POSANOL

S-CCDS-MK5592-OS-T-112016
MK5592-TWN-2016-013980

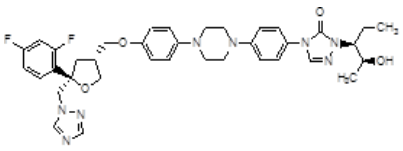
1. NAME OF THE MEDICINAL PRODUCT

Posanol 40 mg/ml oral suspension

2. DESCRIPTION AND QUALITATIVE COMPOSITION

Posanol® (posaconazole) is a triazole antifungal agent available as a suspension for oral administration.

Posaconazole is designated chemically as 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-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one with an empirical formula of $C_{37}H_{42}F_2N_8O_4$ and a molecular weight of 700.8. The structural formula is:



Posaconazole is a white powder and is insoluble in water.

POSANOL Oral Suspension is a white, cherry-flavored immediate-release suspension containing 40 mg of posaconazole per mL and the following inactive ingredients: polysorbate 80, simethicone, sodium benzoate, sodium citrate dihydrate, citric acid monohydrate, glycerin, xanthan gum, liquid glucose, titanium dioxide, artificial cherry flavor, and purified water.

3. PHARMACEUTICAL FORM

Oral suspension

White suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Second-line treatment for invasive aspergillosis in adults with disease that is refractory to amphotericin B, itraconazole or voriconazole, or in adults 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.)
2. Second-line treatment for oropharyngeal candidiasis in adults with disease that is refractory to itraconazole and fluconazole. (Refractoriness is defined as progression of infection or failure to improve after a minimum treatment period: persistent fungemia: 3 days; non-fungemic infections: 7 days; esophageal candidiasis: 14 days of prior therapeutic doses of effective antifungal therapy.)
3. Posanol is also indicated for prophylaxis of invasive fungal infections in the following patient population, 13 years of age and older, who are at high risk of developing these infections due to the following conditions:
   - Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft-vs-host disease (GVHD).
   - Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) expected to result in prolonged neutropenia.

4.2 Posology and method of administration

Each dose of Posanol should be administered with a meal, or with a 240 ml of a nutritional supplement in patients who can not tolerate food to enhance the oral absorption. There are limited pharmacokinetic data in patients with severe gastrointestinal dysfunction (such as severe diarrhea). Patients who have severe diarrhea or vomiting should be monitored closely for breakthrough fungal infections.

The oral suspension must be shaken well before use.

Table 1. Recommended Dose According to Indication

Indication	Dose and Duration of therapy
Refractory Invasive Fungal Infections (IFI)/Intolerant Patients with IFI	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.
Refractory Oropharyngeal Candidiasis	400 mg (10 ml) twice a day. Each dose of **Posanol** should be administered during or immediately after a meal, or a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption and to ensure adequate exposure. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response.
Prophylaxis of Invasive Fungal Infections	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 leukaemia or myelodysplastic syndrome, 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.

Increasing the total daily dose above 800 mg does not further enhance the exposure to **Posanol**.

Use in renal impairment: No dose adjustment is required for renal dysfunction and as **Posanol** is not significantly renally eliminated, an effect of severe renal insufficiency on the pharmacokinetics of **Posanol** is not expected and no dose adjustment is recommended (See CLINICAL PHARMACOLOGY).

Use in hepatic impairment: There is 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 in subjects with a decreased in hepatic function (See CLINICAL PHARMACOLOGY).

Use in Pediatrics: Safety and efficacy in adolescents and children below the age of 13 years have not been established.

Instructions for use/ handling: Shake well before use.

Non-Interchangeability between Noxafil Tablets and Noxafil Oral Suspension

Noxafil tablets and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Co-administration with ergot alkaloids (see section 4.5).

Co-administration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine since this may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes (see sections 4.4 and 4.5).

Co-administration with the HMG-CoA reductase inhibitors simvastatin, lovastatin and atorvastatin (see section 4.5).

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis.

4.4 Special warnings and precautions for use

Special warnings:

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

Hepatic toxicity: Hepatic reactions (e.g. mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin and/or clinical hepatitis) have been reported during treatment with posaconazole. Elevated liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalised without interruption of therapy. Rarely, more severe hepatic reactions with fatal outcomes have been reported.

Posaconazole should be used with caution in patients with severe hepatic impairment. In these patients, the prolonged elimination half-life may lead to increased exposure.

Monitoring of hepatic function: Patients who develop abnormal liver function tests during Posanol therapy must be routinely 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 liver disease.

Calcineurin-inhibitor drug interactions

Concomitant administration of posaconazole with cyclosporine, tacrolimus or sirolimus increases the whole blood trough concentrations of these calcineurin-inhibitors. Nephrotoxicity and leukoencephalopathy (including deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine or tacrolimus concentrations. Frequent monitoring of tacrolimus, cyclosporine or sirolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus, cyclosporine or sirolimus dose adjusted accordingly.

Precautions:

QTc prolongation: Some azoles have been associated with prolongation of the QTc interval. Posanol must not be administered with medicinal products that are substrates for CYP3A4 and are known to prolong the QTc interval (see sections 4.3 and 4.5). Posanol should be administered with caution to patients with pro-arrhythmic conditions such as:

- Congenital or acquired QTc prolongation
- Cardiomyopathy, especially in the presence of cardiac failure
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant use with medicinal products known to prolong the QTc interval

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.

Posaconazole is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolised by CYP3A4 (see section 4.5).

Rifabutin: Concomitant use with posaconazole should be avoided unless the benefit to the patient outweighs the risk (see section 4.5).

Rifamycin antibacterials (rifampicin, rifabutin), certain anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), efavirenz and cimetidine: Posaconazole concentrations may be significantly lowered in combination; therefore, concomitant use with posaconazole should be avoided unless the benefit to the patient outweighs the risk (see section 4.5).

This medicinal product contains approximately 1.75 g of glucose per 5 ml of suspension. Patients with glucose-galactose malabsorption should not take this medicine.

Vincristine Toxicity: Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options (see 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on posaconazole:

Posaconazole is metabolised via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux *in vitro*. Therefore, inhibitors (e.g. verapamil, ciclosporin, quinidine, clarithromycin, erythromycin, etc.) or inducers (e.g. rifampicin, rifabutin, certain anticonvulsants, etc.) of these clearance pathways may increase or decrease posaconazole plasma concentrations, respectively.

Rifabutin (300 mg once a day) decreased the C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration time curve) of posaconazole to 57 % and 51 %, respectively. Concomitant use of posaconazole and rifabutin and similar inducers (e.g. rifampicin) should be avoided unless the benefit to the patient outweighs the risk. See also below regarding the effect of posaconazole on rifabutin plasma levels.

Efavirenz (400 mg once a day) decreased the C_{max} and AUC of posaconazole by 45 % and 50 %, respectively. Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.

Fosamprenavir: Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. Repeat dose administration of fosamprenavir (700 mg BID x 10 days) decreased the C_{max} and AUC of posaconazole

(200 mg QD on the 1st day, 200 mg BID on the 2nd day, then 400 mg BID x 8 Days) by 21% and 23%, respectively.

Phenytoin (200 mg once a day) decreased the C_{max} and AUC of posaconazole by 41 % and 50 %, respectively. Concomitant use of posaconazole and phenytoin and similar inducers (e.g. carbamazepine, phenobarbital, primidone) should be avoided unless the benefit to the patient outweighs the risk.

H_2 receptor antagonists and proton pump inhibitors: Posaconazole plasma concentrations (C_{max} and AUC) were reduced by 39 % when posaconazole was administered with cimetidine (400 mg twice a day) due to reduced absorption possibly secondary to a decrease in gastric acid production. Concomitant use of posaconazole and cimetidine should be avoided unless the benefit to the patient outweighs the risk. The effect of other H_2 receptor antagonists (e.g. famotidine, ranitidine) and proton pump inhibitors (e.g. omeprazole) that may suppress gastric acidity for several hours on plasma levels of posaconazole has not been studied but a reduction in bioavailability may occur so that co-administration should be avoided if possible.

Effects of posaconazole on other medicinal products:

Posaconazole is a potent inhibitor of CYP3A4. Co-administration of posaconazole with CYP3A4 substrates may result in large increases in exposure to CYP3A4 substrates as exemplified by the effects on tacrolimus, sirolimus, atazanavir and midazolam below. Caution is advised during co-administration of posaconazole with CYP3A4 substrates administered intravenously and the dose of the CYP3A4 substrate may need to be reduced. If posaconazole is used concomitantly with CYP3A4 substrates that are administered orally, and for which an increase in plasma concentrations may be associated with unacceptable adverse events, plasma concentrations of the CYP3A4 substrate and/or adverse events should be closely monitored and the dose adjusted as needed. Several of the interaction studies were conducted in healthy volunteers in whom a higher exposure to posaconazole occurs compared to patients administered the same dose. The effect of posaconazole on CYP3A4 substrates in patients might be somewhat lower than that observed in healthy volunteers, and is expected to be variable between patients due to the variable posaconazole exposure in patients. The effect of co-administration with posaconazole on plasma levels of CYP3A4 substrates may also be variable within a patient, unless posaconazole is administered in a strictly standardised way with food, given the large food effect on posaconazole exposure (see section 5.2).

Terfenadine, astemizole, cisapride, pimozide, halofantrine and quinidine (CYP3A4 substrates):

Co-administration of posaconazole and terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine is contraindicated. Co-administration may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes (see section 4.3).

Ergot alkaloids: Posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism. Co-administration of posaconazole and ergot alkaloids is contraindicated (see section 4.3).

HMG-CoA reductase inhibitors primarily metabolised through CYP3A4 (e.g. simvastatin, lovastatin, and atorvastatin): Posaconazole may substantially increase plasma levels of HMG-CoA reductase inhibitors that are primarily metabolised by CYP3A4. Treatment with these HMG-CoA reductase inhibitors should be discontinued during treatment with posaconazole as increased levels have been associated with rhabdomyolysis (see section 4.3).

Vinca alkaloids: Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see 4.4 Special Warnings and Special Precautions for Use). Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.*Rifabutin*: Posaconazole increased the C_{max} and AUC of rifabutin by 31 % and 72%, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk (see also above regarding the effect of rifabutin on plasma levels of posaconazole). If these medicinal products are co-administered, careful monitoring of full blood counts and adverse events related to increased rifabutin levels (e.g. uveitis) is recommended.

Cyclosporin: In heart transplant patients on stable doses of cyclosporin, posaconazole 200 mg once daily increased cyclosporin concentrations requiring dose reductions. Cases of elevated cyclosporin levels resulting in serious adverse events, including nephrotoxicity and one fatal case of leukoencephalopathy, were reported in clinical efficacy studies. When initiating treatment with posaconazole in patients already receiving cyclosporin, the dose of cyclosporin should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of cyclosporin should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of cyclosporin should be adjusted as necessary.

Tacrolimus: Posaconazole increased C_{max} and AUC of tacrolimus (0.05 mg/kg body weight single dose) by 121 % and 358 %, respectively. Clinically significant interactions resulting in hospitalisation and/or posaconazole discontinuation were reported in clinical efficacy studies. When initiating posaconazole treatment in patients already receiving tacrolimus, the dose of tacrolimus should be reduced (e.g. to about one third of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during co-administration, and upon discontinuation of posaconazole, and the dose of tacrolimus should be adjusted as necessary.

Sirolimus: Repeat dose administration of oral posaconazole (400 mg twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9-fold (range 3.1 to 17.5-fold), respectively, in healthy subjects. The effect of posaconazole on sirolimus in patients is unknown, but is expected to be variable due to the variable posaconazole exposure in patients. Co-administration of posaconazole with sirolimus is not recommended and should be avoided whenever possible. If it is considered that co-administration is unavoidable, then it is recommended that the dose of sirolimus should be greatly reduced at the time of initiation of posaconazole therapy and that there should be very frequent monitoring of trough concentrations of sirolimus in whole blood. Sirolimus concentrations should be measured upon initiation, during co-administration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly. It should be noted that the relationship between sirolimus trough concentration and AUC is changed during co-administration with posaconazole. As a result, sirolimus trough concentrations that fall within the usual therapeutic range may result in sub-therapeutic levels. Therefore trough concentrations that fall in the upper part of the usual therapeutic range should be targetted and careful attention should be paid to clinical signs and symptoms, laboratory parameters and tissue biopsies.

HIV Protease Inhibitors: As HIV protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these antiretroviral agents. Following co-administration of oral posaconazole (400 mg twice daily) with atazanavir (300 mg once daily) for 7 days in healthy subjects C_{max} and AUC of atazanavir increased by an average of 2.6-fold and 3.7-fold (range 1.2 to 26-fold), respectively. Following co-administration of oral posaconazole (400 mg twice daily) with atazanavir and ritonavir (300/100 mg once daily) for 7 days in healthy subjects C_{max} and AUC of atazanavir increased by an average of 1.5-fold and 2.5-fold (range 0.9 to 4.1-fold), respectively. The addition of posaconazole to therapy with atazanavir or with atazanavir plus ritonavir was associated with increases in plasma bilirubin levels. Frequent monitoring for adverse events and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with posaconazole.

Midazolam and other benzodiazepines metabolised by CYP3A4: In a study in healthy volunteers posaconazole (200 mg once daily for 10 days) increased the exposure (AUC) of IV midazolam (0.05 mg/kg) by 83 %. In another study in healthy volunteers, repeat dose administration of oral posaconazole (200 mg twice daily for 7 days) increased the C_{max} and AUC of IV midazolam (0.4 mg single dose) by an average of 1.3- and 4.6-fold (range 1.7 to 6.4-fold), respectively; Posaconazole 400 mg twice daily for 7 days increased the IV midazolam C_{max} and AUC by 1.6 and 6.2-fold (range 1.6 to 7.6-fold), respectively. Both doses of posaconazole increased C_{max} and AUC of oral midazolam (2 mg single oral dose) by 2.2 and 4.5-fold, respectively. In addition, oral posaconazole (200 mg or 400 mg) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-10 hours during co-administration.

Due to the risk of prolonged sedation it is recommended that dose adjustments should be considered when posaconazole is administered concomitantly with any benzodiazepine that is metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam).

Calcium channel blockers metabolised through CYP3A4 (e.g. diltiazem, verapamil, nifedipine, nisoldipine): Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during co-administration with posaconazole. Dose adjustment of calcium channel blockers may be required.

Digoxin: Administration of other azoles has been associated with increases in digoxin levels. Therefore, posaconazole may increase plasma concentration of digoxin and digoxin levels need to be monitored when initiating or discontinuing posaconazole treatment.

Sulfonylureas: Glucose concentrations decreased in some healthy volunteers when glipizide was co-administered with posaconazole. Monitoring of glucose concentrations is recommended in diabetic patients.

4.6 Pregnancy and lactation

There is insufficient information on the use of posaconazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Women of childbearing potential have to use effective contraception during treatment. Posaconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Posaconazole is excreted into the milk of lactating rats (see section 5.3). The excretion of posaconazole in human breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with posaconazole.

4.7 Effects on ability to drive and use machines

No studies on the effects of posaconazole on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Treatment-related, adverse events observed in 2,400 subjects dosed with posaconazole are shown in Table 2. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. One hundred seventy two patients received posaconazole for ¤ 6 months; 58 of these received posaconazole 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 %).

Table 2. Treatment-related adverse events (TRAE) reported in posaconazole dosed subjects by body system and frequency
n= 2,400
Includes all TRAEs with incidence of 1 % or higher and all medically significant adverse events regardless of incidence
Common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000)

Blood and lymphatic system disorders	
Common:	neutropenia
Uncommon:	thrombocytopenia, leukopenia, anaemia, eosinophilia, lymphadenopathy
Rare:	haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura , pancytopenia, coagulation disorder, haemorrhage NOS
Immune system disorders	
Uncommon:	allergic reaction
Rare:	Stevens Johnson syndrome, hypersensitivity reaction
Endocrine disorders	
Rare:	adrenal insufficiency, gonadotropins decreased
Metabolism and nutrition disorders	
Common:	
Uncommon:	electrolyte imbalance, anorexia
Rare:	hyperglycaemia renal tubular acidosis
Psychiatric disorders	
Rare:	psychosis, depression
Nervous system disorders	
Common:	paresthesia, dizziness, somnolence, headache
Uncommon:	convulsions, neuropathy, hypoaesthesia, tremor syncope, encephalopathy, peripheral neuropathy
Rare:	
Eye disorders	
Uncommon:	blurred vision
Rare:	diplopia, scotoma
Ear and labyrinth disorder	
Rare:	hearing impairment

Cardiac disorders	
Uncommon:	QTc/QT prolongation, abnormal ECG, palpitation
Rare:	torsades de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders	
Uncommon:	hypertension, hypotension
Rare:	cerebrovascular accident, pulmonary embolism, deep venous thrombosis NOS
Respiratory, thoracic and mediastinal disorders	
Rare:	pulmonary hypertension, interstitial pneumonia, pneumonitis
Gastrointestinal disorders	
Common:	vomiting, nausea, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence
Uncommon:	pancreatitis
Rare:	gastrointestinal tract haemorrhage, ileus
Hepatobiliary disorders	
Common:	elevated liver function tests (including ALT, AST, bilirubin, alkaline phosphatase, GGT)
Uncommon:	hepatocellular damage, hepatitis, jaundice, hepatomegaly
Rare:	hepatic failure, hepatitis cholestatic, cholestasis, hepatosplenomegaly, liver tenderness, asterixis
Skin and subcutaneous tissue disorders	
Common:	rash
Uncommon:	mouth ulceration, alopecia
Rare:	vesicular rash
Musculoskeletal and connective tissue disorders	
Uncommon:	back pain
Renal and urinary disorders	
Uncommon:	acute renal failure, renal failure, increased blood creatinine
Rare:	interstitial nephritis
Reproductive system and breast disorders	
Uncommon:	menstrual disorder
Rare:	breast pain
General disorders and administration site conditions	
Common:	pyrexia (fever), asthenia, fatigue
Uncommon:	oedema, weakness, pain, rigors, malaise
Rare:	tongue oedema, face oedema
Investigations	
Uncommon:	altered medicine levels

Treatment related serious adverse events reported in 428 patients with invasive fungal infections (1 % each) included altered concentration of other medicinal products, increased hepatic enzymes, nausea, rash, and vomiting. Treatment-related serious adverse events reported in 605 patients treated with posaconazole for prophylaxis (1 % each) included bilirubinemia, increased hepatic enzymes, hepatocellular damage, nausea, and vomiting. During clinical development there was a single case of torsade de pointes in a patient taking posaconazole. This report involved a seriously ill patient with multiple confounding, potentially contributory risk factors, such as a history of palpitations, recent cardiotoxic chemotherapy, hypokalemia, and hypomagnesemia. 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 graft vs. host disease.

4.9 Overdose

During clinical trials, patients who received posaconazole doses up to 1,600 mg/day experienced no different adverse reactions from those reported with patients at the lower doses. Accidental overdose was noted in one patient who took 1,200 mg twice a day for 3 days. No adverse reactions were noted by the investigator.

Posaconazole is not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use-triazole derivatives,
ATC code: J02A C04.

Mechanism of action

Posaconazole inhibits the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.

Microbiology

Posaconazole has been shown *in vitro* to be active against the following microorganisms: *Aspergillus* species (*Aspergillus fumigatus, A. flavus, A. terreus, A. nidulans, A. niger, A. ustus*), *Candida* species (*Candida albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, C. dubliniensis, C. famata, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis*), *Coccidioides immitis, Fonsecaea pedrosoi*, and species of *Fusarium, Rhizomucor, Mucor*, and *Rhizopus*. The microbiological data suggest that posaconazole is active against *Rhizomucor, Mucor*, and *Rhizopus*, however the clinical data are currently too limited to assess the efficacy of posaconazole against these causative agents.

Resistance

Clinical isolates with decreased susceptibility to posaconazole have been identified. The principle mechanism of resistance is the acquisition of substitutions in the target protein, CYP51.

Combination with other antifungal agents

The use of combination antifungal therapies should not decrease the efficacy of either posaconazole or the other therapies; however, there is currently no clinical evidence that combination therapy will provide an added benefit.

Pharmacokinetic / Pharmacodynamic relationships:

A correlation between total medicinal product exposure divided by MIC (AUC/MIC) and clinical outcome was observed. The critical ratio for subjects with *Aspergillus* infections was ~200. It is particularly important to try to ensure that maximal plasma levels are achieved in patients infected with *Aspergillus* (see sections 4.2 and 5.2 on recommended dose regimens and the effects of food on absorption).

Clinical experience

Treatment of Invasive aspergillosis

Oral posaconazole 800 mg/day in divided doses was evaluated for the treatment of invasive aspergillosis in patients with disease refractory to amphotericin B (including liposomal formulations) or itraconazole or in patients who were intolerant of these medicinal products in a non-comparative salvage therapy trial. Clinical outcomes were compared with those in an external control group derived from a retrospective review of medical records. The external control group included 86 patients treated with available therapy (as above) mostly at the same time and at the same sites as the patients treated with posaconazole. Most of the cases of aspergillosis were considered to be refractory to prior therapy in both the posaconazole group (88 %) and in the external control group (79 %).

As shown in Table 3, a successful response (complete or partial resolution) at the end of treatment was seen in 42 % of posaconazole-treated patients compared to 26 % of the external group. However, this was not a prospective, randomised controlled study and so all comparisons with the external control group should be viewed with caution.

Table 3. 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 %)	
Success by Species				
All mycologically confirmed *Aspergillus* spp.[1]	34/76	(45 %)	19/74	(26 %)
A. fumigatus	12/29	(41 %)	12/34	(35 %)
A. flavus	10/19	(53 %)	3/16	(19 %)
A. terreus	4/14	(29 %)	2/13	(15 %)
A. niger	3/5	(60 %)	2/7	(29 %)

[1] Includes other less common species or species unknown

Treatment of Oropharyngeal Candidiasis (OPC) refractory to treatment with Fluconazole or Itraconazole

Oral posaconazole was evaluated for the treatment of Oropharyngeal Candidiasis (OPC) in HIV-infected patients with disease refractory to treatment with fluconazole or itraconazole in a non-comparative trial. An episode of OPC was considered refractory if there was failure to improve or worsening of OPC after a standard course of therapy with fluconazole ≥100 mg/day for at least 10 consecutive days or itraconazole 200 mg/day for at least 10 consecutive days and treatment with either fluconazole or itraconazole had not been discontinued for more than 14 days prior to treatment with posaconazole. Of the 199 subjects enrolled in this study, 89 subjects met these strict criteria for refractory OPC infection.

Forty-five subjects with refractory OPC were treated with posaconazole 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. Following a dosing amendment, a further 44 subjects were treated with posaconazole 400 mg BID for 28 days. The efficacy of posaconazole was assessed by the clinical success (cure or improvement) rate after 4 weeks of treatment. The clinical success rate was 74.2% (66/89). The clinical success rates for both the original and the amended dosing regimens were similar (73.3% and 75.0%, respectively).

Prophylaxis of Invasive Fungal Infections (IFIs) (Studies 316 and 1899)

Two randomised, controlled prophylaxis studies were conducted among patients at high risk for developing invasive fungal infections.

Study 316 was a randomised, double-blind trial of posaconazole oral suspension (200 mg three times a day) versus fluconazole capsules (400 mg once daily) in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease (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 medicinal product + 7 days). The majority (377/600, [63 %]) of patients included had Acute Grade 2 or 3 or chronic extensive (195/600, [32.5 %]) GVHD at study start. The mean duration of therapy was 80 days for posaconazole and 77 days for fluconazole.

Study 1899 was a randomised, evaluator-blinded study of posaconazole oral suspension (200 mg three times a day) versus fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) 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. New diagnosis of acute myelogenous leukemia was the most common underlying condition (435/602, [72 %]). The mean duration of therapy was 29 days for posaconazole and 25 days for fluconazole/itraconazole.

In both prophylaxis studies, aspergillosis was the most common breakthrough infection. See Table 5 and 6 for results from both studies. There were fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients.

Table 4. Results from clinical studies in prophylaxis of Invasive Fungal Infections.

Study	Posaconazole	Control[a]	P-Value
Proportion (%) of patients with proven/probable IFIs			
On-treatment period[b]			
1899[d]	7/304 (2)	25/298 (8)	0.0009
316[e]	7/291 (2)	22/288 (8)	0.0038
Fixed-time period[c]			
1899[d]	14/304 (5)	33/298 (11)	0.0031
316[d]	16/301 (5)	27/299 (9)	0.0740

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.

a: FLU/ITZ (1899); FLU (316).

b: In 1899 this was the period from randomization to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.

c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.

d: All randomized
e: All treated

Table 5. Results from clinical studies in prophylaxis of Invasive Fungal Infections.

Study	Posaconazole	Control[a]
Proportion (%) of patients with proven/probable Aspergillosis		
On-treatment period[b]		
1899[d]	2/304 (1)	20/298 (7)
316[e]	3/291 (1)	17/288 (6)
Fixed-time period[c]		
1899[d]	4/304 (1)	26/298 (9)
316[d]	7/301 (2)	21/299 (7)

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.
a: FLU/ITZ (1899); FLU (316).
b: In 1899 this was the period from randomization to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.
c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.
d: All randomized
e: All treated

In Study 1899, a significant decrease in all cause mortality in favour of posaconazole was observed [POS 49/304 (16 %) vs. FLU/ITZ 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 316, overall mortality was similar (POS, 25 %; FLU, 28 %); however, the proportion of IFI-related deaths was significantly lower in the POS group (4/301) compared with the FLU group (12/299; P= 0.0413).

Use in paediatric patients

Sixteen patients 8-17 years of age were treated with 800 mg/day in a study for invasive fungal infections. Based on the available data in 16 of these paediatric patients, the safety profile appears to be similar to patients ≥ 18 years of age.

Additionally, twelve patients 13-17 years of age received 600 mg/day for prophylaxis of invasive fungal infections (Studies 316 and 1899). 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 paediatric patients, the pharmacokinetic profile appears to be similar to patients ≥ 18 years of age.

Safety and efficacy in paediatric patients below the age of 13 years have not been established.

Electrocardiogram evaluation

Multiple, time-matched ECGs collected over a 12 hour period were obtained before and during administration of posaconazole (400 mg twice daily with high fat meals) from 173 healthy male and female volunteers aged 18 to 85 years. No clinically relevant changes in the mean QTc (Fridericia) interval from baseline were observed.

5.2 Pharmacokinetic properties

Absorption

Posaconazole is absorbed with a median t_{max} of 3 hours (fed patients). The pharmacokinetics of posaconazole are linear following single and multiple dose administration of up to 800 mg when taken with a high fat meal. No further increases in exposure were observed when doses above 800 mg daily were administered to patients and healthy volunteers. In the fasting state, AUC increased less than in proportion to dose above 200 mg. In healthy volunteers under fasting conditions, dividing the total daily dose (800 mg) into 200 mg four times daily compared to 400 mg twice daily, was shown to increase posaconazole exposure by 58 % over 48 hours.

Effect of food on oral absorption in healthy volunteers

The AUC of posaconazole is about 2.6 times greater when administered with a non-fat meal or nutritional supplement (14 grams fat) and 4 times greater when administered with a high-fat meal (~ 50 grams fat) relative to the fasted state. Posaconazole should be administered with food or a nutritional supplement (see section 4.2).

Distribution

Posaconazole is slowly absorbed and slowly eliminated with a large apparent volume of distribution (1,774 litres) and is highly protein bound (> 98 %), predominantly to serum albumin.

Metabolism

Posaconazole does not have any major circulating metabolites and its concentrations are unlikely to be altered by inhibitors of CYP450 enzymes. Of the circulating metabolites, the majority are glucuronide conjugates of posaconazole with only minor amounts of oxidative (CYP450 mediated) metabolites observed. The excreted metabolites in urine and faeces account for approximately 17 % of the administered radiolabelled dose.

Excretion

Posaconazole is slowly eliminated with a mean half-life ($t_{½}$) of 35 hours (range 20 to 66 hours). After administration of ^{14}C-posaconazole, radioactivity was predominantly recovered in the faeces (77 % of the radiolabelled dose) with the major component being parent compound (66 % of the radiolabelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radiolabelled dose excreted in urine (< 0.2 % of the radiolabelled dose is parent compound). Steady-state is attained following 7 to 10 days of multiple-dose administration.

Pharmacokinetics in special populations

Children

Following administration of 800 mg per day of posaconazole as a divided dose for treatment of invasive fungal infections, 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 paediatric patients less than 8 years of age. Similarly, in the prophylaxis studies, the mean steady-state posaconazole average concentration (Cav) was comparable among ten adolescents (13-17 years of age) to Cav achieved in adults (≥ 18 years of age).

Gender

The pharmacokinetics of posaconazole are comparable in men and women.

Elderly

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 clinical efficacy trials, the safety profile of posaconazole between the young and elderly patients was similar.

Race

There was a slight decrease (16 %) in the AUC and C_{max} of posaconazole in Black subjects relative to Caucasian subjects. However, the safety profile of posaconazole between the Black and Caucasian subjects was similar.

Renal impairment

Following single-dose administration, there was no effect of mild and moderate renal impairment (n=18, Cl_{cr} ≥ 20 ml/min/1.73 m^2) on posaconazole pharmacokinetics; therefore, no dose adjustment is required. In subjects with severe renal impairment (n=6, Cl_{cr} < 20 ml/min/1.73 m^2), the AUC of posaconazole was highly variable [> 96 % CV (coefficient of variance)] compared to other renal groups [< 40 % CV]. However, as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended. Posaconazole is not removed by haemodialysis.

Hepatic impairment

In a study with small number of subjects (n=12) who had hepatic impairment, there was an increase in exposure associated with prolongation of half-life in hepatic impaired patients (26.6, 35.3, and 46.1 hours for the mild, moderate and severe groups, respectively compared to 22.1 hours in subjects with normal hepatic function). An approximately 2-fold increase in steady-state AUC is estimated in patients with severe hepatic impairment. Due to the limited pharmacokinetic data in patients with hepatic impairment, posaconazole should be used with caution in patients with severe hepatic impairment since the prolonged half-life that may occur will lead to increased exposure.

5.3 Preclinical safety data

As observed with other azole antifungal agents, effects related to inhibition of steroid hormone synthesis were seen in repeated-dose toxicity studies with posaconazole. Adrenal suppressive effects were observed in toxicity studies in rats and dogs at exposures equal to or greater than those obtained at therapeutic doses in humans.

Neuronal phospholipidosis occurred in dogs dosed for ¤ 3 months at lower systemic exposures than those obtained at therapeutic doses in humans. This finding was not seen in monkeys dosed for one year. In twelve-month neurotoxicity studies in dogs and monkeys, no functional effects were observed on the central or peripheral nervous systems at systemic exposures greater than those achieved therapeutically.

Pulmonary phospholipidosis resulting in dilatation and obstruction of the alveoli was observed in the 2-year study in rats. These findings are not necessarily indicative of a potential for functional changes in humans.

No effects on electrocardiograms, including QT and QTc intervals, were seen in a repeat dose safety pharmacology study in monkeys at systemic exposures 4.6-fold greater than the exposures obtained at therapeutic doses in humans. Echocardiography revealed no indication of cardiac decompensation in a repeat dose safety pharmacology study in rats at a systemic exposure 1.4-fold greater than that achieved therapeutically. Increased systolic and arterial blood pressures (up to 29 mm-Hg) were seen in rats and monkeys at systemic exposures 1.4-fold and 4.6-fold greater, respectively, than those achieved with therapeutic doses.

Reproduction, peri- and postnatal development studies were conducted in rats. At exposures lower than those obtained at therapeutic doses in humans, posaconazole caused skeletal variations and malformations, dystocia, increased length of gestation, reduced mean litter size and postnatal viability. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. As observed with other azole antifungal agents, these effects on reproduction were considered to be due to a treatment-related effect on steroidogenesis.

Posaconazole was not genotoxic in *in vitro* and *in vivo* studies. Carcinogenicity studies did not reveal special hazards for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf life

Unopened container: see Labelled in the outer carton or bottle

After first opening the container: 4 weeks

.6.2 Special precaution for storage

Do not freeze. Store below 25°C.

6.3 Nature and contents of container

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.

Manufacturing site: Patheon Inc.
Address: 111 Consumers Drive, Whitby, Ontario, L1N 5Z5, Canada
Packaging site: Cenexi HSC
Address: 2, Rue Louis Pasteur, 14200 Herouville Saint Clair, France