ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Posaconazole SP 40 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 40 mg of posaconazole.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension
White suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Posaconazole SP is indicated for use in the treatment of the following fungal infections in adults (see section 5.1):

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products;
- Oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor.

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.

Posaconazole SP is also indicated for prophylaxis of invasive fungal infections in the following patients:

- Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
- Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

4.2 Posology and method of administration

Treatment should be initiated by a physician experienced in the management of fungal infections or in the supportive care in the high risk patients for which posaconazole is indicated as prophylaxis.

Recommended dosage is shown in Table 1.

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, Posaconazole SP 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	Loading dose of 200 mg (5 ml) once a day on the first day, then 100 mg (2.5 ml) once a day for 13 days. Each dose of Posaconazole SP should be administered with a meal, or with a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption and to ensure adequate exposure.
Prophylaxis of Invasive Fungal Infections	200 mg (5 ml) three times a day. Each dose of Posaconazole SP should be administered with a meal, or with a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption and to ensure adequate exposure. The duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with Posaconazole SP 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.

There are limited pharmacokinetic data in patients with severe gastrointestinal dysfunction (such as severe diarrhoea). Patients who have severe diarrhoea or vomiting should be monitored closely for breakthrough fungal infections.

The oral suspension must be shaken well before use.

Use in renal impairment: An effect of renal impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended (see section 5.2).

Use in hepatic impairment: There are limited pharmacokinetic data in patients with hepatic impairment; therefore, no recommendation for dose adjustment can be made. In the small number of subjects studied who had hepatic impairment, there was an increase in exposure and half-life with a decrease in hepatic function (see sections 4.4 and 5.2).

Use in children: Safety and efficacy in children and adolescents below the age of 18 years have not been established. Therefore posaconazole is not recommended for use in patients below 18 years of age (see sections 5.1 and 5.2).

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).

4.4 Special warnings and precautions for use

Hypersensitivity: There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing Posaconazole SP 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 Posaconazole SP 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 Posaconazole SP should be considered if clinical signs and symptoms are consistent with development of liver disease.

QTc prolongation: Some azoles have been associated with prolongation of the QTc interval. Posaconazole SP 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). Posaconazole SP 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 (other than those mentioned in section 4.3).

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.

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.

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 metabolised through CYP3A4 (e.g. simvastatin, lovastatin, and atorvastatin): Posaconazole may substantially increase plasma levels of HMG-CoA reductase inhibitors that are 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: Posaconazole may increase the plasma concentration of vinca alkaloids (e.g. vincristine and vinblastine), which may lead to neurotoxicity. Therefore, concomitant use of posaconazole and vinca alkaloids should be avoided unless the benefit to the patient outweighs the risk. If co-administered, then it is recommended that dose adjustment of vinca alkaloids be considered.

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.

Ciclosporin: In heart transplant patients on stable doses of ciclosporin, posaconazole 200 mg once daily increased ciclosporin concentrations requiring dose reductions. Cases of elevated ciclosporin 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 ciclosporin, the dose of ciclosporin should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of ciclosporin should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of ciclosporin 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

The safety of posaconazole has been assessed in > 2,400 patients and healthy volunteers enrolled in clinical trials and from post-marketing experience. The most frequently reported serious related adverse events included nausea, vomiting, diarrhoea, pyrexia, and increased bilirubin.

Table 2. Treatment-related adverse events (TRAE) by body system and frequency
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, coagulopathy, haemorrhage
Immune system disorders	
Uncommon:	allergic reaction
Rare:	hypersensitivity reaction
Endocrine disorders	
Rare:	adrenal insufficiency, blood gonadotropin decreased
Metabolism and nutrition disorders	
Common:	electrolyte imbalance, anorexia
Uncommon:	hyperglycaemia
Psychiatric disorders	
Rare:	psychotic disorder, depression
Nervous system disorders	
Common:	paresthesia, dizziness, somnolence, headache
Uncommon:	convulsion, neuropathy, hypoaesthesia, tremor
Rare:	cerebrovascular accident, encephalopathy, peripheral neuropathy, syncope
Eye disorders	
Uncommon:	blurred vision
Rare:	diplopia, scotoma
Ear and labyrinth disorder	
Rare:	hearing impaired
Cardiac disorders	
Uncommon:	long QT syndrome[§], electrocardiogram abnormal[§], palpitations
Rare:	torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders	
Uncommon:	hypertension, hypotension
Rare:	pulmonary embolism, deep vein thrombosis
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 haemorrhage, ileus
Hepatobiliary disorders	
Common:	liver function tests raised (ALT increased, AST increased, bilirubin increased, alkaline phosphatase increased, GGT increased)
Uncommon:	hepatocellular damage*, hepatitis, jaundice, hepatomegaly
Rare:	hepatic failure, hepatitis cholestatic, cholestasis,

	hepatosplenomegaly, liver tenderness, asterixis
Skin and subcutaneous tissue disorders Common: Uncommon: Rare:	 rash mouth ulceration, alopecia Stevens Johnson syndrome, vesicular rash
Musculoskeletal and connective tissue disorders Uncommon:	 back pain
Renal and urinary disorders Uncommon: Rare:	 acute renal failure, renal failure, blood creatinine increased renal tubular acidosis, interstitial nephritis
Reproductive system and breast disorders Uncommon: Rare:	 menstrual disorder breast pain
General disorders and administration site conditions Common: Uncommon: Rare:	 pyrexia (fever), asthenia, fatigue oedema, pain, chills, malaise tongue oedema, face oedema
Investigations Uncommon:	 medicine level changed

§ See section 4.4.

* During post-marketing surveillance severe hepatic injury with fatal outcome has been reported (see section 4.4).

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

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

Fusarium spp.: 11 of 24 patients who had proven or probable fusariosis were successfully treated with posaconazole 800 mg/day in divided doses for a median of 124 days and up to 212 days. Among eighteen patients who were intolerant or had infections refractory to amphotericin B or itraconazole, seven patients were classed as responders.

Chromoblastomycosis/Mycetoma: 9 of 11 patients were successfully treated with posaconazole 800 mg/day in divided doses for a median of 268 days and up to 377 days. Five of these patients had chromoblastomycosis due to *Fonsecaea pedrosoi* and 4 had mycetoma, mostly due to *Madurella* species.

Coccidioidomycosis: 11 of 16 patients were successfully treated (at the end of treatment complete or partial resolution of signs and symptoms present at baseline*)* with posaconazole 800 mg/day in divided doses for a median of 296 days and up to 460 days.

Treatment of azole-susceptible Oropharyngeal Candidiasis (OPC)
A randomised, evaluator-blind, controlled study was completed in HIV-infected patients with azole-susceptible oropharyngeal candidiasis (most patients studied had C. albicans isolated at baseline). 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 twice a day for 1 day followed by 100 mg once a day for 13 days).

The clinical response rates from the above study are shown in the Table 4 below.
Posaconazole was shown to be non-inferior to fluconazole for clinical success rates at Day 14 as well as 4 weeks after the end of treatment.

Table 4. Clinical success rates in Oropharyngeal Candidiasis

Endpoint	Posaconazole	Fluconazole
Clinical success rate at 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)

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.

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 5. 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 6. 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 18 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 (< 18 years)
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 (≥ 65 years)
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, $Cl_{cr} \geq 20$ 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 List of excipients

Polysorbate 80
Simeticone
Sodium benzoate (E211)
Sodium citrate dihydrate

Citric acid monohydrate
Glycerol
Xanthan gum
Liquid glucose
Titanium dioxide (E171)
Artificial cherry flavour containing benzyl alcohol and propylene glycol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened container: 2 years

After first opening the container: 4 weeks.

6.4 Special precautions for storage

Do not freeze.

6.5 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.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/321/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 October 2005

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Schering-Plough S.A., 2, rue Louis Pasteur; 14200 Hérouville St Clair, France

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription. (See Annex I: Summary of Product Characteristics, 4.2)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE (*Outer Carton*)

1. NAME OF THE MEDICINAL PRODUCT

Posaconazole SP 40 mg/ml oral suspension
posaconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral suspension contains 40 mg of posaconazole.

3. LIST OF EXCIPIENTS

Contains also liquid glucose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

One bottle of 105 ml of oral suspension
Measuring spoon

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Any product remaining four weeks after opening the bottle should be discarded.

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/321/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Posaconazole SP

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE (*Bottle label*)

1. NAME OF THE MEDICINAL PRODUCT

Posaconazole SP 40 mg/ml oral suspension
posaconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral suspension contains 40 mg of posaconazole.

3. LIST OF EXCIPIENTS

Contains also liquid glucose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

One bottle of 105 ml of oral suspension
Measuring spoon

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Any product remaining four weeks after opening the bottle should be discarded.

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SP Europe
Rue de Stalle, 73
B-1180 Bruxelles, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/321/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Posaconazole SP 40 mg/ml oral suspension
posaconazole

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT POSACONAZOLE SP IS AND WHAT IT IS USED FOR

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

Posaconazole SP can be used to treat the following types of fungal infections in adults:
- 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;
- Infections caused by fungi of the *Fusarium* family that have not improved during treatment with amphotericin B or when amphotericin B has had to be stopped;
- Infections caused by fungi that cause the conditions known as chromoblastomycosis and mycetoma that have not improved during treatment with itraconazole or when itraconazole has had to be stopped;
- Infections due to fungi called *Coccidioides* that have not improved during treatment with one or more of amphotericin B, itraconazole or fluconazole or when these medicines have had to be stopped;
- Infections in the mouth or throat area (known as "thrush") caused by fungi called *Candida*, which are initial infections.

Posaconazole SP can be used to prevent fungal infections in patients whose immune systems may be weakened due to other medicines or diseases.

2. BEFORE YOU TAKE POSACONAZOLE SP

Do not take Posaconazole SP
- If you are allergic (hypersensitive) to posaconazole or to any of the other ingredients of Posaconazole SP.
- If you are taking medicines that contain ergot alkaloids (used to treat migraines). Posaconazole can increase the blood levels of these medicines, which can lead to severe reductions in blood flow to some parts of the body and damage tissues.

- If you are taking any of the following medicines. Posaconazole can increase the blood levels of these medicines, which can lead to very serious disturbances in heart rhythm:
  - terfenadine (used to treat allergies)
  - astemizole (used to treat allergies)
  - cisapride (used to treat stomach problems)
  - pimozide (used to treat symptoms of Tourette's disorder)
  - halofantrine (used to treat malaria)
  - quinidine (used to treat abnormal heart rhythms).
- If you are taking simvastatin, lovastatin, atorvastatin and some similar medicines (called HMG-CoA reductase inhibitors or statins) that are used to treat high cholesterol levels in the blood.

Please see the section "Taking other medicines" for information on other medicines which may interact with Posaconazole SP.

Take special care with Posaconazole SP
Ask your doctor or pharmacist for advice before taking any medicine. In addition to the medicines named above that must not be taken with posaconazole because of the risk of heart rhythm disturbances, there are other medicines that carry a risk of rhythm problems that may be greater when they are taken with posaconazole. Please make sure you tell your doctor about all the medicines you are taking (prescribed or non prescribed).

Tell your doctor:
- If you have ever had an allergic reaction to other medicines of the azole or triazole family. These include ketoconazole, fluconazole, itraconazole and voriconazole.
- If you have or have had liver problems. You may need special blood tests to be done while you are taking Posaconazole SP.
- If you have kidney problems and are taking medicines that affect the kidney.
- If you develop severe diarrhoea or vomiting, as these conditions may limit the effectiveness of Posaconazole SP.
- If you have ever been told that you have any of the following conditions:
  - An abnormal heart rhythm tracing (ECG) that shows a problem called long QTc interval
  - A weakness of the heart muscle or heart failure
  - A very slow heartbeat
  - Any heart rhythm disturbance
  - Any problem with amounts of potassium, magnesium or calcium in your blood.

Please note that Posaconazole SP is only for use in adults (older than 18 years of age).

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Please look at the list of medicines that must not be taken while you are taking Posaconazole SP that is given above.
There are other medicines that can sometimes be given while you are taking Posaconazole SP but special care may be needed.

Certain medicines may increase (possibly increasing the risk of side effects) or decrease (possibly causing lack of effectiveness) the blood levels of posaconazole.
Medicines that can decrease blood levels of posaconazole include:
- Rifabutin and rifampicin (used to treat certain infections). If you are already being treated with rifabutin, your blood counts and some possible side effects to rifabutin will need to be monitored.
- Some medicines used to treat or prevent fits, such as phenytoin, carbamazepine, phenobarbital, primidone.
- Efavirenz, which is used to treat HIV infection.

- Medicines used to decrease stomach acid such as cimetidine and ranitidine or omeprazole and similar medicines that are called proton pump inhibitors.

Posaconazole SP may increase (possibly increasing the risk of side effects) the blood levels of some other medicines. These include:
- Vincristine, vinblastine and other vinca alkaloids (used to treat cancer)
- Ciclosporin (used in transplant surgery)
- Tacrolimus and sirolimus (used in transplant surgery)
- Rifabutin (used to treat certain infections)
- Medicines used to treat HIV called protease inhibitors (including lopinavir and atazanavir, which are given with ritonavir) and non nucleoside reverse transcriptase inhibitors (NNRTIs)
- Midazolam, triazolam, alprazolam and some similar medicines called benzodiazepines (used as sedatives or muscle relaxants)
- Diltiazem, verapamil, nifedipine, nisoldipine and some of the other medicines called calcium channel blockers (used to treat high blood pressure)
- Digoxin (used to treat heart failure)
- Sulfonylureas such as glipizide (used to treat high blood sugar).

Taking Posaconazole SP with food and drink
Each dose of Posaconazole SP should be taken with food or a nutritional supplement if you are unable to tolerate food to enhance the oral absorption. See section 3 of this leaflet for more information on how to take the suspension.

Pregnancy and breast-feeding
Tell your doctor if you are or think you are pregnant before you start to take Posaconazole SP. Do not use Posaconazole SP during pregnancy unless you are told by your doctor. You should use effective contraception while you are taking Posaconazole SP if you are a woman who could become pregnant. Contact your doctor immediately if you become pregnant while being treated with Posaconazole SP.

Do not breast-feed while being treated with Posaconazole SP.

Driving and using machines
There is no information on the effect of Posaconazole SP on the ability to drive and use machines. Please inform your doctor if you experience any effects that may cause you to have problems with driving or using other machinery such as sleepiness or blurred vision.

Important information about some of the ingredients of Posaconazole SP
Posaconazole SP contains approximately 1.75 g of glucose per 5 ml of suspension. You should not take this medicine if you have a condition called glucose-galactose malabsorption and should take note of this amount of glucose if you need to watch your sugar intake for any reason.

3. HOW TO TAKE POSACONAZOLE SP

Posaconazole SP must only be used as directed by your doctor. Your doctor will monitor your response and condition to determine how long Posaconazole SP needs to be given and whether any change is needed to your daily dose.

Indication	Dose
Treatment of refractory 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 unable to tolerate food. 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 200 mg (one 5 ml spoonful) once. After the first day, take 100 mg (2.5 ml) once a day with food or nutritional supplement if you are unable to tolerate food.
Prevention of serious Fungal Infections	Take 200 mg (one 5 ml spoonful) three times a day with food or nutritional supplement if you are unable to tolerate food.

If you take more Posaconazole SP than you should
If you are concerned that you may have taken too much, contact your doctor or healthcare professional immediately.

If you forget to take Posaconazole SP
If you have missed a dose, take it as soon as you remember and then carry on as before. However, if it is almost time for your next dose, take your dose when it is due. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Posaconazole SP can cause side effects, although not everybody gets them.

Common side effects (occurring in at least 1 in 100 patients) are:
Headache, dizziness, numbness or tingling
Sleepiness
Nausea (feeling or being sick), loss of appetite, stomach pain, diarrhoea, upset stomach, vomiting, wind, dry mouth
Abnormal liver function tests
Rash
Weakness, tiredness
A decrease in white blood cells (that can increase the risk of infections)
Fever
Abnormal levels of salts in the blood.

Uncommon side effects (occurring in at least 1 in 1,000 patients) are:
Anaemia, low numbers of cells called platelets that help the blood to clot, low numbers of some types of white blood cells, enlargement of lymph glands
Allergic reaction
High blood levels of glucose
Disturbances in feeling or moving, tremor, fits
Heart rhythm problems including very fast heartbeat (palpitations), abnormal findings on heart tests (like ECGs that show heart rhythm)
High or low blood pressure
Inflammation of the pancreas
Inflammation of liver, liver damage, jaundice (yellow colour of the skin or the eyes)
Problems with kidney function, failure of the kidneys
Menstrual disorder
Blurred vision
Hair loss, itching
Mouth ulcers

Shivering, generally feeling unwell or weak
Scattered body pain, including in muscles and joints, back pain
Fluid retention, altered medicine levels.

Rare side effects (occurring in at least 1 in 10,000 patients) are:
Pneumonia and other lung damage
Low numbers of all blood cells, blood clotting disorder, bleeding
Severe allergic reactions, including widespread blistering rash and skin peeling
Poor functioning of the adrenal gland
Altered brain function, fainting
Sudden behaviour changes, problems with thinking or speech
Pain, weakness, numbness, or tingling in the arm or leg
Depression
Double vision, a blind or dark spot in the visual field
Hearing problems
Heart failure or heart attack, heart rhythm disorders
Stroke, blood clots in brain, limbs or lungs
Bleeding into the gut
Inflammation or failure of the liver, rarely leading to death
Enlargement of both the liver and spleen, liver tenderness
Blistering rash, large purple discolourations on the skin caused by bleeding underneath the skin
Inflammation of the kidneys
Breast pain
Swelling of the face or tongue.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE POSACONAZOLE SP

Keep out of the reach and sight of children.

Do not freeze.

Do not use Posaconazole SP after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

If you have any suspension left in a bottle more than four weeks after it was first opened, you should not use this medicine. Please return the bottle containing any left over suspension to your pharmacist.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Posaconazole SP contains

- The active substance in Posaconazole SP oral suspension is posaconazole. Each millilitre of oral suspension contains 40 milligrams of posaconazole.
  The other ingredients in the suspension are polysorbate 80, simeticone, sodium benzoate (E211), sodium citrate dihydrate, citric acid monohydrate, glycerol, xanthan gum, liquid glucose, titanium dioxide (E171), artificial cherry flavour containing benzyl alcohol and propylene glycol, and purified water.

What Posaconazole SP looks like and contents of the pack

Posaconazole SP is a white, cherry flavoured, 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 oral suspension.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
SP Europe
Rue de Stalle, 73
B-1180 Bruxelles
Belgium

Manufacturer:
SP S.A.
2, rue Louis Pasteur
F-14200 Hérouville St Clair
France

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/