tolerated** (see 7 WARNINGS AND PRECAUTIONS, General and 8 ADVERSE REACTIONS)**.**

- POSANOL® Solution for Injection is a single-dose unpreserved sterile solution. Therefore, from a microbiological point of view, once admixed, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2°-8°C. Equilibrate to room temperature. This medicinal product is for single use only and any unused solution should be discarded.

A study was conducted to evaluate physical compatibility of POSANOL® Solution for Injection with injectable drug products and commonly used IV diluents during simulated Y-site infusion. Compatibility was determined through visual observations, measurement of particulate matter and turbidity.

Based on the results of the study, the following drug products can be infused at the same time through the same IV line (or cannula) as POSANOL® Solution for Injection:

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

Any products not listed in the table above should not be co-administered through the same IV line (or cannula).

Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit. Once admixed, the solution of POSANOL® ranges from colorless to pale yellow. Variations of color within this range do not affect the quality of the product.

POSANOL® Tablet and POSANOL® Oral Suspension
POSANOL® tablets and 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.

POSANOL® Delayed-Release Tablets and Oral Suspension are intended for oral administration only.

POSANOL® 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.

Shake POSANOL® Oral Suspension well before each use.

4.5 Missed Dose

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

5 OVERDOSAGE

There is no experience with overdosage of POSANOL® Delayed-Release Tablets.

During clinical trials, patients who received POSANOL® 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 POSANOL® 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), POSANOL® was not removed by hemodialysis.

Activated charcoal may be used to remove unabsorbed drug.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
intravenous (IV)	solution for injection, 300 mg/vial (18 mg/mL) posaconazole	Betadex Sulfobutyl Ether Sodium (SBECD), edetate disodium, hydrochloric acid, sodium hydroxide, and water for injection.
oral	delayed-release tablets, 100 mg posaconazole	Croscarmellose sodium, hydroxypropylcellulose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, Opadry† II Yellow [consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350 (polyethylene glycol 3350), titanium dioxide, talc, and iron oxide yellow], and silicon dioxide.
	suspension, 40 mg/mL posaconazole	Artificial cherry flavor, citric acid monohydrate, glycerin, liquid glucose, polysorbate 80, purified water, simethicone, sodium benzoate, sodium citrate dihydrate, titanium dioxide, and xanthan gum.

POSANOL® Solution for Injection

POSANOL® Solution for Injection is available as a clear colorless to yellow liquid essentially free of foreign matter. Each vial contains 18 mg of posaconazole per mL and the following inactive ingredients: Betadex Sulfobutyl Ether Sodium (SBECD), edetate disodium, hydrochloric acid, sodium hydroxide, and water for injection.

POSANOL® Solution for Injection is available in Type I glass vials closed with bromobutyl rubber stopper and aluminum seal containing 16.7 mL of solution (18 mg of posaconazole per mL; 300 mg/vial). POSANOL® Solution for Injection must be diluted for IV administration.

POSANOL® Delayed-Release Tablets

POSANOL® Delayed-Release Tablet is a yellow-coated, capsule-shaped tablet debossed with "100" on one side. Each tablet contains 100 mg of posaconazole and the following inactive ingredients: croscarmellose sodium, hydroxypropylcellulose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, Opadry† II Yellow [consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350 (polyethylene glycol 3350), titanium dioxide, talc, and iron oxide yellow], and silicon dioxide.

White HDPE bottle with a white PP child-resistant closure with pulp board liner with foil induction seal liner. Each 120 mL bottle contains 60 tablets.

POSANOL® Oral Suspension

POSANOL® Oral Suspension is a white, cherry flavored immediate-release suspension containing 40 mg of posaconazole per mL and the following inactive ingredients: artificial cherry flavor, citric acid

monohydrate, glycerin, liquid glucose, polysorbate 80, purified water, simethicone, sodium benzoate, sodium citrate dihydrate, titanium dioxide, and xanthan gum.

105 mL of oral suspension in a 123 mL bottle (glass amber type IV) closed with a plastic child-resistant cap (polypropylene) and a measuring spoon (polystyrene) with 2 graduations: 2.5 mL and 5 mL.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Oral Formulations: POSANOL® delayed-release tablets and POSANOL® oral solution are not interchangeable (see 4 DOSAGE AND ADMINISTRATION).
Posaconazole plasma concentrations following administration of POSANOL® tablets are generally higher than those obtained with posaconazole oral suspension. Posaconazole plasma concentrations following administration of POSANOL® tablets may increase over time in some patients. Safety data at higher exposure levels achieved with POSANOL® tablets are limited (see 10 CLINICAL PHARMACOLOGY).

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

This medicine contains glucose. Patients with rare glucose-galactose malabsorption should not take this medicine.

No data on the effects of POSANOL® 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
POSANOL® 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, POSANOL® 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 POSANOL® therapy.

Caution should be exercised if POSANOL® 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 POSANOL® levels,

with possible resulting QT effects. Such drugs include tacrolimus, HIV protease inhibitors and macrolide antibiotics (see 2 CONTRAINDICATIONS, 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY). During clinical development there was a single case of torsade de pointes in a patient taking POSANOL®. This report involved a seriously ill patient with multiple confounding risk factors (see 8 ADVERSE REACTIONS, Less Common Clinical Trial Adverse Drug Reactions (< 2%)).

Dependence/Tolerance
There is no known abuse potential for POSANOL®.

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 POSANOL®. 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 POSANOL®.

Monitoring of hepatic function: Liver function tests should be evaluated at the start of and during the course of POSANOL® therapy. Patients who develop abnormal liver function tests during POSANOL® 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 POSANOL® should be considered if clinical signs and symptoms are consistent with development of worsening liver disease.

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

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

Neurologic
Vincristine Toxicity: Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options (see 9 DRUG INTERACTIONS).

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

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

A specific study has not been conducted with POSANOL® Solution for Injection in patients with moderate and severe renal impairment (estimated glomerular filtration rate (eGFR) <50 mL/min). When these patients are administered the POSANOL® Solution for Injection, accumulation of the intravenous (IV) vehicle, Betadex Sulfobutyl Ether Sodium (SBECD), is expected to occur. POSANOL® Solution for Injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of POSANOL® Solution for Injection. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral POSANOL® therapy.

7.1 Special Populations

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

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

Hepatic Impairment: POSANOL® 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 POSANOL® 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).

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

POSANOL® Solution for Injection

In initial studies of healthy volunteers, multiple doses of posaconazole solution for injection administered via a peripheral venous catheter were associated with thrombophlebitis (60% incidence).

The safety of POSANOL® Solution for Injection has been assessed in 268 patients in a clinical trial. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of POSANOL® Solution for Injection when given as antifungal prophylaxis (Solution for Injection Study 1). Patients were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 55% male, had a mean age of 51 years (range 18-82 years, 19% of patients were ≥65 years of age), and were 95% white and 8% Hispanic. Ten patients received a single dose of 200 mg POSANOL® Solution for Injection, 21 patients received 200 mg daily dose for a median of 14 days, and 237 patients received 300 mg daily dose for a median of 9 days. Each patient in the multiple dose cohorts received BID dosing on Day 1. In each cohort, following POSANOL® IV therapy, patients received POSANOL® oral suspension to complete 28 days of total POSANOL® therapy.

The most frequently reported adverse reaction (>30%) with an onset during the POSANOL® IV phase of dosing with 300 mg once daily (QD) was diarrhea (32%).

The most common adverse reaction (>1%) leading to discontinuation of POSANOL® Solution for Injection 300 mg QD was acute myelogenous leukemia (AML) (1%).

POSANOL® Delayed-Release Tablets
The safety of POSANOL® 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 POSANOL® Delayed-Release Tablets when given as antifungal prophylaxis. Patients were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. POSANOL® 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 POSANOL® 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 ≥ 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 POSANOL® Delayed-Release Tablets 300 mg once daily (QD) were diarrhea and nausea.

The most frequently reported adverse reaction leading to discontinuation of POSANOL® Delayed-Release Tablets 300 mg QD was nausea.

POSANOL® Oral Suspension
The safety of POSANOL® Oral Suspension therapy has been assessed in 1,844 patients and healthy volunteers enrolled in clinical trials and from post-marketing experience. This includes 605 patients in the prophylaxis studies, 796 in OPC/rOPC studies and 428 patients treated for invasive fungal infections (IFIs). POSANOL® therapy was given to 171 patients for ≥ 6 months, with 58 patients receiving POSANOL® therapy for ≥ 12 months.

The most frequently reported adverse reactions reported across the whole population of healthy volunteers and patients were nausea (6%) and headache (6%).

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

Clinical Trial Safety Experience with POSANOL® Solution for Injection

Solution for Injection Study 1
Solution for Injection Study 1 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of POSANOL® Solution for Injection. Solution for Injection Study 1 was conducted in a similar patient population to that previously studied in the pivotal posaconazole oral suspension clinical program.

Table 5: POSANOL® Solution for Injection Study 1: Number (%) of Subjects Treated with 300 mg Daily Dose Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10%

Adverse Reactions	POSANOL® Solution for Injection Treatment Phase n=237 (%)[a]	Posaconazole Solution for Injection Treatment Phase or Subsequent Oral Suspension Treatment Phase n=237(%)[b]
Subjects Reporting any Adverse Reaction	220 (93)	235 (99)
Blood and Lymphatic System		
Anemia	16 (7)	23 (10)
Febrile Neutropenia	44 (19)	54 (23)
Thrombocytopenia	17 (7)	25 (11)
Gastrointestinal		
Abdominal Pain Upper	15 (6)	25 (11)
Abdominal Pain	30 (13)	41 (17)
Constipation	18 (8)	31 (13)
Diarrhea	75 (32)	93 (39)
Nausea	46 (19)	70 (30)
Vomiting	29 (12)	45 (19)
General and Administration Site Conditions		
Chills	28 (12)	38 (16)
Edema Peripheral	28 (12)	35 (15)
Fatigue	19 (8)	24 (10)
Mucosal Inflammation	37 (16)	44 (19)
Pyrexia	49 (21)	73 (31)
Metabolism and Nutrition		
Decreased Appetite	23 (10)	29 (12)
Hypokalemia	51 (22)	67 (28)
Hypomagnesemia	25 (11)	30 (13)
Nervous System		
Headache	33 (14)	49 (21)
Respiratory, Thoracic and Mediastinal		
Cough	21 (9)	31 (13)
Dyspnea	16 (7)	24 (10)
Epistaxis	34 (14)	40 (17)
Skin and Subcutaneous Tissue		
Petechiae	20 (8)	24 (10)
Rash	35 (15)	56 (24)
Vascular		

Adverse Reactions	POSANOL® Solution for Injection Treatment Phase n=237 (%)[a]	Posaconazole Solution for Injection Treatment Phase or Subsequent Oral Suspension Treatment Phase n=237(%)[b]
Hypertension	(8)	26 (11)

a: Adverse reactions reported in patients with an onset during the posaconazole IV dosing phase of the study.
b: Adverse reactions reported with an onset at any time during the study in patients who were treated for up to 28 days of posaconazole therapy.

Clinical Trial Safety Experience with POSANOL® 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 POSANOL® Delayed-Release Tablet. Study P05615 was conducted in a similar patient population to that previously studied in the pivotal POSANOL® Oral Suspension clinical program.

Table 6: Treatment-related adverse reactions reported in POSANOL® Delayed-Release Tablet subjects treated with 300 mg daily dose reported at an incidence of ≥ 1% for the P05615 Study

Adverse Reactions	POSANOL® 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)

Adverse Reactions	POSANOL® Delayed-Release Tablet (300 mg) n=210 (%)
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 POSANOL® Oral Suspension

Studies P01899 and C/I98-316

Study P01899 was a randomised, evaluator-blinded study that compared POSANOL® 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, POSANOL®; 25 days, fluconazole/itraconazole). In this study, 304 patients were randomly assigned to POSANOL® 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 POSANOL® 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, POSANOL®; 77 days, fluconazole). In this study, 301 patients were randomly assigned to POSANOL® therapy and 299 patients were assigned to fluconazole therapy.

Table 7 - Treatment-related adverse reactions reported in POSANOL® Oral Suspension, fluconazole and itraconazole subjects reported at an incidence of ≥ 1% for the prophylaxis studies C/I98-316 and P01899

Adverse Reactions	POSANOL® n=605 (%)	fluconazole n=539 (%)	Itraconazole n=58 (%)
Blood and Lymphatic System			
Anemia	5 (1)	2 (< 1)	0
Thrombocytopenia	4 (1)	3 (1)	0
Cardiovascular			
QT/QT_c prolongation	14 (2)	6 (1)	4 (7)
Hypertension	3 (< 1)	5 (1)	0
Tachycardia	4 (1)	1 (< 1)	0
Bradycardia	1 (< 1)	0	2 (3)
Vasculitis	0	0	1 (2)
Eye			
Vision blurred	3 (< 1)	6 (1)	0
Gastrointestinal			
Nausea	44 (7)	45 (8)	8 (14)
Vomiting	27 (4)	29 (5)	6 (10)
Diarrhea	28 (5)	24 (4)	9 (16)
Abdominal pain	13 (2)	15 (3)	1 (2)
Constipation	4 (1)	12 (2)	0
Dyspepsia	8 (1)	9 (2)	0
Loose stools	1 (< 1)	5 (1)	0
Abdominal distension	4 (1)	2 (< 1)	0
Gastritis	2 (< 1)	3 (1)	0
Nausea aggravated	2 (< 1)	1 (< 1)	2 (3)
Dry mouth	3 (< 1)	1 (< 1)	1 (2)
Mucositis not otherwise specified	7 (1)	0	0
Stomatitis aphtous	1 (< 1)	0	1 (2)
Gastric disorder	0	0	1 (2)
Rectal pain	0	0	1 (2)
General and Administration Site Conditions			
Fatigue	7 (1)	7 (1)	0
Weakness	3 (< 1)	5 (1)	0
Asthenia	2 (< 1)	3 (1)	0
Fever	2 (< 1)	3 (1)	0
Hepatobiliary			
Bilirubinemia	15 (2)	10 (2)	3 (5)
Hepatic enzymes increased	15 (2)	10 (2)	0

Adverse Reactions	POSANOL® n=605 (%)	fluconazole n=539 (%)	Itraconazole n=58 (%)
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)

Adverse Reactions	POSANOL® n=605 (%)	fluconazole n=539 (%)	Itraconazole n=58 (%)
Pruritus	4 (1)	5 (1)	0
Rash pruritic	3 (< 1)	5 (1)	0
Rash maculopapular	5 (1)	2 (< 1)	0
Sweating increased	1 (< 1)	0	1 (2)
Cellulitis	0	0	1 (2)
Investigations			
Alkaline phosphatase increased	6 (1)	6 (1)	1 (2)
Drug level altered	5 (1)	2 (< 1)	0
LDH increased	5 (1)	0	0

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

Studies P01893 and P00041

Study P01893 was an open-label, randomized, parallel group, study of the safety, tolerability, efficacy, and pharmacokinetic profile of POSANOL® in the treatment of immunocompromised patients with rIFI or in febrile neutropenic subjects who required empiric antifungal therapy. POSANOL® 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 POSANOL® therapy.

Study P00041 was an open-label, non-comparative study of the safety and efficacy of POSANOL® 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 POSANOL® Oral Suspension 800 mg/day in divided doses. In this study, 330 patients received POSANOL® therapy. The median duration of POSANOL® therapy was 102.5 days (1 – 609 days). The majority of patients were severely immunocompromised with underlying conditions such as hematologic malignancies, including bone marrow transplantation; solid organ transplantation; solid tumors and/or AIDS.

Studies C/I96-209, C/I97-331, C/I97-330 and P00298

Study C/I96-209 was a randomised, double-blind, controlled study of four different dose levels of POSANOL® as compared to fluconazole in the treatment of HIV-infected patients with azole-susceptible OPC. Patients were treated with POSANOL® capsules 400 mg BID for 1 day, followed by 50 mg, 100 mg, 200 mg, or 400 mg QD for 13 days, or with fluconazole 200 mg QD for 1 day, followed by 100 mg QD for 13 days. In this study, 379 patients received POSANOL® therapy and 90 patients received fluconazole therapy.

Study C/I97-331 was a randomised, evaluator-blinded, controlled study in HIV-infected patients with azole-susceptible OPC. Patients were treated with POSANOL® or fluconazole Oral Suspension (both-POSANOL® and fluconazole were given as follows: 100 mg BID for 1 day followed by 100 mg QD for 13 days). In this study, 182 patients received POSANOL® therapy and 184 patients received fluconazole therapy.

Study C/I97-330 was an open-label, non-comparative study in 199 HIV-infected patients with azole-refractory OPC treated with one of two POSANOL® Oral Suspension regimens: 400 mg BID for 3 days, followed by 400 mg QD for 25 days with an option for further treatment during a 3-month maintenance period, or 400 mg BID for 28 days.

Study P00298 was an open-label, non-comparative, long-term safety study in 100 HIV-infected patients with azole-refractory OPC treated with POSANOL® 400 mg BID for up to 15 months. A total of 60 of these patients had been previously treated in Study C/I97-330 and 1 patient had been previously treated in Study P00041.

Table 8 - Treatment-related adverse reactions reported in POSANOL® Oral Suspension-treated subjects (divided into subgroups Bone Marrow Transplant [BMT], non-BMT, Non-Refractory OPC & Refractory OPC) by body systems reported at an incidence of ≥ 2% for the rIFI studies (P01893 & P00041) and OPC studies (C/I96-209, C/I97-331, C/I97-330 & P00298)

Adverse Reactions	rIFI Studies (P01893 and P00041)		OPC Studies (C/I96-209, C/I97-331, C/I97-330 and P00298)		
	POSANOL®		Non-Refractory OPC		Refractory OPC
	BMT n=124 (%)	non-BMT n=304 (%)	POSANOL® n=557 (%)	fluconazole n=262 (%)	POSANOL® n=239 (%)
Blood and Lymphatic System					
Neutropenia	0	0	10 (2)	4 (2)	20 (8)
Anemia	0	4 (1)	2 (< 1)	0	6 (3)
Thrombocytopenia	0	2 (1)	3 (1)	0	4 (2)
Cardiovascular					
QT/QT_c prolongation	0	6 (2)	0	0	0
Gastrointestinal					
Nausea	10 (8)	25 (8)	27 (5)	18 (7)	20 (8)
Diarrhea	3 (2)	12 (4)	19 (3)	13 (5)	26 (11)
Vomiting	7 (6)	18 (6)	20 (4)	4 (2)	16 (7)
Abdominal pain	3 (2)	15 (5)	10 (2)	8 (3)	12 (5)
Dry mouth	0	6 (2)	7 (1)	6 (2)	5 (2)
Flatulence	0	3 (1)	6 (1)	0	11(5)
General and Administration Site Conditions					

Fatigue	4 (3)	3 (1)	8 (1)	5 (2)	7 (3)
Asthenia	1 (1)	3 (1)	4 (1)	2 (1)	6 (3)
Fever	1 (1)	2 (1)	10 (2)	1 (< 1)	6 (3)
Hepatobiliary					
ALT (SGPT) increased	2 (2)	9 (3)	4 (1)	3 (1)	3 (1)
AST (SGOT) increased	1 (1)	8 (3)	5 (1)	2 (1)	1 (< 1)
Hepatic enzymes increased	2 (2)	5 (2)	1 (< 1)	0	5 (2)
Hepatic function abnormal	1 (1)	2 (1)	3 (1)	4 (2)	0
Metabolism and Nutrition					
Anorexia	2 (2)	6 (2)	6 (1)	1 (< 1)	7 (3)
Muscoskeletal System					
Myalgia	0	1 (< 1)	1 (< 1)	0	4 (2)
Nervous System					
Headache	3 (2)	17 (6)	16 (3)	5 (2)	18 (8)
Dizziness	1 (1)	6 (2)	9 (2)	5 (2)	8 (3)
Somnolence	0	3 (1)	4 (1)	5 (2)	3 (1)
Paresthesia	1 (1)	5 (2)	3 (1)	2 (1)	2 (1)
Convulsions	2 (2)	0	0	0	2 (1)
Psychiatric					
Insomnia	0	0	3 (1)	0	6 (3)
Renal and Urinary System					
Blood creatinine increased	0	5 (2)	2 (< 1)	0	2 (1)
Reproductive System and Breast					
Menstrual disorder	0	2 (2)	0	0	0
Skin and Subcutaneous Tissue					
Rash	2 (2)	8 (3)	8 (1)	4 (2)	10 (4)
Pruritus	1 (1)	3 (1)	6 (1)	2 (1)	5 (2)
Investigations					
Alkaline phosphatase increased	1 (1)	5 (2)	3 (1)	3 (1)	5 (2)
Drug level altered	2 (2)	5 (2)	0	0	0

Treatment-related serious adverse events reported in 428 patients with IFIs (1% each) included altered concentration of other medicinal products, increased hepatic enzymes, nausea, rash, and vomiting.

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

Treatment-related SAEs were reported for 14% (34/239) of these patients and included neutropenia (5%) and abdominal pain (2%). POSANOL® was discontinued in two patients who developed

neutropenia that was considered serious and treatment-related. All other reported treatment-related SAEs occurred in < 1% of subjects on POSANOL®.

8.3 Less Common Clinical Trial Adverse Reactions

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

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

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

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

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

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

Endocrine: adrenal insufficiency, glucocorticoids decreased, gonadotropins decreased.

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

Gastrointestinal: abdominal distention, abdominal pain aggravated, abdominal tenderness, ascites, ascites aggravated, bowel motility decreased, cheilitis, diverticulitis aggravated, dysphagia, eructation, esophagitis, esophagus ulceration, feces malodorous, gastritis, gastroenteritis, gastroesophageal reflux, gastrointestinal tract hemorrhage, hiccup, gingivitis, glossitis, hemorrhagic diarrhea, hemorrhagic gastritis, ileus, loose stools, melena, mouth ulceration, odynophagia, pancreatic enzymes NOS increased, pancreatitis, proctalgia, retching, saliva altered, stomatitis, tenesmus, thirst, tongue discoloration, tongue disorder, tooth discoloration, vomiting aggravated.

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

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

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

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

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

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

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

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

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

Reproductive System and Breast: balanoposthitis, breast pain.

Respiratory, Thoracic and Mediastinal: atelectasis, chest pain, nonproductive cough, dry throat, dyspnea, dyspnea aggravated, epistaxis, epistaxis aggravated, interstitial pneumonia, nasal congestion, nasal irritation, pharyngitis, pneumonitis, postnasal drip, pulmonary hypertension, pulmonary infiltration, rales, respiratory disorder, rhinitis, rhinorrhea.

Surgical and Medical Procedures: cardioversion.

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

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

Clinical Trial Findings

Clinical Chemistry Findings

In (uncontrolled) trials of patients with IFIs treated with POSANOL® Oral Suspension doses ≥ 800 mg/day, the incidence of clinically significant liver function test abnormalities was: ALT and AST (> 3 X Upper Limit Normal [ULN]) 6% and 5%, respectively; total bilirubin (> 1.5 X ULN) 4%; and alkaline phosphatase (> 3 X ULN) 4%. In healthy volunteers, elevation of hepatic enzymes did not appear to be associated with higher plasma concentrations of POSANOL®. 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 patients infected with HIV and OPC treated with POSANOL® Oral Suspension at doses up to 400 mg, the incidence of clinically significant liver function test abnormalities was as follows; ALT and AST (> 3 X ULN), 1% and 3%, respectively: total bilirubin (> 1.5 X ULN), < 1%; and alkaline phosphatase (> 3 X ULN), 1%.

In the comparative trials of hematopoietic stem cell recipients or patients with AML receiving POSANOL® Oral Suspension as prophylaxis at doses up to 600 mg, the incidence of clinically significant liver function test abnormalities was as follows; ALT and AST (> 3 X ULN), 12% and 4%, respectively: total bilirubin (> 1.5 X ULN), 8%; and alkaline phosphatase (> 3 X ULN), 2%.

8.5 Post-Market Adverse Reactions

The following adverse events have been reported during the post-approval use of POSANOL® 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 POSANOL® could not be excluded for these adverse events, which included:

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- **Contraindicated Drugs: ergot alkaloids, terfenadine, astemizole, cisapride, pimozide, quinidine, HMG-CoA reductase inhibitors (statins) and sirolimus (see 2 CONTRAINDICATIONS).**
- **Drugs whose concomitant use should be avoided: cimetidine, rifabutin and phenytoin (see Tables 9 and 10)**
- **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 10)**
- **Drugs whose concomitant use requires consideration of dose reduction and close monitoring for adverse events during treatment: vinca alkaloids, midazolam, calcium channel blockers and venetoclax (see Table 9)**

The interactions described in the following subsections apply to POSANOL® Delayed-Release Tablets and Oral Suspension unless otherwise specified.

The following information was derived from data with POSANOL® Oral Suspension or early tablet formulation. All drug interactions with POSANOL® Oral Suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility) are considered relevant to POSANOL® Solution for Injection as well.

9.2 Drug Interactions Overview

Effects of Other Drugs on POSANOL® Pharmacokinetics
POSANOL® is metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate from p-glycoprotein efflux. Therefore, inhibitors or inducers of these clearance pathways may affect POSANOL® plasma concentrations. POSANOL® 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 POSANOL® on Pharmacokinetics of Other Drugs
POSANOL® 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 POSANOL®.

9.3 Drug-Behavioural Interactions
Not applicable.

9.4 Drug-Drug Interactions

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

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

Table 9 – Summary of the Effect of Co-administered Drugs on POSANOL ® in Healthy Volunteers

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	POSANOL® Dose/Schedule	Effect on Bioavailability of POSANOL®		Recommendations
				Change in Mean C_{max} (ratio estimate[a]; 90% CI of the ratio estimate)	Change in Mean AUC[b] (ratio estimate; 90% CI of the ratio estimate)	
Rifabutin (UDP-G Induction)	clinical trial	300 mg QD[c] x17 days	200 mg (tablets) QD x 10 days	↓ 43% (0.57; 0.43-0.75)	↓ 49% (0.51; 0.37-0.71)	Concomitant use of POSANOL® 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 POSANOL® and phenytoin should be avoided unless the benefit to the patient outweighs the risk.

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	POSANOL® Dose/Schedule	Effect on Bioavailability of POSANOL®		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)	
Efavirenz (UDP-G Induction)	clinical trial	400 mg QD × 10 and 20 days	400 mg (oral suspension) BID × 10 and 20 days	↓ 45% (0.55; 0.47-0.66)	↓ 50% (0.50; 0.43-0.60)	Concomitant use of POSANOL® and efavirenz should be avoided unless the benefit to the patient outweighs the risk.
Fosamprenavir	clinical trial	700 mg BID x 10 days	200 mg QD on the 1st day, 200 mg BID on the 2nd day, then 400 mg BID x 8 Days	↓ 21% 0.79 (0.71-0.89)	↓ 23% 0.77 (0.68-0.87)	If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended.
Glipizide	clinical trial	10 mg single dose	400 mg BID oral suspension x 10 Days	Glipizide had no clinically significant effect on posaconazole C_{max} and AUC.		No dose adjustments required. Glucose concentrations decreased in some healthy volunteers when glipizide was co-administered with POSANOL®. Glucose concentrations should be monitored in accordance with the current standard of care for patients with diabetes when POSANOL® is co-administered with glipizide.
H_2 receptor antagonists, proton pump inhibitors (PPIs) and antacids						
Antacids/H_2 receptor antagonists (H2RA)/Proton pump inhibitors (PPI)	clinical trial	Single dose 20 mL of Mylanta† ultimate strength liquid; AM dose of 150 mg ranitidine tablet BID; esomeprazole 40 mg once in the morning QAM x 5 days (Day-4 to 1)	400 mg single dose (4x100 mg) delayed release tablets	No clinically relevant effects were observed when posaconazole tablets are concomitantly used with antacids, H_2 receptor antagonists and proton pump inhibitors.		No dosage adjustment of POSANOL® Delayed-Release Tablets is required when POSANOL® 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 POSANOL® 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 (oral suspension) single dose	↓ 46% (0.54; 0.43-0.69)	↓ 32% (0.68; 0.57-0.81)	Concomitant use of POSANOL® Oral Suspension with proton pump inhibitors should be avoided if possible.

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	POSANOL® Dose/Schedule	Effect on Bioavailability of POSANOL®		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)	
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 POSANOL® Delayed-Release Tablets is required when given concomitantly with metoclopramide.
		10 mg TID[g] × 2 days	400 mg (oral suspension) single dose	Metoclopramide, when given with posaconazole oral suspension, decreases posaconazole plasma concentrations.		If metoclopramide is concomitantly administered with POSANOL® Oral Suspension, it is recommended to closely monitor for breakthrough fungal infections.
Loperamide	clinical trial	4 mg single dose (two 2 mg tablets)	400 mg single dose (oral suspension) administered with a nutritional supplement	Loperamide does not affect posaconazole oral suspension plasma concentrations.		No dosage adjustment of POSANOL® Oral Suspension is required when loperamide and POSANOL® Oral Suspension are used concomitantly.

Table 10 - Summary of the Effect of POSANOL® on Co-administered Drugs in Healthy Volunteers and Patients

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	POSANOL® 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 POSANOL®)	clinical trial	Stable maintenance dose in heart transplant recipients	200 mg (tablets) QD[c] x 10 days	↑ cyclosporine whole blood trough concentrations. Cyclosporine dose reductions of up to 29% were required.		When initiating treatment with POSANOL® 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 POSANOL® treatment, the dose of cyclosporine should be adjusted as necessary.
Tacrolimus (inhibition of CYP3A4 by POSANOL®)	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 POSANOL® 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 POSANOL®, and the dose of tacrolimus should be adjusted as necessary.
Rifabutin (inhibition of CYP3A4 by POSANOL®)	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 POSANOL® 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.

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	POSANOL® 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)	
Midazolam (inhibition of CYP3A4 by POSANOL®)	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 POSANOL®.
		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)	
Phenytoin (inhibition of CYP34A by POSANOL®)	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 POSANOL® 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 POSANOL® and ergot alkaloids is contraindicated (see CONTRAINDICATIONS).
Terfenadine Astemizole Cisapride Pimozide Quinidine	theoretical	NA, since theoretical		Co-administration of posaconazole oral suspension and certain drugs such as cisapride*, pimozide, and quinidine, metabolized through the CYP3A4 system may result in ↑ plasma concentrations of these medicinal products, leading to potentially serious and/or life threatening adverse events (QT prolongation and rare occurrences of torsade de pointes).		Co-administration of these drugs with POSANOL® 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 POSANOL® and sirolimus is contraindicated (see CONTRAINDICATIONS).

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	POSANOL® 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)	
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 POSANOL® and HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 is contraindicated (see CONTRAINDICATIONS).
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	clinical trial	300 mg QD x 14 days	400 mg (oral suspension) BID x 7 days	↑ 155% (2.55; 1.89-3.45)	↑ 268% (3.68; 2.89-4.70)	Frequent monitoring for adverse events and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with POSANOL®.
Atazanavir/ ritonavir boosted regimen		300 mg/100 mg QD x 14 days	400 mg (oral suspension) BID x 7 days	↑ 53% (1.53; 1.13-2.07)	↑ 146% (2.46; 1.93-3.13)	

Co-administered Drug (Postulated Mechanism of Interaction)	Ref	Co-administered Drug Dose/Schedule	POSANOL® 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)	
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 POSANOL®. 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, POSANOL® may increase plasma concentration of digoxin and digoxin levels should be monitored when initiated or discontinuing POSANOL® treatment.
Venetoclax	clinical trial	Refer to venetoclax product monograph.		Concomitant use of venetoclax (a CYP3A4 substrate) with posaconazole increases venetoclax C_{max} and AUC_{0-INF}, which may increase venetoclax toxicities (see 7 WARNINGS AND PRECAUTIONS)		Refer to venetoclax product monograph

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

9.5 Drug-Food Interactions

Table 11 – Established or Potential Drug-Food Interactions

Proper name	Ref	Effect	Clinical comment
Caffeine	clinical trial	No clinically significant effect has been noted.	No dose adjustments required.
Food or nutritional supplement	clinical trial	POSANOL® Delayed-Release Tablets when given in the fasted state as a single dose has comparable or greater relative bioavailability as compared to the POSANOL® Oral Suspension given with a high fat meal as a single dose. The AUC of POSANOL® 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. The AUC of POSANOL® Oral Suspension is about 4 times greater when administered with a high-fat meal (~ 50 grams fat) and about 2.6 times greater when administered with a nonfat meal or nutritional supplement (14 grams fat) relative to the fasted state.	POSANOL® 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 POSANOL® Delayed-Release Tablets is needed (see 10 CLINICAL PHARMACOLOGY). Each dose of POSANOL® Oral Suspension should be administered with food or nutritional supplement (see 4 DOSAGE AND ADMINISTRATION).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

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

Exposure Response Relationship:
In clinical studies of neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS or HSCT recipients with GVHD, a wide range of plasma exposures to posaconazole was noted following administration of POSANOL® Oral Suspension. A pharmacokinetic-pharmacodynamic analysis of patient data revealed an apparent association between average posaconazole concentrations (C_{avg}) and efficacy outcomes (Table 12). A lower C_{avg} may be associated with an increased risk of treatment failure.

Table 12 – POSANOL® Oral Suspensions Exposure Analysis (C_{avg}) in Clinical Trials

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

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

10.3 Pharmacokinetics

General Pharmacokinetic Characteristics:

POSANOL® Solution for Injection
POSANOL® Solution for Injection exhibits dose proportional pharmacokinetics after single doses between 200 and 300 mg in healthy volunteers. The mean pharmacokinetic parameters after single doses with posaconazole solution for injection in healthy volunteers are shown in Table 13.

Table 13 - Summary of Mean Pharmacokinetic Parameters (%CV) in Healthy Volunteers after Single Dosing with Posaconazole Solution for Injection

Single dose				
Dose (mg)	$AUC_{0-\infty}$	C_{max} (ng/mL)	$t_{1/2}$ (h)	CL (L/h)
100	11,228	1,330	20	9.4
200	31,763	1,862	24	7.0
300	44,501	3,676	27	7.3
$AUC_{0-\infty}$: Area under the plasma concentration-time curve from time zero to infinity; C_{max}: maximum observed concentration; $t_{½}$: terminal phase half-life; CL: total body clearance				

Table 14 displays the pharmacokinetic parameters of POSANOL® in patients following administration of POSANOL® Solution for Injection 300 mg taken once a day for 10 or 14 days following BID dosing on Day 1.

Table 14 - Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Patients Following Dosing of Posaconazole Solution for Injection (300 mg)*

Day	n	C_{max} (ng/mL)	T_{max} † (hr)	$AUC_{interval}$ (ng·hr/mL)	C_{avg} (ng/mL)	C_{min} (ng/mL)
10/14	49	3,280 (74)	1.5 (0.98-4.0)	36,100 (35)	1,500 (35)	1,090 (44)

$AUC_{interval}$ = area under the concentration-time curve over the dosing interval (i.e. 24 hours); C_{avg} = AUC interval/interval;
C_{min} = POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; C_{max} = observed maximum plasma concentration; CV = coefficient of variation, expressed as a percent (%); Day = study day on treatment; T_{max} = time of observed maximum plasma concentration.
* 300 mg dose administered over 90 minutes once a day following BID dosing on Day 1
† Median (minimum-maximum)

POSANOL® Delayed-Release Tablets

POSANOL® 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 POSANOL® 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 15.

Table 15: 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)**	**$t_{½}$ (hr)**	**CL/F (L/hr)**
Healthy Volunteers	12	51618 (25)	2151 (25)	2764 (21)	1785 (29)	4 (3-6)	31 (40)	7.5 (26)
Patients	50	37900 (42)	1580 (42)	2090 (38)	1310 (50)	4 (1.3-8.3)	-	9.39 (45)

CV = coefficient of variation expressed as a percentage (%CV); AUC_{0-T} = Area under the plasma concentration-time curve from time zero to 24 hr; C_{max} = maximum observed concentration; C_{min} = minimum observed plasma concentration; T_{max} = time of maximum observed concentration; $t_{½}$ = terminal phase half-life; CL/F = Apparent total body clearance
* 300 mg BID on Day 1, then 300 mg QD thereafter
† C_{avg} = time-averaged concentrations (i.e., $AUC_{0-24\ hr/24\ hr}$)
‡ Median (minimum-maximum)

POSANOL® Oral Suspension

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

mg BID to 400 mg BID in healthy volunteers. No further increases in exposure were observed when the dose of the oral suspension increased from 400 mg BID to 600 mg BID in febrile neutropenic patients or those with refractory invasive fungal infections.

The mean (%CV) [min-max] posaconazole oral suspension average steady-state plasma concentrations (C_{avg}) and steady-state pharmacokinetic parameters in patients following administration of 200 mg TID and 400 mg BID of the oral suspension are provided in Table 16.

Table 16: The Mean (%CV) [min-max] Posaconazole Steady-State Pharmacokinetic Parameters in Patients Following Oral Administration of Posaconazole Oral Suspension 200 mg TID and 400 mg BID

Dose*	C_{avg} (ng/mL)	AUC† (ng·hr/mL)	CL/F (L/hr)	V/F (L)	$t_{½}$ (hr)
200 mg TID‡ (n=252)	1103 (67) [21.5 – 3,650]	ND§	ND§	ND§	ND§
200 mg TID¶ (n=215)	583 (65) [89.7 – 2,200]	15,900 (62) [4,100 - 56,100]	51.2 (54) [10.7 - 146]	2425 (39) [828 – 5,702]	37.2 (39) [19.1 - 148]
400 mg BID# (n=23)	723 (86) [6.70 – 2,256]	9,093 (80) [1,564 - 26,794]	76.1 (78) [14.9 - 256]	3,088 (84) [407 - 13,140]	31.7 (42) [12.4 - 67.3]

C_{avg} = the average posaconazole concentration when measured at steady state
* Oral suspension administration
† $AUC_{(0\text{-}24\ hr)}$ for 200 mg TID and $AUC_{(0\text{-}12\ hr)}$ for 400 mg BID
‡ HSCT recipients with GVHD
§ Not done
¶ Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes
# Febrile neutropenic patients or patients with refractory invasive fungal infections, C_{avg} n=24
The variability in average plasma posaconazole concentrations in patients was relatively higher than that in healthy subjects

Absorption:

POSANOL® Solution for Injection

Posaconazole solution for injection was infused over 30 minutes or over 90 minutes in the different studies. In general, Tmax was reached at a time around the end of the infusion both after single and multiple doses and peripheral or central venous administration. Mean C_{max} values were higher after shorter infusion time and are shown in Table 17 below.

Table 17 - Infusion Duration, Median T_{max}, and Mean C_{max} following Posaconazole Solution for Injection Administration – Presented by Dose Level (200 or 300 mg), Regimen, and Study

Study	Posaconazole Dose	Infusion duration (min)	Mean C_{max} (%CV) (ng/mL)
P04985 (SD, HV)	200 mg	90	1,470 (24)
P06356 (SD, HV)	200 mg	30	2,250 (29)
	300 mg	30	2,840 (30)
P07783 (SD, HV)	300 mg	30	4,258 (19)
P05520 (SD/MD, patients)	200 mg SD	90	990 (47)
	200 mg MD	90	1,950 (50)
	300 mg MD	90	3,280 (74)

HV: healthy volunteers; SD: single dose; MD: multiple dose; C_{max}: maximum plasma concentration attained.

POSANOL® Delayed-Release Tablets

POSANOL® 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 POSANOL® Delayed-release tablets is increased 16% and 51%, respectively, when given with a high fat meal compared to a fasted state (see Table 18). However, the effect of food on the absorption of POSANOL® 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 POSANOL® Delayed-release tablets without regard to food intake. POSANOL® Delayed-release tablet can therefore be administered with or without food.

Table 18: Statistical Comparison of Plasma Pharmacokinetics of Posaconazole Following Single Oral Dose Administration of 300 mg POSANOL® Delayed-Release Tablet to Healthy Subjects under Fasting and Fed Conditions

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

GM = Geometric least-squares mean
GMR = Geometric least-squares mean ratio
CI = Confidence interval
* 48.5 g fat
† C_{max} = maximum observed concentration
‡ $AUC_{0\text{-}last}$ = $AUC_{0\text{-}72hr}$
§ Median (Min, Max) reported for T_{max}

POSANOL® Oral Suspension

POSANOL® Oral Suspension is absorbed with a median tmax of ~ 3 to 5 hours. Dose proportional increases in plasma exposure (AUC) to POSANOL® Oral Suspension were observed following single oral doses from 50 mg to 800 mg and following multiple-dose administration from 50 mg BID to 400 mg BID. No further increases in exposure were observed when the dose was increased from 400 mg BID to 600 mg BID in febrile neutropenic patients or those with rIFIs. Steady-state plasma concentrations are attained at 7 to 10 days following multiple-dose administration.

Following single-dose administration of 200 mg, the mean AUC and Cmax of POSANOL® Oral Suspension are approximately 3 times higher when administered with a nonfat meal and approximately 4 times higher when administered with a high-fat meal (~ 50 gm fat) relative to the fasted state. Following single-dose administration of 400 mg, the mean AUC and C_{max} of POSANOL® Oral Suspension are approximately 3 times higher when administered with a liquid nutritional supplement (14 gm fat) relative to the fasted state (see Table 19). In order to assure attainment of adequate plasma

concentrations, it is recommended to administer POSANOL® Oral Suspension with food or a nutritional supplement (see 4 DOSAGE AND ADMINISTRATION).

Table 19 - The Mean (%CV) [min-max] POSANOL® Pharmacokinetic Parameters Following Single-Dose Suspension Administration of 200 mg and 400 mg Under Fed and Fasted Conditions

Dose (mg)	C_{max} (ng/mL)	t_{max}[a] (h)	AUC(I) (ng·h/mL)	CL/F (L/h)	$t_{1/2}$ (h)
200 mg fasted (n=20)[c]	132 (50) [45 - 267]	3.50 [1.5 - 36[b]]	4179 (31) [2,705 - 7,269]	51 (25) [28 - 74]	23.5 (25) [15.3 - 33.7]
200 mg nonfat (n=20)[c]	378 (43) [131 - 834]	4 [3 - 5]	10,753 (35) [4,579 - 17,092]	21 (39) [12 - 44]	22.2 (18) [17.4 - 28.7]
200 mg high fat (54 gm fat) (n=20)[c]	512 (34) [241 - 1,016]	5 [4 - 5]	15,059 (26) [10,341 - 24,476]	14 (24) [8.2 - 19]	23.0 (19) [17.2 - 33.4]
400 mg fasted (n=23)[d]	121 (75) [27 - 366]	4 [2 - 12]	5258 (48) [2,834 - 9,567]	91 (40) [42 - 141]	27.3 (26) [16.8 - 38.9]
400 mg with liquid nutritional supplement (14 gm fat) (n=23)[d]	355 (43) [145 - 720]	5 [4 - 8]	11,295 (40) [3,865 - 20,592]	43 (56) [19 - 103]	26.0 (19) [18.2 - 35.0]

a: Median [min-max]
b: The subject with t_{max} of 36 hrs had relatively constant plasma levels over 36 hrs (1.7 ng/mL difference between 4 hrs and 36 hrs)
c: n=15 for AUC(I), CL/F and $t_{½}$
d: n=10 for AUC(I), CL/F and $t_{½}$

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

Distribution:
POSANOL® has a mean (CV%) volume of distribution of 287 L (24%) in healthy volunteers.

POSANOL® is highly bound to human proteins (> 98%), predominantly to albumin.

Metabolism:
POSANOL® primarily circulates as the parent compound in plasma. Of the circulating metabolites, the majority are glucuronide conjugates formed via UDP glucuronidation (phase 2 enzymes). POSANOL® 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.

POSANOL® 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 POSANOL® is an inhibitor primarily of CYP3A4. A clinical study in healthy volunteers also indicates that POSANOL® 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 POSANOL®.

Elimination:
POSANOL® Solution for Injection is eliminated with a mean terminal half-life (t½) of 27 hours and a total body clearance (CL) of 7.3 L/h.

POSANOL® 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).

POSANOL® Delayed-Release Tablet is eliminated with a mean half-life (t½) ranging between 26 and 31 hours and a mean apparent clearance ranging from 7.5 to 11 L/hr.

POSANOL® Oral Suspension is eliminated with a mean half-life (t½) of 35 hours (range 20 to 66 hours) and apparent total body clearance (CL/F) of 32 L/hr.

No additional clinical radioactivity studies have been performed with POSANOL® Solution for Injection, as data obtained with the oral suspension are considered applicable. The total cumulative excretion should not change after POSANOL® Solution for Injection administration, but excretion in urine may be slightly higher.

Special Populations and Conditions

- **Pediatrics:** The safety and effectiveness of POSANOL® Solution for Injection in pediatric patients below the age of 18 years of age has not been established. POSANOL® Solution for Injection should not be used in pediatric patients because of pre-clinical safety concerns (see DETAILED PHARMACOLOGY).

  Use of POSANOL® Delayed-Release Tablet in patients 13 to 17 years of age is supported by evidence from adequate and well-controlled studies of POSANOL® Oral Suspension in adults.

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

- **Geriatrics:** Of the 279 patients treated with POSANOL® Solution for Injection, 52 (19%) were greater than 65 years of age. The pharmacokinetics of POSANOL® Solution for Injection 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 POSANOL® Solution for Injection in geriatric patients.

  Of the 230 patients treated with POSANOL® Delayed-Release Tablets, 38 (17%) were greater than 65 years of age. The pharmacokinetics of POSANOL® 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.

The pharmacokinetics of POSANOL® Oral Suspension are comparable in young and elderly subjects (≥ 65 years of age). No adjustment in the dosage of POSANOL® is necessary in elderly patients (≥ 65 years of age) based on age.

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

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

- **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 POSANOL® Oral Suspension be used with caution in patients with hepatic impairment (see 7 WARNINGS and PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

  Similar recommendations apply to POSANOL® Delayed-Release Tablets; however, a specific study has not been conducted with POSANOL® Delayed-Release Tablets.

  Similar recommendations apply to POSANOL® Solution for Injection; however, a specific study has not been conducted with the POSANOL® Solution for Injection.

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

  Similar recommendations apply to POSANOL® Delayed-Release Tablets; however, a specific study has not been conducted with POSANOL® Delayed-Release Tablets.

  A specific study has not been conducted with POSANOL® Solution for Injection in patients with moderate and severe renal impairment (see 7 WARNINGS and PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

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

11 STORAGE, STABILITY AND DISPOSAL

Storage

POSANOL® Solution for Injection
Store refrigerated at 2°-8°C.

POSANOL® Delayed-Release Tablets
Store at room temperature (15 to 30°C). Do not use past expiry date on the label.

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

Shelf life

POSANOL® Solution for Injection
If not used immediately, the diluted solution can be stored up to 24 hours refrigerated 2°-8°C.

POSANOL® Oral Suspension
After first opening the container: 4 weeks.

12 SPECIAL HANDLING INSTRUCTIONS

POSANOL® Tablets
No special requirements.

POSANOL® Oral Suspension
The oral suspension must be shaken well before each use.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

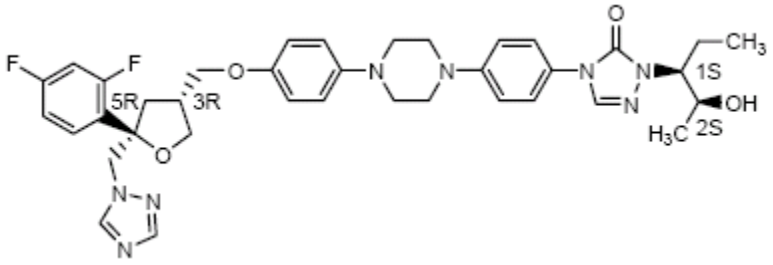
Drug Substance

Proper name: Posaconazole

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

Molecular formula and molecular mass: $C_{37}H_{42}F_2N_8O_4$ 700.8

Structural formula:



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

Product Characteristics:

pH and pKa values:

pH: 5.9 (10 mg/mL aqueous slurry)

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

Melting range: 167.9°C - 169.2°C

14 CLINICAL TRIALS

Pharmacokinetics and Safety of Posaconazole Solution for Injection in Patients

Solution for Injection Study 1

Solution for Injection Study 1 was an open-label, sequential, non-comparative multi-centre study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole solution for injection. The study was conducted in 4 Cohorts of a similar patient population to that previously studied in the pivotal posaconazole oral suspension clinical program.

Cohorts 0, 1, and 2 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 Cohorts 1 and 2: 200 mg BID on Day 1, followed by 200 mg QD thereafter (Cohort 1) and 300 mg BID on Day 1, followed by 300 mg QD thereafter (Cohort 2).

The Cohort 3 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 Cohorts 1 and 2, all subjects in Cohort 3 received 300 mg BID on Day 1, followed by 300 mg QD thereafter.

The posaconazole solution for injection was administered via a central line.

The total subject population (n=237) had a mean age of 51 years (range = 18-82 years), 95% were White, the major ethnicity was not Hispanic or Latino (92%), and 55% were male. The study treated 155 (65%) subjects with AML or MDS, and 82 (35%) subjects with HSCT, as the primary diseases at study entry.

The serial PK analysis demonstrated that 94% of the subjects treated with the 300 mg QD dose attained steady state Cavg between 500-2,500 ng/mL. This exposure target was selected based on PK/PD considerations with posaconazole oral suspension. 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 Cavg at steady state of 1,500 ng/mL. The PK findings from the Solution for Injection Study 1 support a 300-mg daily dose of posaconazole IV solution for use in prophylaxis.

Pharmacokinetics and Safety of Posaconazole Delayed-Release Tablets in Patients

Study P05615

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

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

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

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

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

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

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

Pharmacokinetics and Safety of Posaconazole Oral Suspension in Patients
Study P01899 and Study C/I98-316

Two large, randomised, controlled studies were conducted using posaconazole oral suspension as prophylaxis for the prevention of IFIs among patients at high risk.

Study demographics and trial design

Table 20 - Summary of Patient Demographics and Trial Design for Pivotal Study P01899

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number randomized [treated])	Mean age (Range)	Gender
P01899	evaluator-blind; active-control	Dosage: posaconazole: 200 mg TID[a]; fluconazole: 400 mg QD[b] or itraconazole: 200 mg BID[c] Route of administration: oral Duration: up to 84 days	n=602 [589] posaconazole: 304 [297] FLU/ITZ: 298 [292]	posaconazole: 49 (13 - 82) FLU/ITZ: 50 (13 - 81)	posaconazole: Men: 158 Women: 146 FLU/ITZ: Men: 160 Women: 138

a: TID = three times a day
b: QD = once daily
c: BID = twice a day
FLU: fluconazole, ITZ: itraconazole

Study P01899 was a randomised, evaluator-blinded study that compared posaconazole oral suspension (200 mg 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 AML or MDS. The primary efficacy endpoint was the incidence of proven/probable IFIs as determined by an independent, blinded external expert panel during the on-treatment period. A key secondary endpoint was the incidence of proven/probable IFIs at 100 days post-randomization. The mean duration of therapy was comparable between the two treatment groups (29 days, posaconazole; 25 days, fluconazole/itraconazole).

Table 21 - Summary of Patient Demographics and Trial Design for Pivotal Study C/I98-316

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number randomized [treated])	Mean age (Range)	Gender
C/I98-316	double-blind; active-control	Dosage: posaconazole: 200 mg TID[a]; fluconazole: 400 mg QD[b] Route of administration: oral Duration: up to 16 weeks	n = 600 [579] posaconazole: 301 [291] fluconazole: 299 [288]	posaconazole: 42.2 years (13-72 years) fluconazole: 40.4 years (13-70 years)	posaconazole: Men: 203 Women: 98 fluconazole: Men: 187 Women: 112

a: TID = three times a day
b: QD = once daily

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 primary efficacy endpoint was the incidence of proven/probable IFIs at 16 weeks post-randomization as determined by an independent, blinded external expert panel. A key secondary endpoint was the incidence of proven/probable IFIs during the on-treatment period (first dose to last dose of study medication + 7 days). The mean duration of therapy was comparable between the two treatment groups (80 days, posaconazole; 77 days, fluconazole).

Study results

Prophylaxis of IFIs

In both prophylaxis studies, aspergillosis was the most common breakthrough infection. There were significantly fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients receiving fluconazole or itraconazole. See Tables 22 and 23 for results from both studies.

Table 22 - Results from Clinical Study C/I98-316 in Prophylaxis of IFIs

Study C/I 98316	posaconazole	fluconazole	P-Value
Proportion (%) of Patients With Proven/Probable IFIs			
On-Treatment Period			
All IFIs	7/291 (2)	22/288 (8)	0.0038
Aspergillus	3 (1)	17 (6)	0.0013
Candida	1 (< 1)	3 (1)	
Other	3 (1)	2 (< 1)	
Fixed-Time Period			

All IFIs	16/301 (5)	27/299 (9)	0.0740
Aspergillus	7 (2)	21 (7)	0.0059
Candida	4 (1)	4 (1)	
Other	5 (2)	2 (< 1)	

Table 23 - Results from Clinical Study P01899 in Prophylaxis of IFIs

Study P01899	posaconazole oral suspension	fluconazole or itraconazole	fluconazole	Itraconazole	P-Value
Proportion (%) of Patients With Proven/Probable IFIs					
On-Treatment Period					
All IFIs	7/304 (2)	25/298 (8)	19/240 (8)	6/58 (10)	< 0.001
Aspergillus	2 (1)	20 (7)	15 (6)	5 (9)	< 0.001
Candida	3 (1)	2 (1)	2 (1)	0	
Other	2 (1)	3 (1)	2 (1)	1 (2)	
Fixed-Time Period					
All IFIs	14/304 (5)	33/298 (11)	26/240 (11)	7/58 (12)	
Aspergillus	4 (1)	26 (9)	20 (8)	6 (10)	
Candida	8 (3)	4 (1)	4 (2)	0	
Other	2 (1)	3 (1)	2 (1)	1 (2)	

In Study P01899, a significant decrease in all-cause mortality in favour of posaconazole was observed [posaconazole 49/304 (16%) vs. fluconazole/itraconazole 67/298 (22%) *P* = 0.048]. Based on Kaplan-Meier estimates, the probability of survival up to day 100 after randomization, was significantly higher for posaconazole recipients; this survival benefit was demonstrated when the analysis considered all causes of death (*P* = 0.0354) as well as IFI-related deaths (*P* = 0.0209).

In Study C/I98-316, overall mortality was similar (posaconazole, 25%; fluconazole, 28%); however, the proportion of IFI-related deaths was significantly lower in the posaconazole group (4/301) compared with the fluconazole group (12/299; *P* = 0.0413).

Study P00041

Study demographics and trial design

Table 24 – Summary of Patient Demographics and Trial Design for Pivotal Study P00041

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
P00041	open-label; non-comparative	Dosage: 800 mg/day (posaconazole oral suspension was taken with food or nutritional supplement) Route of administration: oral Duration: maximum of 12 months	n = 330	43.6 years (8 - 84 years)	Men: 217; Women: 113

Patients were enrolled to receive posaconazole for treatment if the investigator confirmed a diagnosis of invasive aspergillosis, in accordance with the European Organization for Research and Treatment-Mycoses Study Group (EORTC-MSG) criteria, and if they were refractory to at least 7 days of antifungal therapy (defined as failure to improve or as disease progression) or were intolerant of conventional therapy, as defined by renal impairment, severe infusion-related toxicity, or other organ dysfunction or were considered to be at high risk for development of toxicity on the basis of underlying disease or concomitant receipt of nephrotoxic medications. The majority of patients received amphotericin B (including lipid formulations, total n=98) and/or itraconazole (total n=51) as prior therapy for invasive aspergillosis prior to treatment with posaconazole. Of the 104 posaconazole-treated subjects who received prior antifungal therapy, five patients were refractory to voriconazole and five were refractory to an echinocandin. Patients were administered posaconazole oral suspension 800 mg/day in divided doses. 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. The duration of previous antifungal therapy was similar in both the posaconazole and control populations. The median duration of posaconazole treatment (for treatment of all pathogens) in this study was 102.5 days (range 1-372 days). The median duration of posaconazole treatment (for the modified intent to treat subset) of patients with invasive aspergillosis was 56 days (range 1-372 days).

Study results

Invasive aspergillosis

The efficacy and survival benefit of oral posaconazole for the treatment of invasive aspergillosis in patients with disease refractory to amphotericin B (including liposomal formulations) (n=98), itraconazole (n=51), voriconazole (n=5) or echinocandins (n=5) or in patients who were intolerant of these medicinal products, was demonstrated in 107 patients. An independent expert panel reviewed

all patient data, including diagnosis of invasive aspergillosis, refractoriness and intolerance to previous therapy, and clinical outcome in a parallel and blinded fashion with an external control group of 86 patients (acquired via a retrospective review of medical records) treated with standard therapy mostly at the same time and at the same sites as the patients enrolled in the posaconazole trial. A success was defined as either complete resolution (complete response) or a clinically meaningful improvement (partial response) of all signs, symptoms and radiographic findings attributable to the fungal infection. Stable, non-progressive disease and failure were considered to be a non-success. Most of the cases of aspergillosis were considered to be refractory in both the posaconazole group (88%) and in the external control group (79%). The majority of the subjects (74% for posaconazole and 78% for control) had a pulmonary site of infection; of the remainder, 9% of the subjects in each group had disseminated fungal infection (with or without pulmonary involvement), and the remainder had extrapulmonary infections. Among the extrapulmonary infections, the CNS was the site of infection in four (4%) subjects in the posaconazole-treated group and two (2%) in the control group.

As shown in Table 25, a successful global response at end of treatment was seen in 42% of posaconazole-treated patients compared to 26% of the external group (P = 0.006).

This was not a prospective, randomized, controlled study and so all comparisons with the external control group should be viewed with caution.

Table 25 - Overall Efficacy of posaconazole at the End of Treatment for Invasive Aspergillosis in Comparison to an External Control Group

	posaconazole		**External Control Group**	
Overall Response	45/107 (42%)		22/86 (26%)	
	Odds Ratio 4.06† (95% CI: 1.50, 11.04) P = 0.006			
Survival at day 365	**(38%)**		**(22%)**	
Success by Species All mycologically confirmed *Aspergillus* species (spp.)*	34/76	(45%)	19/74	(26%)
A. fumigatus	12/29	(41%)	12/34	(35%)
A. flavus	10/19	(53%)	3/16	(19%)
A. terreus	4/14	(29%)	2/13	(15%)
A. niger	3/5	(60%)	2/7	(29%)

* includes other less common species or species unknown

†Odds Ratio represents the response rate of posaconazole versus control and is based on a logistic regression model that adjusts for key prognostic variables (age, site of infection, baseline neutropenia, duration of prior antifungal therapy, region of enrollment, and basis of enrollment (refractory disease or intolerance), and 5 other variables that showed imbalance between the treatment groups (race, enrollment time, nonmalignant hematologic disorder, renal disease, and hepatic disease).

The cumulative rates of survival at 30 days and at the end of posaconazole oral suspension therapy were 74% and 38%, respectively; for control subjects, those survival rates were 49% and 22%,

respectively. As determined on the basis of a log rank statistic, a survival benefit for posaconazole compared to standard treatment was observed ($P < 0.001$).

Other Serious Fungal Pathogens
Posaconazole oral suspension has been shown to be effective against the following additional pathogens when other therapy had been ineffective or when the patient had developed intolerance of the prior therapy:
- *Zygomycosis* (n=11) with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B.
- *Fusariosis* (n=18) with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B.
- *Chromoblastomycosis/mycetoma* (n=11) with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole.
- *Coccidioidomycosis* (n=16) with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these therapies.

Study C/I97-331

Study demographics and trial design

Table 26 - Summary of Patient Demographics and Trial Design for Pivotal Study C/I97-331

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number randomized [treated])	Mean age (Range)	Gender
C/I97-331	evaluator-blind; active-control	Dosage (for posaconazole and fluconazole): 100 mg BID[a] for 1 day followed by 100 mg QD[b] for 13 days (posaconazole and fluconazole were taken with food or nutritional supplement) Route of administration: oral Duration: 14 days	n=366 [350] posaconazole: 182 [178] fluconazole: 184 [172]	posaconazole: 36.4 years (20-61 years) fluconazole: 37.6 years (19-78 years)	posaconazole: Men:131; Women: 47 fluconazole: Men: 131 Women: 41

a: BID = twice a day
b: QD = once daily

A randomised, evaluator-blind, controlled study was completed in HIV-infected patients with azole-susceptible OPC. The primary efficacy variable was the clinical success rate (defined as cure or

improvement) after 14 days of treatment. Patients were treated with posaconazole or fluconazole oral suspension (both- posaconazole and fluconazole were given as follows: 100 mg BID for 1 day followed by 100 mg QD for 13 days).

Study results

Treatment of Azole-susceptible OPC

The clinical and mycological response rates from the above study are shown in the Table 27 below. Posaconazole and fluconazole demonstrated equivalent clinical success rates at Day 14 as well as 4 weeks after the end of treatment. However, posaconazole oral suspension demonstrated a significantly better sustained mycological response rate 4 weeks after the end of treatment than fluconazole.

Table 27 - Clinical Success Rates and Mycological Response Rates in OPC

Endpoint	posaconazole	fluconazole
Clinical Success Rate at End of Therapy (Day 14)	91.7% (155/169)	92.5% (148/160)
Clinical Success Rate 4 Weeks After End of Treatment	68.5% (98/143)	61.8% (84/136)
Mycological Response Rate at End of Therapy (Day 14)	68.0% (115/169)	68.1% (109/160)
Mycological Response Rate 4 Weeks After End of Treatment*	40.6% (41/101)	26.4% (24/91)

*Statistically significant (P = 0.0376)

Clinical success rate was defined as the number of cases assessed as having a clinical response (cure or improvement) divided by the total number of cases eligible for analysis.

Mycological response rate was defined as mycological success (≤ 20 CFU/mL) divided by the total number of cases eligible for analysis.

Study C/I97-330

Study demographics and trial design

Table 28 - Summary of Patient Demographics and Trial Design for Pivotal Study C/I97-330

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number randomized [treated])	Mean age (Range)	Gender
C/I97-330	open-label; non-comparative	Dosage: 400 mg BID Route of administration: oral Duration: 4 weeks with an option for further treatment during a 3-month maintenance period	n=199 [199]	38.8 years (20 - 69 years)	Men: 174 Women: 25

The primary efficacy parameter in Study C/I97-330 was the clinical success rate (cure or improvement) after 4 weeks of treatment. HIV-infected patients were treated with posaconazole oral suspension 400 mg BID with an option for further treatment during a 3-month maintenance period.

Study results

Treatment of Azole-refractory OPC

In Study C/I97-330, a 75% (132/176) clinical success rate and a 36.5% (46/126) mycological response rate (≤ 20 CFU/mL) were achieved after 4 weeks of posaconazole treatment. Clinical success rates ranged from 71% to 100%, inclusive, for all azole-resistant *Candida* species identified at Baseline, including *C. glabrata* and *C. krusei*.

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.

Posaconazole Solution for injection exhibits dose proportional pharmacokinetics after single doses between 200 and 300 mg in healthy volunteers.

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.

The exposure to posaconazole following administration of 400 mg oral suspension BID was ~ 3 times higher in healthy volunteers than in patients, without additional safety findings at the higher concentrations.

Special Populations and Conditions

Pediatrics
The safety and effectiveness of POSANOL® Solution for Injection in pediatric patients below the age of 18 years of age has not been established. POSANOL® Solution for Injection should not be used in pediatric patients because of pre-clinical safety concerns.

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

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

Geriatrics
Of the 279 patients treated with POSANOL® Solution for Injection, 52 (19%) were greater than 65 years of age. The pharmacokinetics of POSANOL® Solution for Injection 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 POSANOL® Solution for Injection in geriatric patients.

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.

An increase in C_{max} (26%) and AUC (29%) was observed in elderly subjects (24 subjects ≥ 65 years of age) receiving the posaconazole oral suspension relative to younger subjects (24 subjects 18 – 45 years of age). However, in a population pharmacokinetic analysis (Study P01899) age did not influence the pharmacokinetics of posaconazole oral suspension. Further, in clinical efficacy trials, the safety profile of posaconazole oral suspension between the young and elderly patients was similar. Therefore, no dose adjustment is required for age.

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

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

Animal Pharmacology
Posaconazole Solution for Injection
In a nonclinical study using IV administration of posaconazole in very young dogs (dosed from 2 to 8 weeks of age), an increase in the incidence of brain ventricle enlargement was observed in treated animals as compared with concurrent control animals. No difference in the incidence of brain ventricle enlargement between control and treated animals was observed following the subsequent 5-month treatment-free period. There were no neurologic, behavioral or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to juvenile dogs (4 days to 9 months of age).
The clinical significance of this finding is unknown; therefore, the use of posaconazole solution for injection to patients under 18 is not recommended.

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

autonomic function, compared with vehicle-treated rats. A single dose of 3 or 10 mg/kg did not affect renal function.

In vitro effects of posaconazole on ventricular repolarization were evaluated by measuring both the action potential and the recombinant hERG channel current. In Purkinje fibers isolated from dog heart, exposure to posaconazole at measured concentrations of 25 ng/mL (36 nM), 69 ng/mL (98 nM) and 365 ng/mL (521 nM) induced a small (< 10%) but statistically significant increase in action potential duration at 60% (APD_{60}) and/or 90% (APD_{90}) repolarization. In mouse L-929 cells stably transfected with the human α-subunit (hERG) of the cardiac delayed rectifier, I_{Kr}, a measured concentration of 770 ng/mL (1.1 μM) posaconazole decreased hERG current by 7%. Accounting for protein binding, the drug concentration in the hERG assay was 18-times the free posaconazole Cmax value in healthy volunteers. Changes of the magnitude noted in the recombinant hERG channel and isolated Purkinje fiber systems would be unlikely to elicit QT interval prolongation *in vivo*.

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

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

15 MICROBIOLOGY

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

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

Additionally, the following *in vitro* data are available (see Tables 24 and 25). 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 29.

Table 29 - MIC_{90} Values for Mould Strains Tested

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

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

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

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

The posaconazole MIC_{90} values for yeast strains tested are summarized in Table 30.

Table 30 - MIC_{90} Values for Yeast Strains Tested

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

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

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

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

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

Drug Resistance

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

Antifungal medicinal products combinations

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

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

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

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

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

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

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

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

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

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

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

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

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

17 SUPPORTING PRODUCT MONOGRAPHS

Not Applicable.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

POSANOL®

Posaconazole, Solution for Injection, Delayed-Release Tablets, Oral Suspension

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

Serious Warnings and Precautions

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

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

  If you are taking POSANOL with any of the following your healthcare professional may have to reduce your dose and monitor you closely:
  - cyclosporine or tacrolimus, used in transplant patients
  - vinca alkaloids, including vincristine, used to treat cancer
  - venetoclax, used to treat cancer
  - midazolam, used as a sedative to help you sleep
  - calcium channel blockers, used to treat high blood pressure

- **Heart Problems:** POSANOL can cause serious heart problems including problems with your heart rhythm. Tell a healthcare professional immediately if you have any of the following symptoms while you are being treated with POSANOL:
  - very slow, fast or irregular heartbeat
  - shortness of breath
  - light-headedness
  - fainting

- **Liver Problems (including Liver Failure):** POSANOL can cause serious liver problems including liver failure. Your healthcare professional will do blood tests to see how well your liver is working before you start treatment with POSANOL and while you are being treated. Tell a healthcare professional immediately if you have any of the following symptoms while you are being treated with POSANOL:
  - dark colored urine
  - pale stools
  - yellowing of the skin and eyes
  - abdominal pain
  - nausea and vomiting

What is POSANOL used for?

- POSANOL Solution for Injection, Delayed-Release Tablets and Oral Suspension are used:

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

- POSANOL Oral Suspension can also be used to treat fungal infections in the mouth or throat area known as "thrush", caused by *Candida*.
- POSANOL Solution for Injection can be used in patients 18 years of age and older.
- POSANOL Delayed-Release Tablets and Oral Suspension can be used in patients 13 years of age and older.

How does POSANOL work?
POSANOL belongs to a group of medicines called triazole antifungal agents. POSANOL works by killing or stopping the growth of some types of fungi that can cause infections in humans.

What are the ingredients in POSANOL?
Medicinal ingredients: Posaconazole

Non-medicinal ingredients:
POSANOL Solution for Injection: Betadex Sulfobutyl Ether Sodium (SBECD), edetate disodium, hydrochloric acid, sodium hydroxide, and water for injection.

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

POSANOL Oral Suspension: Artificial cherry flavor, citric acid monohydrate, glycerin, liquid glucose, polysorbate 80, purified water, simethicone, sodium benzoate, sodium citrate dihydrate, titanium dioxide, and xanthan gum.

POSANOL comes in the following dosage forms:
POSANOL Solution for Injection: 300 mg / vial (18 mg / mL)

POSANOL Delayed-Release Tablets: 100 mg

POSANOL Oral Suspension: 40 mg / mL

Do not use POSANOL® if:
- you are hypersensitive (allergic) to posaconazole or to any of the other ingredients in POSANOL (see **What are the ingredients in POSANOL?** section).
- you are taking any of the following medicines:
  - ergot alkaloids, used to treat migraines
  - cisapride, used to treat stomach problems
  - pimozide, used to treat mental health problems

- quinidine, used to treat irregular heartbeat
- terfenadine and astemizole, used to treat allergies
- certain statin medicines that lower cholesterol, such as atorvastatin, lovastatin, simvastatin
- sirolimus, used in transplant patients

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

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

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

Other warnings you should know about:

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

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

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

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

The following may interact with POSANOL:

- rifabutin or rifampin, antibiotics used to treat bacterial infections like tuberculosis
- phenytoin, used to prevent seizures
- cimetidine and metoclopramide, used to treat stomach problems – (only if you are being treated with POSANOL Oral Suspension)
- proton pump inhibitors, such as esomeprazole – (only if you are being treated with POSANOL Oral Suspension)
- efavirenz, fosamprenavir, atazanavir and atazanavir/ritonavir, used to treat HIV infection
- vinca alkaloids, including vincristine, used to treat cancer
- venetoclax, used to treat cancer
- cyclosporine and tacroliumus, used in transplant patients
- midazolam, used as a sedative to help you sleep
- statins, used to treat high cholesterol
- calcium channel blockers, used to treat high blood pressure
- digoxin, used to treat heart failure

How to take POSANOL:

- POSANOL must only be used as directed by your healthcare professional.
- Your healthcare professional will decide how long you are to be treated with POSANOL and your dose depending on your condition and how you respond to treatment.
- Do not stop treatment early because your infection may not be fully cured. Even if you feel well, your immune system may still be weakened and you may still need treatment to prevent an infection.
- Do not switch between POSANOL Delayed-Release Tablets and POSANOL Oral Suspension without talking to your healthcare professional. The dosing is different for the 2 formulations.
- If you are being treated with POSANOL Solution for Injection:
  - It will be given to you by a healthcare professional directly into your vein (IV).
- If you are being treated with POSANOL Delayed-Release Tablets:
  - POSANOL Delayed-Release Tablets can be taken with or without food.
  - POSANOL 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.
- If you are being treated with POSANOL Oral Suspension:
  - Shake POSANOL Oral Suspension well before each use.

- Take POSANOL Oral Suspension with a meal or with a nutritional supplement if you are unable to eat a full meal.

Usual dose:

POSANOL Solution for Injection:
- You will be given 300 mg twice on the first day.
- After the first day you will be given 300 mg once a day.

POSANOL Delayed-Release Tablets:
- Take 300 mg (three 100 mg tablets) twice on the first day.
- After the first day take 300 mg (three 100 mg tablets) once a day.

POSANOL Oral Suspension:

Indication	Dose
Prevention of Fungal Infections	Take 200 mg (one 5 mL spoonful) three times a day with food or nutritional supplement.
Treatment of Fungal Infections Not Treated by Other Medicines	Take 400 mg (two 5 mL spoonfuls) twice a day with food or with a nutritional supplement. If you are not able to take food or nutritional supplement, your healthcare professional will tell you to take 200 mg (one 5 mL spoonful) four times a day.
Initial Treatment of Thrush	Take 100 mg (2.5 mL) twice on the first day. After the first day, take 100 mg (2.5 mL) once a day. Always take with food or nutritional supplement.

Overdose:
Take your bottle of POSANOL with you.

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

Missed Dose:
If you miss taking a dose of POSANOL, take it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take a double dose to make up for the forgotten dose.

What are possible side effects from using POSANOL?
These are not all the possible side effects you may have when taking POSANOL®. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:
- diarrhea
- gas

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

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

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Allergic reaction: severe skin blistering, peeling, rash, swollen lips, mouth and throat, difficulty in breathing.			✓
Liver problems (including liver failure): dark colored urine, pale stools, yellowing of the skin and eyes, abdominal pain, nausea, vomiting.			✓

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

Reporting Side Effects

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

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

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

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

POSANOL Solution for Injection:
Your healthcare professional will store POSANOL Solution for Injection.

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

POSANOL Oral Suspension:
Store at room temperature (15 to 30°C). Do not freeze. Once opened, use the suspension within 4 weeks.

If you want more information about POSANOL:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this

Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.merck.ca, or by calling 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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