

PRODUCT MONOGRAPH

 **POSANOL™**

posaconazole

Oral Suspension 40 mg/mL

Antifungal Agent

™ Trademark of Schering-Plough Ltd., used under license by
Schering-Plough Canada Inc.

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POSANOL™

posaconazole

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	suspension, 40 mg/mL posaconazole	For a complete listing see the Dosage Forms, Composition and Packaging section of the product monograph.

INDICATIONS AND CLINICAL USE

POSANOL™ (posaconazole) is indicated for:

- prophylaxis of *Aspergillus* and *Candida* infections in patients, 13 years of age and older, 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 13 years of age or older 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.
- treatment of oropharyngeal candidiasis (OPC) in patients 13 years of age or older.

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

Geriatrics (≥ 65 years of age):

Limited evidence from clinical studies and experience suggests that use in the geriatric population is associated with no overall differences in safety or effectiveness.

Pediatrics (13 - 17 years of age):

Safety and effectiveness in pediatric subjects below the age of 13 years have not been studied. A limited number of subjects between the ages of 13 and 17 have received POSANOL™ 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.

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 the Drug Interactions section of the product monograph).
- Co-administration of POSANOL™ and certain medicinal products metabolized through the CYP3A4 system: terfenadine¹, astemizole², cisapride³, pimozone, and quinidine. Although not studied *in vitro* or *in vivo*, co-administration of these CYP3A4 substrates may result in increased plasma concentrations of those medicinal products, leading to potentially serious and/or life threatening adverse events, such as QT prolongation and rare occurrences of torsade de pointes (see the Drug Interactions section of the product monograph).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

General

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.

¹ Please note that terfenadine is no longer available on the Canadian market.

² Please note that astemizole is no longer available on the Canadian market.

³ Please note that cisapride is no longer available on the Canadian market.

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 isoenzymes may be affected by POSANOL™ levels, with possible resulting QT effects. Such drugs include tacrolimus, HIV protease inhibitors and macrolide antibiotics. (See the Contraindications section, the Drug Interactions section and the Action and Clinical Pharmacology section of the product monograph.)

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 the Adverse Reactions - Less Common Clinical Trial Adverse Drug Reactions (< 2%) section of the product monograph.)

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.

Special Populations

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 the Toxicology section of the product monograph). 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.

Nursing Women: POSANOL™ is excreted into the milk of lactating rats (see the Toxicology section of the product monograph). 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, tacrolimus, and sirolimus should be performed when POSANOL™ therapy is initiated. (See the Drug Interactions section of the product monograph.)

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of POSANOL™ therapy has been assessed in 1844 patients. 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%).

Clinical Trial Adverse Drug Reactions

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

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) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day [BID]) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes. 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 three times a day) with fluconazole capsules (400 mg once daily) 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 1 - Treatment-related adverse reactions reported in POSANOL™, 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 aphthous	1 (<1)	0	1 (2)
gastric disorder	0	0	1 (2)
rectal pain	0	0	1 (2)
General and administration site conditions			
fatigue	7 (1)	7 (1)	0
weakness	3 (<1)	5 (1)	0
asthenia	2 (<1)	3 (1)	0
fever	2 (<1)	3 (1)	0
Hepatobiliary			
bilirubinemia	15 (2)	10 (2)	3 (5)
hepatic enzymes increased	15 (2)	10 (2)	0
ALT (SGPT) increased	16 (3)	8 (1)	1 (2)
gamma glutamyl transferase (GGT) increased	14 (2)	8 (1)	1 (2)
AST (SGOT) increased	14 (2)	7 (1)	1 (2)
hepatic function abnormal	2 (<1)	5 (1)	0
jaundice	5 (1)	2 (<1)	0
hepatocellular damage	5 (1)	0	0

Adverse Reactions	POSANOL™ n=605 (%)	fluconazole n=539 (%)	itraconazole n=58 (%)
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			
coughing	2 (<1)	2 (<1)	1 (2)
Skin and subcutaneous tissue			
rash	12 (2)	10 (2)	1 (2)
pruritus	4 (1)	5 (1)	0
rash pruritic	3 (<1)	5 (1)	0
rash maculopapular	5 (1)	2 (<1)	0
sweating increased	1 (<1)	0	1 (2)
cellulitis	0	0	1 (2)
Investigations			
phosphatase alkaline 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, 400 mg administered 4 times daily, 800 mg administered twice daily for 2 days followed by 400 mg administered twice daily, 600 mg administered twice daily, 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™ 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 once a day 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™ 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 2 - Treatment-related adverse reactions reported in POSANOL™-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)
Musculoskeletal System					
Myalgia	0	1 (<1)	1 (<1)	0	4 (2)

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 (%)
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					
phosphatase alkaline 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™.

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, heptosplenomegaly, jaundice, liver tenderness.

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

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

Injury and poisoning: drug toxicity NOS, ecchymoses, overdose NOS, skin trauma.

Metabolism and nutrition: amylase increased, dehydration, electrolyte abnormality, hypercalcemia, hypercholesterolemia, hypercholesterolemia aggravated, hyperlipemia, hypernatremia, hyperphosphatemia, hyperproteinemia, hypertriglyceridemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hyponatremia, hypophosphatemia, lipase increased, malnutrition, metabolic acidosis, metabolic disorder NOS, NPN increased, renal tubular acidosis, vitamin K deficiency.

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

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

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

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

Reproductive system and breast: balanoposthitis, breast pain.

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

Surgical and medical procedures: cardioversion.

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

Clinical Chemistry Findings

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

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

Post-Market Adverse Drug 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);
- **Cardiovascular:** QT prolongation, torsades de pointes;
- **Infections and infestations:** *Trichosporon* sepsis.

DRUG INTERACTIONS

Serious Drug Interactions

Contraindicated Drugs: ergot alkaloids, terfenadine, astemizole, cisapride, pimozone and quinidine (see the Contraindications section of the product monograph)

Drugs whose concomitant use should be avoided: cimetidine, rifabutin and phenytoin (see Tables 3 and 4 in the Drug Interactions section of the product monograph)

Drugs whose concomitant use requires consideration of dose reduction at initiation of concomitant treatment and close therapeutic monitoring of drug levels during treatment: cyclosporine, tacrolimus and sirolimus (see Table 4 in the Drug Interactions section of the product monograph)

Drugs whose concomitant use requires consideration of dose reduction and close monitoring for adverse events during treatment: vinca alkaloids, midazolam, HMG - CoA reductase inhibitors (statins), calcium channel blockers (see Table 4 in the Drug Interactions section of the product monograph)

Overview

Effect of Other Drugs on POSANOL™ Pharmacokinetics

POSANOL™ is metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein efflux. Therefore, inhibitors or inducers of these clearance pathways may affect 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 an inhibitor of CYP3A4 and thus the plasma levels of medicinal products that are metabolized through this enzyme pathway may increase when administered with POSANOL™.

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 POSANOL™ tablet, which is 36% less bioavailable than the suspension. The majority of drug interaction studies were performed using the 200mg QD schedule whereas the recommended dosing schedule depends on the indication and may be as high as 400mg BID (rIFIs) or 200mg TID (prophylaxis). As a

result of these limitations, the maximal exposure was not studied in the majority of these drug interaction studies.

Table 3 - 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.
Cimetidine (Alteration of Gastric pH)	clinical trial	400 mg BID ^d x 10 days	200 mg (tablets) QD x 10 days	↓ 39% (0.61; 0.53-0.70)	↓ 39% (0.61; 0.54-0.69)	Concomitant use of POSANOL™ and cimetidine should be avoided unless the benefit outweighs the risk.
Antacids	clinical trial			No clinically relevant effect on POSANOL™ bioavailability was observed when administered with an antacid.		No differences in prophylactic efficacy or safety were observed, suggesting these agents may be used concomitantly with POSANOL™

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)	
H ₂ receptor antagonists (H2RA) other than cimetidine	clinical trial			No clinically relevant effect on POSANOL™ bioavailability was observed when administered with an H2RA other than cimetidine. The effect of other H2RA (e.g., famotidine, ranitidine) on POSANOL™ Cav was evaluated in a large prophylaxis study (Study P01899). The concomitant use of H2RA, other than cimetidine, did not affect POSANOL™ Cav.		No differences in prophylactic efficacy or safety were observed, suggesting these agents may be used concomitantly with POSANOL™.
Proton pump inhibitors (PPI)	clinical trial			No clinically relevant effect on POSANOL™ bioavailability was observed when administered with a PPI. The effect of other PPI (e.g., omeprazole) on POSANOL™ Cav was evaluated in a large prophylaxis study (Study P01899). The concomitant use of PPI was associated with an approximately 29 % reduction in the mean POSANOL™ plasma Cav.		No differences in prophylactic efficacy or safety were observed, suggesting these agents may be used concomitantly with POSANOL™.

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)	
Glipizide	clinical trial	10 mg single dose		Glipizide had no clinically significant effect on POSANOL™ 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.
Ritonavir	clinical trial	600 mg BID		Ritonavir had no clinically significant effect on POSANOL™ C _{max} and AUC.		No dose adjustments required.

a: Ratio Estimate = ratio of co-administered drug plus POSANOL™ to POSANOL™ alone for C_{max} or AUC

b: AUC = area under the plasma concentration time curve

c: QD = once daily

d: BID = twice a day

Table 4 - 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 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)	
Cyclosporine (inhibition of CYP3A4 by POSANOL™)	clinical trial	Stable maintenance dose in heart transplant recipients	200 mg (tablets) QD ^c x 10 days	<p>↑ cyclosporine whole blood trough concentrations</p> <p>Cyclosporine dose reductions of up to 29% were required</p>		When initiating treatment with 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.

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 (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.
Midazolam (inhibition of CYP3A4 by POSANOL™)	clinical trial	Single 30 min IV infusion of 0.05 mg/kg	200 mg (tablets) QD x 10 days	NA*	↑ 83% (1.83; 1.57-2.14)	Dose adjustments of benzodiazepines metabolized by CYP3A4 should be considered during co-administration with POSANOL™.
Phenytoin (inhibition of CYP3A4 by POSANOL™)	clinical trial	200 mg QD PO ^c 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		Although not studied <i>in vitro</i> or <i>in vivo</i> , POSANOL™ 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 the Contraindications section of the product monograph).

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)	
Terfenadine Astemizole Cisapride Pimozide Quinidine	theoretical	NA, since theoretical		Although not studied <i>in vitro</i> or <i>in vivo</i> , co-administration of POSANOL™ 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 the Contraindications section of the product monograph).
Sirolimus	theoretical	NA, since theoretical		Although not studied <i>in vitro</i> or <i>in vivo</i> , POSANOL™ may ↑ the plasma concentration of sirolimus.		Monitoring of sirolimus blood levels should be performed upon initiation, during co-administration, and at discontinuation of POSANOL™ treatment, with sirolimus doses adjusted accordingly.
Vinca alkaloids	theoretical	NA, since theoretical		Although not studied <i>in vitro</i> or <i>in vivo</i> , POSANOL™ may ↑ the plasma concentration of vinca alkaloids (e.g., vincristine and vinblastine), which may lead to neurotoxicity.		It is recommended that the dose adjustment of vinca alkaloids be considered.
HMG-CoA reductase inhibitors metabolized through CYP3A4	theoretical	NA, since theoretical		Although not studied <i>in vitro</i> or <i>in vivo</i> , ↑ HMG-CoA reductase inhibitor concentrations in plasma can be associated with rhabdomyolysis.		Dose adjustments of HMG-CoA reductase inhibitors metabolized by CYP3A4 should be considered during co-administration with POSANOL™.

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)	
Zidovudine (AZT) Lamivudine (3TC) Ritonavir 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), ritonavir (600 mg BID) and/or indinavir (800 mg every 8 h).	200 mg (tablets) QD ^c x 10 days	POSANOL™ had no clinically significant effect on the C _{max} and AUC of these medicinal products.		No dose adjustments required.
Calcium channel blockers metabolized through CYP3A4	theoretical	NA, since theoretical		Although not studied <i>in vitro</i> or <i>in vivo</i> , co-administration of POSANOL™ 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		POSANOL™ 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.

a: Ratio Estimate = ratio of co-administered drug plus POSANOL™ to POSANOL™ 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: PO = per os

* NA: Not applicable if administered as an IV

Drug-Food Interactions

Table 5 – 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	The AUC of POSANOL™ 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.	Each dose of POSANOL™ should be administered with food or nutritional supplement (see the Dosage and Administration section of the product monograph).

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Each dose of POSANOL™ 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, 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 the Drug Interactions section of the product monograph.)

Recommended Dose and Dosage Adjustment

Table 6 - Recommended Dose According to Indication

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 .
Refractory IFIs / Intolerant Patients with IFIs	400 mg (10 mL) twice a day. 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.
Oropharyngeal Candidiasis (OPC)	Loading dose of 100 mg (2.5 mL) twice a day on the first day, then 100 mg (2.5 mL) once a day for 13 days.

Increasing the total daily dose above 800 mg does not further enhance the exposure to POSANOL™.

Use in renal impairment

POSANOL™ is not significantly renally eliminated. No dose adjustment is required in patients with renal dysfunction. (See the Action and Clinical Pharmacology section of the product monograph.)

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 the Action and Clinical Pharmacology section of the product monograph). Use with caution in patients with severe hepatic impairment. (See the Action and Clinical Pharmacology section of the product monograph.)

Use in Pediatrics (13 - 17 years)

A total of 11 patients 13 - 17 years of age were treated with 800 mg/day in a study for IFIs. Additionally, 12 patients 13 - 17 years of age received 600 mg/day 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 the Action and Clinical Pharmacology section of the product monograph).

Missed Dose

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

Administration

Shake well before each use.

OVERDOSAGE

During clinical trials, patients who received POSANOL™ 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 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

POSANOL™ is a potent inhibitor of the enzyme lanosterol 14 α -demethylase, which catalyses an essential step in ergosterol biosynthesis. Consequently, POSANOL™ 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* POSANOL™ 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 POSANOL™ 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.

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 the Dosage and Administration section and the Action and Clinical Pharmacology – Pharmacokinetics section of the product monograph on recommended dose regimens and the effects of food on absorption).

Pharmacokinetics

The mean pharmacokinetic parameters in healthy volunteers following administration of POSANOL™ 400 mg BID for 7 days are displayed in Table 7.

Table 7- Mean Pharmacokinetic Parameters of POSANOL™ in Healthy Volunteers

Population	Dose	Mean (%CV)				
		C _{max} (ng/mL)	t _½ (h)	AUC _(τ) (ng·h/mL)	Clearance (L/h)	Volume of distribution (L)
Healthy Volunteers	400 mg BID (n=174)	2,850	35	29,453	32.3	1,744

Dose proportional increases in plasma exposure (AUC) to POSANOL™ 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 BID to 600 mg BID in febrile neutropenic patients or those with rIFIs.

Absorption: POSANOL™ is absorbed with a median T_{max} of ~3 to 5 hours. Dose proportional increases in plasma exposure (AUC) to POSANOL™ 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 C_{max} of POSANOL™ 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™ are approximately 3 times higher when administered with a liquid nutritional supplement (14 gm fat) relative to the fasted state (see Table 8). In order to assure attainment of adequate plasma concentrations, it is recommended to administer POSANOL™ with food or a nutritional supplement. (See the Dosage and Administration section of the product monograph.)

Table 8 - 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) [2705-7269]	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) [4579-17,092]	21 (39) [12-44]	22.2 (18) [17.4-28.7]
200 mg high fat (54 gm fat) (n=20) ^c	512 (34) [241-1016]	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) [2834-9567]	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) [3865-20,592]	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_{1/2}

d: n=10 for AUC(I), CL/F and t_{1/2}

Distribution: POSANOL™ has an apparent volume of distribution of 1,774 L, suggesting extensive extravascular distribution and penetration into the body tissues.

POSANOL™ is highly protein bound (>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.

Excretion: POSANOL™ is eliminated with a mean half-life (t_{1/2}) of 35 hours (range 20 to 66 hours) and a total body clearance (CL/F) of 32 L/hr. POSANOL™ is predominantly eliminated in the feces (71% of the radiolabeled dose up to 120 hours) with the major component eliminated as parent drug (66% of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 13% of the radiolabeled dose excreted in urine up to 120 hours (<0.2% of the radiolabeled dose is parent drug).

Summary of Pharmacokinetic Parameters

The mean (%CV) [min-max] POSANOL™ average steady-state plasma concentrations (Cav) 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 9.

Table 9 - The Mean (%CV) [min-max] POSANOL™ Steady-State Pharmacokinetic Parameters in Patients Following Oral Administration of Posaconazole 200 mg TID and 400 mg BID

Dose ^a	Cav (ng/mL)	AUC ^c (ng-h/mL)	CL/F (L/h)	V/F (L)	t _{1/2} (h)
200 mg TID ^b (n=252)	1103 (67) [21.5-3650]	ND ^f	ND ^f	ND ^f	ND ^f
200 mg TID ^c (n=215)	583 (65) [89.7-2200]	15,900 (62) [4100-56,100]	51.2 (54) [10.7-146]	2425 (39) [828-5702]	37.2 (39) [19.1-148]
400 mg BID ^d (n=23)	723 (86) [6.70-2256]	9093 (80) [1564-26,794]	76.1 (78) [14.9-256]	3088 (84) [407-13,140]	31.7 (42) [12.4-67.3]

Note: Cav based on observed data; other pharmacokinetic parameters based on estimates from population pharmacokinetic analyses

a: Oral suspension administration

b: Allogeneic hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease

c: Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes

d: Febrile neutropenic patients or patients with refractory invasive fungal infections, Cav n=24

e: AUC (0-24 hr) for 200 mg TID and AUC (0-12 hr) for 400 mg BID

f: Not done

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

Special Populations and Conditions

Pediatrics: 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: The pharmacokinetics of POSANOL™ 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.

Gender: The pharmacokinetics of POSANOL™ are comparable in men and women. No adjustment in the dosage of POSANOL™ is necessary based on gender.

Race: The AUC and C_{max} of POSANOL™ 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™ be used with caution in patients with hepatic impairment. (See the Warnings and Precautions section and the Dosage and Administration section of the product monograph.)

Renal Insufficiency: Following single-dose administration of 400 mg of the oral suspension, there was no significant effect of mild (Cl_{cr} : 50-80 mL/min/1.73m², n=6) and moderate (Cl_{cr} : 20-49 mL/min/1.73m², n=6) renal insufficiency on posaconazole pharmacokinetics; therefore, no dose adjustment is required in patients with mild to moderate renal impairment. In subjects with severe renal insufficiency (Cl_{cr} : <20 mL/min/1.73m²), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (Cl_{cr} : >80 mL/min/1.73m²); however, the range of the AUC estimates was highly variable (CV=96%) in these subjects with severe renal insufficiency as compared to that in the other renal impairment groups (CV<40%). Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections. (See the Dosage and Administration section of the product monograph.)

STORAGE AND STABILITY

Store at room temperature (15 to 30°C). Do not freeze.

Do not use past expiry date on the label.

Shelf life

After first opening the container: 4 weeks

SPECIAL HANDLING INSTRUCTIONS

The oral suspension must be shaken well before each use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

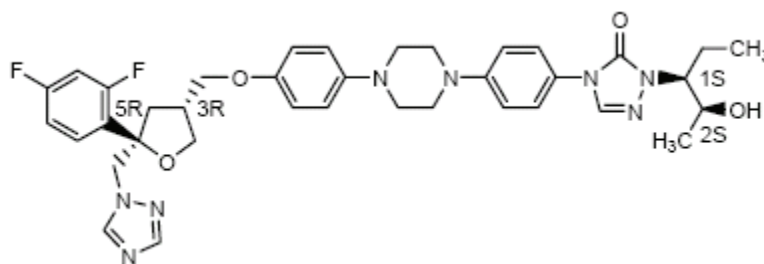
Drug Substance

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:
C₃₇H₄₂F₂N₈O₄ 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.

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

CLINICAL TRIALS

Study P01899 and Study C/I98-316

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

Study demographics and trial design

Table 10 – 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	<u>Dosage</u> : posaconazole: 200 mg three times a day; fluconazole: 400 mg once daily or itraconazole: 200 mg BID <u>Route of administration</u> : oral <u>Duration</u> : up to 84 days	n=602 [589] <u>posaconazole</u> : 304 [297] <u>FLU/ITZ</u> : 298 [292]	<u>posaconazole</u> : 49 (13-82) <u>FLU/ITZ</u> : 50 (13-81)	<u>posaconazole</u> : Men: 158 Women: 146 <u>FLU/ITZ</u> : Men: 160 Women: 138

FLU: fluconazole
ITZ: itraconazole

Study P01899 was a randomised, evaluator-blinded study that compared posaconazole oral suspension (200 mg three times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg BID) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes. 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 11– 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	<u>Dosage</u> : posaconazole: 200 mg three times a day; fluconazole: 400 mg once daily <u>Route of administration</u> : oral <u>Duration</u> : up to 16 weeks	n = 600 [579] <u>posaconazole</u> : 301 [291] <u>fluconazole</u> : 299 [288]	<u>posaconazole</u> : 42.2 years (13-72 years) <u>fluconazole</u> : 40.4 years (13-70 years)	<u>posaconazole</u> : Men: 203 Women: 98 <u>fluconazole</u> : Men: 187 Women: 112

Study C/I98-316 was a randomised, double-blind trial that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) 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 12 and 13 for results from both studies.

Table 12– 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 13– Results from Clinical Study P01899 in Prophylaxis of IFIs

Study P01899	posaconazole	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 14– 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	<u>Dosage</u> : 800 mg/day (posaconazole was taken with food or nutritional supplement) <u>Route of administration</u> : oral <u>Duration</u> : 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 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 15, 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 15 – 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 <i>Aspergillus</i> species (spp.)*	34/76	(45%)	19/74	(26%)
<i>A. fumigatus</i>	12/29	(41%)	12/34	(35%)
<i>A. flavus</i>	10/19	(53%)	3/16	(19%)
<i>A. terreus</i>	4/14	(29%)	2/13	(15%)
<i>A. niger</i>	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 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 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 16 – 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	<u>Dosage (for posaconazole and fluconazole):</u> 100 mg BID for 1 day followed by 100 mg once a day for 13 days (posaconazole and fluconazole were taken with food or nutritional supplement) <u>Route of administration:</u> oral <u>Duration:</u> 14 days	n=366 [350] <u>posaconazole:</u> 182 [178] <u>fluconazole:</u> 184 [172]	<u>posaconazole:</u> 36.4 years (20-61 years) <u>fluconazole:</u> 37.6 years (19-78 years)	<u>posaconazole:</u> Men: 131; Women: 47 <u>fluconazole:</u> Men: 131 Women: 41

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 once a day 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 17 below. Posaconazole and fluconazole demonstrated equivalent clinical success rates at Day 14 as well as 4 weeks after the end of treatment. However, posaconazole demonstrated a significantly better sustained mycological response rate 4 weeks after the end of treatment than fluconazole.

Table 17 - 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 18 – 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	<u>Dosage</u> : 400 mg BID <u>Route of administration</u> : oral <u>Duration</u> : 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 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 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

Summary of the mean pharmacokinetic parameters in patients

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. In addition, the phenomenon of dose-limited absorption of posaconazole at 800 mg/day was observed both in healthy volunteers and patients.

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

Absorption

Posaconazole is absorbed with a median t_{max} of 3 h (patients) and 5 h (healthy volunteers). The pharmacokinetics of posaconazole are linear following single and multiple dose administration of up to 800 mg. No further increases in exposure were observed when doses above 800 mg daily were administered to patients and healthy volunteers. There is no effect of altered pH on the absorption of posaconazole.

Dividing the total posaconazole daily dose (800 mg) as 400 mg BID results in a 184% higher exposure relative to once-a-day administration in patients.

Distribution

Posaconazole has a large apparent volume of distribution (1, 744 L) suggesting extensive penetration into the peripheral tissues. Posaconazole is highly protein bound (> 98%), predominantly to serum albumin.

Metabolism

Posaconazole primarily circulates as the parent compound in plasma. Of the circulating metabolites, the majority are glucuronide conjugates formed via UDP glucuronidation (phase 2 enzymes). Posaconazole does not have any major circulating oxidative (CYP450 mediated) metabolites and its concentrations are thus unlikely to be altered by inhibitors of CYP450 enzymes. The excreted metabolites in urine and feces account for ~17% of the administered radiolabeled dose.

Excretion

Posaconazole is slowly eliminated with a mean half-life ($t_{1/2}$) of 35 h (range 20 to 66 h) and a total body clearance of 32 L/h. Posaconazole is predominantly excreted in the feces (77% of 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). Steady state is attained following 7 to 10 days of multiple-dose administration.

Special Populations and Conditions

Pediatrics

Following administration of 800 mg per day of posaconazole 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_{av} was comparable among 10 adolescents (13 – 17 years of age) to C_{av} achieved in adults (≥ 18 years of age).

Geriatrics

An increase in C_{max} (26%) and AUC (29%) was observed in elderly subjects (24 subjects ≥ 65 years of age) 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. Further, in clinical efficacy trials, the safety profile of posaconazole 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

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 in Black subjects relative to Caucasian subjects, therefore, no dose adjustment for race is required.

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.

Renal Insufficiency

Following single-dose administration, there was no effect of mild and moderate renal insufficiency (n=18, $Cl_{cr} \geq 20$ mL/min/1.73 m²) on posaconazole pharmacokinetics, therefore, no dose adjustment is required. In subjects with severe renal insufficiency (n=6, $Cl_{cr} < 20$ mL/min/1.73 m²), the exposure of posaconazole was highly variable (96% CV) compared to the exposure in the other renal groups (< 40% CV). However, as posaconazole is not significantly renally eliminated, an effect of severe renal insufficiency on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended. Posaconazole is not removed by hemodialysis.

Animal Pharmacology

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 intravenous dose of a lipid-containing formulation of posaconazole (bolus) at 30 or 60 mg/kg did not demonstrate changes in respiratory rate, tidal volume, or minute volume, or in behavior, neurologic or autonomic function, compared with vehicle-treated rats. A single dose of 3 or 10 mg/kg did not affect renal function.

In vitro effects of posaconazole on ventricular repolarization were evaluated by measuring both the action potential and the recombinant hERG channel current. In Purkinje fibers isolated from dog heart, exposure to posaconazole at measured concentrations of 25 ng/mL (36 nM), 69 ng/mL (98 nM) and 365 ng/mL (521 nM) induced a small (<10%) but statistically significant increase in action potential duration at 60% (APD₆₀) and/or 90% (APD₉₀) repolarization. In mouse L-929 cells stably transfected with the human α -subunit (hERG) of the cardiac delayed rectifier, I_{Kr} , a measured concentration of 770 ng/mL (1.1 μ M) posaconazole decreased hERG current by 7%. Accounting for protein binding, the drug concentration in the hERG assay was 18-times the free posaconazole C_{max} value in healthy volunteers. Changes of the magnitude noted in the recombinant hERG channel and isolated Purkinje fiber systems would be unlikely to elicit QT interval prolongation *in vivo*.

At an oral dose of 90 mg/kg in rats, posaconazole was associated with a minimal increase in systolic (13 to 23 mm Hg) and mean arterial (10 to 19 mm Hg) blood pressures after four weeks of dosing. There were no changes in heart rate. After four weeks of dosing, rats given posaconazole had a decreased intraventricular systolic diameter and increased fractional

shortening, which may be indicative of increased cardiac contractility. However, there was no concomitant increase in stroke volume. No other echocardiographic indices of cardiac function were altered by posaconazole.

Cardiovascular parameters in monkeys were assessed in two safety pharmacology studies with the lipid-containing intravenous 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.

MICROBIOLOGY

Posaconazole has been shown *in vitro* and in clinical infections to be active against the following microorganisms (see the Indications and Clinical Use section of the product monograph):

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 19 and 20). 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 19.

Table 19 - MIC₉₀ Values for Mould Strains Tested

Pathogen	MIC ₉₀ ^a (µg/mL)	Pathogen	MIC ₉₀ ^a (µg/mL)	Pathogen	MIC ₉₀ ^a (µg/mL)
<i>Absidia coerulea</i>	(2.0) ^b	<i>Curvularia</i> spp	(0.031-0.125)	<i>Phialophora verrucosa</i>	(0.5-4.0)
<i>Absidia corymbifera</i>	2.0	<i>Epidermophyton floccosum</i>	0.125	<i>Pseudallescheria boydii</i>	2.0
<i>Absidia glauca</i>	(2.0)	<i>Exophiala dermatidis</i>	(0.125)	<i>Ramichloridium obovoideum</i>	(0.031-0.063)
<i>Absidia pseudocylindrospora</i>	(16.0)	<i>Exophiala jeanselmei</i>	0.5	<i>Rhizomucor miehei</i>	(0.016)
<i>Absidia repens</i>	(4.0)	<i>Exophiala moniliae</i>	(0.016)	<i>Rhizomucor pusillus</i>	(0.031-0.25)
<i>Absidia</i> spp	(0.031-0.5)	<i>Exserohilum rostratum</i>	(0.063-0.25)	<i>Rhizomucor</i> spp	(0.016)
<i>Alternaria alternata</i>	(0.016-4.0)	<i>Fonsecaea pedrosoi</i>	0.5	<i>Rhizopus arrhizus</i>	(0.5-32.0)
<i>Alternaria</i> spp	0.25	<i>Fusarium dimerum</i>	(1.0-4.0)	<i>Rhizopus microsporus</i>	16.0
<i>Apophysomyces</i> spp	(0.031-4.0)	<i>Fusarium moniliforme</i>	2.0	<i>Rhizopus microsporus v chinensis</i>	(16.0)
<i>Aspergillus candidus</i>	(0.031-0.063)	<i>Fusarium oxysporum</i>	16.0	<i>Rhizopus microsporus v oligosporus</i>	(16.0)
<i>Aspergillus flavus</i>	1.0	<i>Fusarium proliferatum</i>	(0.5-8.0)	<i>Rhizopus oryzae</i>	4.0
<i>Aspergillus fumigatus</i>	0.5	<i>Fusarium solani</i>	128.0	<i>Rhizopus schipperae</i>	(1.0-8.0)
<i>Aspergillus glaucus</i>	(0.063-16.0)	<i>Fusarium</i> spp	16.0	<i>Rhizopus</i> spp	4.0
<i>Aspergillus nidulans</i>	0.25	<i>Geotrichum candidum</i>	(0.125)	<i>Rhizopus stolonifer</i>	(2.0-16.0)
<i>Aspergillus niger</i>	0.5	<i>Geotrichum</i> spp	(0.25-32.0)	<i>Saksenaea vasiformis</i>	(0.016-2.0)
<i>Aspergillus ochraceus</i>	(0.063-0.125)	<i>Histoplasma capsulatum</i>	0.5	<i>Scedosporium apiospermum</i>	2.0
<i>Aspergillus oryzae</i>	(0.25)	<i>Microsporum audouinii</i>	(0.25)	<i>Scedosporium prolificans</i>	32.0
<i>Aspergillus sydowii</i>	0.5	<i>Microsporum canis</i>	0.5	<i>Schizophyllum commune</i>	(0.125-0.25)
<i>Aspergillus terreus</i>	0.25	<i>Microsporum fulvum</i>	(0.5)	<i>Scopulariopsis brevicaulis</i>	8.0
<i>Aspergillus ustus</i>	16.0	<i>Microsporum gypseum</i>	(0.008-0.5)	<i>Scytalidium dimidiatum</i>	(0.5)
<i>Aspergillus versicolor</i>	2.0	<i>Microsporum persicolor</i>	(0.25)	<i>Sporothrix schenckii</i>	2.0
<i>Bipolaris hawaiiensis</i>	(0.016)	<i>Mucor circinelloides</i>	16.0	<i>Trichoderma</i> spp	(1.0)
<i>Bipolaris spicifera</i>	(0.016-0.125)	<i>Mucor hiemalis</i>	32.0	<i>Trichophyton krajdienii</i>	(0.063)
<i>Bipolaris</i> spp	(0.125-1.0)	<i>Mucor mucedo</i>	(2.0)	<i>Trichophyton mentagrophytes</i>	0.125
<i>Bjerkandera adusta</i>	0.25	<i>Mucor racemosus</i>	(0.008-1.0)	<i>Trichophyton raubitschekii</i>	(0.25)
<i>Blastomyces dermatitidis</i>	0.5	<i>Mucor ramosissimus</i>	(0.125-0.5)	<i>Trichophyton rubrum</i>	0.25
<i>Cladophialophora bantiana</i>	(0.031-0.5)	<i>Mucor rouxii</i>	(1.0-32.0)	<i>Trichophyton soudanense</i>	(0.5)
<i>Cladophialophora carionii</i>	0.5	<i>Mucor</i> spp	16.0	<i>Trichophyton</i> spp	0.063
<i>Coccidioides immitis</i>	0.5	<i>Paecilomyces lilacinus</i>	2.0	<i>Trichophyton terrestre</i>	(0.125)
<i>Cunninghamella bertholletiae</i>	(0.5-16.0)	<i>Paecilomyces</i> spp	0.5	<i>Trichophyton tonsurans</i>	0.125
<i>Cunninghamella blakesleeana</i>	(16.0)	<i>Paecilomyces variotii</i>	(0.016-0.063)	<i>Trichophyton verrucosum</i>	(0.5)
<i>Cunninghamella echinulata</i>	(4.0-16.0)	<i>Paracoccidioides brasiliensis</i>	0.125	<i>Tritirachium</i> spp	(1.0-16.0)
<i>Cunninghamella elegans</i>	(16.0)	<i>Penicillium marneffeii</i>	0.016	<i>Ulocladium</i> spp	(0.25)
<i>Cunninghamella</i> spp	2.0	<i>Penicillium</i> spp	1.0	<i>Wangiella dermatitidis</i>	(0.063-0.125)
<i>Curvularia lunata</i>	(0.016-0.25)	<i>Phialophora</i> 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 MIC₉₀ values for yeast strains tested are summarized in Table 20.

Table 20 - MIC₉₀ Values for Yeast Strains Tested

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

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

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

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

Drug Resistance

C. albicans strains resistant to posaconazole could not be generated in the laboratory; spontaneous laboratory *Aspergillus fumigatus* mutants exhibiting a decrease in susceptibility to posaconazole arose at a frequency of 1×10^{-8} to 1×10^{-9} . Clinical isolates of *Candida albicans* and *Aspergillus fumigatus* exhibiting significant decreases in posaconazole susceptibility are rare. In those rare instances where decreased susceptibility was noted, there was no clear correlation between decreased susceptibility and clinical failure. Clinical success has been observed in patients infected with organisms resistant to other azoles; consistent with these observations posaconazole was active *in vitro* against many *Aspergillus* and *Candida* strains that developed resistance to other azoles and/or amphotericin B. Breakpoints for posaconazole have not been established for any fungi.

Antifungal medicinal products combinations

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

TOXICOLOGY

Acute Toxicity

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

Long-Term Toxicity

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

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

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

Reproductive Toxicity

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

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

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

Mutagenicity

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

Carcinogenicity

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

Local Tolerance

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

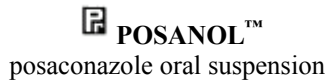
Immunotoxicity Studies

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

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PART III: CONSUMER INFORMATION



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

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

ABOUT THIS MEDICATION

What the medication is used for:

- POSANOL™ can be used to prevent invasive fungal infections caused by *Aspergillus* and *Candida* in patients 13 years of age or older whose immune systems may be weakened due to other medicines or diseases.
- POSANOL™ can be used to treat the following types of fungal infections in patients 13 years of age or older:
 - Infections caused by fungi of the *Aspergillus* family that have not improved during treatment with the anti-fungal medicines amphotericin B or itraconazole or when these medicines have had to be stopped.
- POSANOL™ can be used to treat, in patients 13 years of age or older, infections in the mouth or throat area known as "thrush", caused by fungi called *Candida*.

What it does:

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

When it should not be used:

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

What the medicinal ingredient is:

Posaconazole

What the important nonmedicinal ingredients are:

Artificial cherry flavor, citric acid monohydrate, glycerin, liquid glucose, polysorbate 80, purified water, simethicone, sodium benzoate, sodium citrate dihydrate, titanium dioxide, and xanthan gum. You may also refer to the POSANOL™ labels for a full listing of nonmedicinal ingredients.

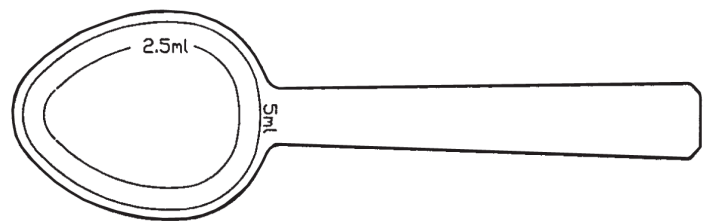
If you know that you have intolerance to glucose, please tell your doctor before being treated with POSANOL™.

What dosage forms it comes in:

40 mg/mL oral suspension

POSANOL™ is a white, cherry flavored, 105 mL oral suspension packaged in amber glass bottles. A measuring spoon is provided with each bottle for measuring 2.5 and 5 mL doses of the drug product.

It is recommended that the spoon is rinsed with water after each administration and before storage.



WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

BEFORE you use POSANOL™ talk to your doctor or pharmacist if:

- you have had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole or voriconazole;
- you are taking certain drugs that suppress your immune system like cyclosporine, tacrolimus and sirolimus. Serious and rare fatal toxicity from cyclosporine has occurred when taken in combination with POSANOL™. Therefore the doctor may adjust the dosage of these immune suppressants and monitor their blood levels when taken with POSANOL™.
- you have or have had liver problems;
- you are taking or have taken any other medicines, even those that are obtained without a prescription. Some medicines may affect the way POSANOL™ works or POSANOL™ may affect the way they work. Please see the section “Interactions with this medication” for medicines which may interact with POSANOL™.
- you have any of the following conditions: history of heart disease, or an irregular beat;
- you are a nursing mother. Do not breast feed while being treated with POSANOL™ unless you are told by your doctor.
- you are pregnant or planning on becoming pregnant. Do not use POSANOL™ during pregnancy unless you are told by your doctor. Use effective contraception if you are a woman who could become pregnant. Contact your doctor immediately if you become pregnant while being treated with POSANOL™.
- you think you have galactose intolerance or glucose-galactose malabsorption. Please check with your doctor before starting to take POSANOL™ suspension since it contains glucose.

Your doctor may ask you to have your blood tested during treatment with POSANOL™.

Please inform your doctor if you experience sleepiness or blurred vision, which can affect your ability to drive or operate machinery.

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

INTERACTIONS WITH THIS MEDICATION

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

The following list of medicines should not be taken during your course of POSANOL™ treatment:

- cisapride* (a medicine for stomach problems)
- pimozide (a medicine for treating mental illness)
- quinidine (a medicine for treating irregular heart beat)
- ergot alkaloids (a medicine to treat migraines along with other indications)
- terfenadine* (a medicine to treat allergies)
- astemizole* (a medicine to treat allergies)

* no longer marketed in Canada

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

- rifabutin or rifampin (a medicine to treat bacterial infections like tuberculosis)
- phenytoin (a medicine to treat seizures)
- cimetidine (a medicine to treat stomach ulcers)

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

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

PROPER USE OF THIS MEDICATION

POSANOL™ must only be used as directed by your doctor. Your doctor will monitor your response and condition to determine what POSANOL dose is needed. Shake well before each use.

Usual dose (adults and children 13 years of age and older):

Take each dose of POSANOL™ with food or with a nutritional supplement if you are unable to eat a full meal, to help absorb the medicine well.

Indication	Dose
Prevention of Certain Serious Fungal Infections	Take 200 mg (one 5 mL spoonful) three times a day with food or nutritional supplement.
Treatment of Certain Refractory (not successfully treated by other therapies) Fungal Infections	Take 400 mg (two 5 mL spoonfuls) of the suspension twice a day with food or with a nutritional supplement. If you are not able to take food or nutritional supplement, your doctor will tell you to take 200 mg (one 5 mL spoonful) four times a day.
Initial Treatment of Thrush	On the first day of treatment take 100 mg (2.5 mL) twice a day. After the first day, take 100 mg (2.5 mL) once a day with food or nutritional supplement.

Your doctor will determine how long the duration of your treatment will be and may change your dose depending on your condition. Do not stop treatment early because your infection may not be fully cured. If you are given POSANOL™ for preventing infections, take the full course as prescribed by your doctor, as your immune system may still be weakened and you may need treatment to prevent an infection from occurring even if you feel well.

Overdose:

If you take more POSANOL™ than prescribed (or someone else takes your suspension) you should seek medical advice from your doctor or healthcare professional immediately. Take your bottle of POSANOL™ suspension with you.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

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

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

Other reported side effects include infrequent cases of liver reactions (e.g., mild to moderate elevations in liver tests called ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis). The elevations in liver function tests were generally reversible when POSANOL™ was stopped, and in some instances these tests went back to normal without stopping POSANOL™. These effects rarely required stopping POSANOL™. Rarely, more severe liver reactions including cholestasis (back-up of bile in the liver) or liver failure were reported in patients with serious underlying medical conditions (e.g., leukemia or other blood cancers) during treatment with POSANOL™. As POSANOL™ has been known to affect the liver in patients who already have liver problems, your doctor may wish to monitor the function of your liver by doing blood tests. Some of the symptoms of liver problems include yellowing of the eyes or skin, “flu-like” feeling or feeling more tired than usual, stomach pains, light colored stools, nausea or vomiting. Please let your doctor know if you have any of these symptoms.

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

which have been reported primarily among patients who had been receiving concomitant cyclosporine or tacrolimus for management of transplant rejection or graft vs. host disease.

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

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

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

HOW TO STORE IT

Keep out of the reach and sight of children. Store at room temperature (15 to 30°C). Do not freeze. Do not use this product after the expiry date stated on the label. Once opened, use the suspension within 4 weeks.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:

National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

For this document plus the full product monograph, prepared for health professionals, please contact the sponsor, Merck Canada Inc. at: 1-800-463-5442. This leaflet was prepared by Merck Canada Inc. Last revised: February 21, 2011