ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 40 mg/mL oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral suspension contains 40 mg of posaconazole.

Excipient with known effect:
This medicinal product contains approximately 1.75 g of glucose per 5 mL of suspension.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

White suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Noxafil oral suspension 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.

Noxafil oral suspension 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

Non-Interchangeability between Noxafil Tablets and Noxafil Oral Suspension

The tablet and oral suspension are not to be used interchangeably due to the differences between these

two formulations in frequency of dosing, administration with food and plasma drug concentration achieved. Therefore, follow the specific dosage recommendations for each formulation.

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.

Posology
Noxafil is also available as 100 mg gastro-resistant tablet and 300 mg concentrate for solution for infusion. Noxafil tablets are the preferred formulation to optimize plasma concentrations and generally provide higher plasma drug exposures than Noxafil oral suspension.

Recommended dose is shown in Table 1.

Table 1. Recommended dose according to indication

Indication	**Dose and duration of therapy** (See section 5.2)
Refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy	200 mg (5 mL) four times a day. Alternatively, patients who can tolerate food or a nutritional supplement may take 400 mg (10 mL) twice a day during or immediately following a meal or nutritional supplement. 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 Noxafil 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.
Prophylaxis of invasive fungal infections	200 mg (5 mL) three times a day. Each dose of Noxafil 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. The duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with Noxafil 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.

Special populations

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).

Hepatic impairment
Limited data on the effect of hepatic impairment (including Child-Pugh C classification of chronic liver disease) on the pharmacokinetics of posaconazole demonstrate an increase in plasma exposure compared to subjects with normal hepatic function, but do not suggest that dose adjustment is necessary (see sections 4.4 and 5.2). It is recommended to exercise caution due to the potential for higher plasma exposure.

Paediatric population
The safety and efficacy of Noxafil in children aged below 18 years have not been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration
For oral use

The oral suspension must be shaken well before use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 Noxafil 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 hepatic impairment due to limited clinical experience and the possibility that posaconazole plasma levels may be higher in these patients (see sections 4.2 and 5.2).

Monitoring of hepatic function
Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during Noxafil 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 Noxafil 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. Noxafil 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). Noxafil 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).

Gastrointestinal dysfunction
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.

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).

Midazolam and other benzodiazepines metabolised by CYP3A4
Due to the risk of prolonged sedation and possible respiratory depression co-administration of posaconazole with any benzodiazepines metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) should only be considered if clearly necessary. Dose adjustment of benzodiazepines metabolised by CYP3A4 should be considered (see section 4.5).

Excipients
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
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
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 twice daily x

10 days) decreased the C_{max} and AUC of posaconazole oral suspension (200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days) by 21 % and 23 %, respectively. The effect of posaconazole on fosamprenavir levels when fosamprenavir is given with ritonavir is unknown.

Phenytoin
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. Co-administration of posaconazole with H_2 receptor antagonists should be avoided if possible.
Similarly, administration of 400 mg posaconazole with esomeprazole (40 mg daily) decreased mean C_{max} and AUC by 46 % and 32 %, respectively, compared to dosing with 400 mg posaconazole alone. Co-administration of posaconazole with proton pump inhibitors should be avoided if possible.

Food
The absorption of posaconazole is significantly increased by food (see sections 4.2 and 5.2).

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 reactions, plasma concentrations of the CYP3A4 substrate and/or adverse reactions 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 reactions related to increased rifabutin levels (e.g. uveitis) is recommended.

Sirolimus
Repeat dose administration of posaconazole oral suspension (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 targeted and careful attention should be paid to clinical signs and symptoms, laboratory parameters and tissue biopsies.

Ciclosporin
In heart transplant patients on stable doses of ciclosporin, posaconazole oral suspension 200 mg once daily increased ciclosporin concentrations requiring dose reductions. Cases of elevated ciclosporin levels resulting in serious adverse reactions, 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.

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 posaconazole oral suspension (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 posaconazole oral suspension (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 reactions 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 oral suspension (200 mg once daily for 10 days) increased the exposure (AUC) of intravenous midazolam (0.05 mg/kg) by 83 %. In another study in healthy volunteers, repeat dose administration of posaconazole oral suspension (200 mg twice daily for 7 days) increased the C_{max} and AUC of intravenous 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 oral suspension 400 mg twice daily for 7 days increased the intravenous 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, posaconazole oral suspension (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) (see section 4.4).

Calcium channel blockers metabolised through CYP3A4 (e.g. diltiazem, verapamil, nifedipine, nisoldipine)
Frequent monitoring for adverse reactions 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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding
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.

Fertility
Posaconazole had no effect on fertility of male rats at doses up to 180 mg/kg (1.7 times the 400-mg twice daily regimen based on steady-state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 times the 400-mg twice daily regimen). There is no clinical experience assessing the impact of posaconazole on fertility in humans.

4.7 Effects on ability to drive and use machines

Since certain adverse reactions (e.g. dizziness, somnolence, etc.) have been reported with posaconazole use, which potentially may affect driving/operating machinery, caution needs to be used.

4.8 Undesirable effects

Summary of the safety profile

The safety of posaconazole oral suspension 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 reactions included nausea, vomiting, diarrhoea, pyrexia, and increased bilirubin.
The safety of posaconazole tablet has been assessed in 336 patients and healthy volunteers enrolled in clinical trials. The safety profile of tablets was similar to that of the oral suspension.

Tabulated list of adverse reactions
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known.

Table 2. Adverse reactions by body system and frequency*

Blood and lymphatic system disorders	
Common:	neutropenia
Uncommon:	thrombocytopenia, leukopenia, anaemia, eosinophilia, lymphadenopathy, splenic infarction
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, decreased appetite, hypokalaemia, hypomagnesaemia
Uncommon:	hyperglycaemia, hypoglycaemia
Psychiatric disorders	
Uncommon:	abnormal dreams, confusional state, sleep disorder
Rare:	psychotic disorder, depression
Nervous system disorders	
Common:	paresthesia, dizziness, somnolence, headache, dysgeusia
Uncommon:	convulsions, neuropathy, hypoaesthesia, tremor, aphasia, insomnia

Rare:	cerebrovascular accident, encephalopathy, peripheral neuropathy, syncope
Eye disorders	
Uncommon:	blurred vision, photophobia, visual acuity reduced
Rare:	diplopia, scotoma
Ear and labyrinth disorder	
Rare:	hearing impairment
Cardiac disorders	
Uncommon:	long QT syndrome[§], electrocardiogram abnormal[§], palpitations, bradycardia, supraventricular extrasystoles, tachycardia
Rare:	torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders	
Common:	hypertension
Uncommon:	hypotension, vasculitis
Rare:	pulmonary embolism, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	cough, epistaxis, hiccups, nasal congestion, pleuritic pain, tachypnoea
Rare:	pulmonary hypertension, interstitial pneumonia, pneumonitis
Gastrointestinal disorders	
Very Common:	nausea
Common:	vomiting, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, constipation, anorectal discomfort
Uncommon:	pancreatitis, abdominal distension, enteritis, epigastric discomfort, eructation, gastrooesophageal reflux disease, oedema mouth
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, cholestasis, hepatic toxicity, hepatic function abnormal
Rare:	hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, asterixis
Skin and subcutaneous tissue disorders	
Common:	rash, pruritis
Uncommon:	mouth ulceration, alopecia, dermatitis, erythema, petechiae
Rare:	Stevens Johnson syndrome, vesicular rash
Musculoskeletal and connective tissue disorders	
Uncommon:	back pain, neck pain, musculoskeletal pain, pain in extremity
Renal and urinary disorders	
Uncommon:	acute renal failure, renal failure, blood creatinine increased
Rare:	renal tubular acidosis, 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, pain, chills, malaise, chest discomfort, drug intolerance, feeling jittery, mucosal inflammation
Rare:	tongue oedema, face oedema
Investigations	
Uncommon:	altered medicine levels, blood phosphorus decreased, chest x-ray abnormal

* Based on adverse reactions observed with the oral suspension, gastro-resistant tablets, and concentrate for solution for infusion.

§ See section 4.4.

Description of selected adverse reactions

Hepatobiliary disorders

During post-marketing surveillance of posaconazole oral suspension, severe hepatic injury with fatal outcome has been reported (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

During clinical trials, patients who received posaconazole oral suspension 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 posaconazole oral suspension 1,200 mg twice a day for 3 days. No adverse reactions were noted by the investigator.

Posaconazole is not removed by haemodialysis. There is no special treatment available in the case of overdose with posaconazole. Supportive care may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC04.

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.

Epidemiological Cut-off (ECOFF) Values for *Aspergillus* spp.
The ECOFF values for posaconazole, which distinguish the wild type population from isolates with acquired resistance have been determined by EUCAST methodology.

EUCAST ECOFF values:
- *Aspergillus flavus*: 0.5 mg/L
- *Aspergillus fumigatus*: 0.25 mg/L
- *Aspergillus nidulans*: 0.5 mg/L
- *Aspergillus niger*: 0.5 mg/L
- *Aspergillus terreus*: 0.25 mg/L

There are currently insufficient data to set clinical breakpoints for *Aspergillus* spp. ECOFF values do not equate to clinical breakpoints.

Breakpoints
EUCAST MIC breakpoints for posaconazole [susceptible (S); resistant (R)]:
- *Candida albicans*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida tropicalis*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida parapsilosis*: S ≤0.06 mg/L, R >0.06 mg/L

There are currently insufficient data to set clinical breakpoints for other Candida species.

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

Summary of posaconazole oral suspension studies

Invasive aspergillosis
Oral posaconazole suspension 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 (Study 0041). 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 oral suspension at the end of treatment for invasive aspergillosis in comparison to an external control group

	Posaconazole oral suspension		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 %)

Fusarium spp.
11 of 24 patients who had proven or probable fusariosis were successfully treated with posaconazole oral suspension 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 oral suspension 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 oral suspension 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.

[1] Includes other less common species or species unknown

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 leukaemia 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 leukaemia 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 oral suspension	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 oral suspension	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).

Paediatric population

Sixteen patients 8-17 years of age were treated with posaconazole oral suspension 800 mg/day in a study for invasive fungal infections (Study 0041). 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 posaconazole oral suspension 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. In a study (Study 03579) of 136 neutropenic paediatric patients 11 months – 17 years treated with posaconazole oral suspension at doses up to 18 mg/kg/day divided TID, approximately 50% met the prespecified target (Day 7 Cav between 500 ng/mL-2,500 ng/mL) (see section 5.2).

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 oral suspension (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 2.6-fold.

Effect of food on oral absorption in healthy volunteers
The absorption of posaconazole was significantly increased when posaconazole 400 mg (once daily) was administered during and immediately after the consumption of a high fat meal (~ 50 grams fat) compared to administration before a meal, with C_{max} and AUC increasing by approximately 330 % and 360 %, respectively. The AUC of posaconazole is: 4 times greater when administered with a high-fat meal (~ 50 grams fat) and about 2.6 times greater when administered during a non-fat meal or nutritional supplement (14 grams fat) relative to the fasted state (see sections 4.2 and 4.5).

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.

Biotransformation
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.

Elimination
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). 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). In a study of 136 neutropenic paediatric patients 11 months – 17 years treated with posaconazole oral suspension at doses up to 18 mg/kg/day divided TID, approximately 50% met the prespecified target (Day 7 Cav between 500 ng/mL-2,500 ng/mL). In general, exposures tended to be higher in the older patients (7 to <18 years) than in younger patients (2 to <7 years).

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 oral suspension in Black subjects relative to Caucasian subjects. However, the safety profile of posaconazole between the Black and Caucasian subjects was similar.

Weight
Pharmacokinetic modeling with an oral tablet formulation suggests that patients weighing greater than 120 kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg. Patients with a low body weight (< 60 kg) are more likely to experience higher plasma concentrations of posaconazole and should be closely monitored for adverse events.

Renal impairment
Following single-dose administration of posaconazole oral suspension, 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
After a single oral dose of 400 mg posaconazole oral suspension to patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (six per group), the mean AUC was 1.3 to 1.6-fold higher compared to that for matched control subjects with normal hepatic function. Unbound concentrations were not determined and it cannot be excluded that there is a larger increase in unbound posaconazole exposure than the observed 60 % increase in total AUC. The elimination half-life ($t^{1/2}$) was prolonged from approximately 27 hours up to ~43 hours in respective groups. No dose adjustment is recommended for patients with mild to severe hepatic impairment but caution is advised due to the potential for higher plasma 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 concentrations

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 the human 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: 3 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 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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/320/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 25 October 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 100 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 100 mg of posaconazole.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet (tablet)
Yellow-coated, capsule-shaped tablet of 17.5 mm length debossed with “100” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Noxafil gastro-resistant tablets are 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.

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.

Noxafil gastro-resistant tablets are 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.

Please refer to the Summary of Product Characteristics of Noxafil oral suspension for use in oropharyngeal candidiasis.

4.2 Posology and method of administration

Non-Interchangeability between Noxafil Tablets and Noxafil Oral Suspension

The tablet and oral suspension are not to be used interchangeably due to the differences between these two formulations in frequency of dosing, administration with food and plasma drug concentration achieved. Therefore, follow the specific dosage recommendations for each formulation.

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.

Posology
Noxafil is also available as 40 mg/mL oral suspension and 300 mg concentrate for solution for infusion. Noxafil tablets are the preferred formulation to optimize plasma concentrations and generally provide higher plasma drug exposures than Noxafil oral suspension.

Recommended dose is shown in Table 1.

Table 1. Recommended dose according to indication

Indication	**Dose and duration of therapy** (See section 5.2)
Refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Prophylaxis of invasive fungal infections	Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with Noxafil 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.

Special populations

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).

Hepatic impairment
Limited data on the effect of hepatic impairment (including Child-Pugh C classification of chronic liver disease) on the pharmacokinetics of posaconazole demonstrate an increase in plasma exposure compared to subjects with normal hepatic function, but do not suggest that dose adjustment is necessary (see sections 4.4 and 5.2). It is recommended to exercise caution due to the potential for higher plasma exposure.

Paediatric population
The safety and efficacy of Noxafil in children aged below 18 years have not been established. Currently available data are described in sections 5.1 and 5.2, but no recommendation on a posology can be made.

No data are available for the tablet formulation.

Method of administration
For oral use

Noxafil gastro-resistant tablets may be taken with or without food (see section 5.2). The tablets should be swallowed whole with water and should not be crushed, chewed, or broken.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 Noxafil 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 hepatic impairment due to limited clinical experience and the possibility that posaconazole plasma levels may be higher in these patients (see sections 4.2 and 5.2).

Monitoring of hepatic function
Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during Noxafil 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 Noxafil 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. Noxafil 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). Noxafil 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).

Gastrointestinal dysfunction
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.

Rifamycin antibacterials (rifampicin, rifabutin), certain anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), and efavirenz.
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).

Midazolam and other benzodiazepines metabolised by CYP3A4
Due to the risk of prolonged sedation and possible respiratory depression co-administration of posaconazole with any benzodiazepines metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) should only be considered if clearly necessary. Dose adjustment of benzodiazepines metabolised by CYP3A4 should be considered (see section 4.5).

Plasma exposure
Posaconazole plasma concentrations following administration of posaconazole tablets are generally higher than those obtained with posaconazole oral suspension. Posaconazole plasma concentrations following administration of posaconazole tablets may increase over time in some patients (see section 5.2). Safety data at higher exposure levels achieved with posaconazole tablets are at present limited.

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
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
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 twice daily x 10 days) decreased the C_{max} and AUC of posaconazole oral suspension (200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days) by 21 % and 23 %, respectively. The effect of posaconazole on fosamprenavir levels when fosamprenavir is given with ritonavir is unknown.

Phenytoin
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
No clinically relevant effects were observed when posaconazole tablets are concomitantly used with antacids, H_2-receptor antagonists and proton pump inhibitors. No dosage adjustment of posaconazole tablets is required when posaconazole tablets are concomitantly used with antacids, H_2-receptor antagonists and proton pump inhibitors.

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 reactions, plasma concentrations of the CYP3A4 substrate and/or adverse reactions 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.

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 reactions related to increased rifabutin levels (e.g. uveitis) is recommended.

Sirolimus
Repeat dose administration of posaconazole oral suspension (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 targeted and careful attention should be paid to clinical signs and symptoms, laboratory parameters and tissue biopsies.

Ciclosporin
In heart transplant patients on stable doses of ciclosporin, posaconazole oral suspension 200 mg once daily increased ciclosporin concentrations requiring dose reductions. Cases of elevated ciclosporin levels resulting in serious adverse reactions, 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.

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 posaconazole oral suspension (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 posaconazole oral suspension (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 reactions 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 oral suspension (200 mg once daily for 10 days) increased the exposure (AUC) of intravenous midazolam (0.05 mg/kg) by 83 %. In another study in healthy volunteers, repeat dose administration of posaconazole oral suspension (200 mg twice daily

for 7 days) increased the C_{max} and AUC of intravenous 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 oral suspension 400 mg twice daily for 7 days increased the intravenous 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, posaconazole oral suspension (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) (see section 4.4).

Calcium channel blockers metabolised through CYP3A4 (e.g. diltiazem, verapamil, nifedipine, nisoldipine)
Frequent monitoring for adverse reactions 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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding
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.

Fertility
Posaconazole had no effect on fertility of male rats at doses up to 180 mg/kg (3.4 times the 300-mg tablet based on steady-state plasma concentrations in patients) or female rats at a dose up to 45 mg/kg (2.6 times the 300-mg tablet based on steady-state plasma concentrations in patients). There is no clinical experience assessing the impact of posaconazole on fertility in humans.

4.7 Effects on ability to drive and use machines

Since certain adverse reactions (e.g. dizziness, somnolence, etc.) have been reported with posaconazole use, which potentially may affect driving/operating machinery, caution needs to be used.

4.8 Undesirable effects

Safety data mainly derive from studies with the oral suspension.

The tablet formulation was investigated in AML and MDS patients and those after HSCT with or at risk for Graft versus Host Disease (GvHD) only. Maximum duration of exposure to the tablet formulation was shorter than with the oral suspension. Plasma exposure resulting from the tablet formulation was higher than observed with the oral suspension. A higher incidence of adverse reactions cannot be ruled out.

Summary of the safety profile

Posaconazole tablets
The safety of posaconazole tablets has been assessed in 230 patients enrolled in the pivotal clinical study. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole tablets when given as antifungal prophylaxis. Patients were immunocompromised with underlying conditions including haematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. Posaconazole therapy was given for a median duration of 28 days. Twenty patients received 200 mg daily dose and 210 patients received 300 mg daily dose (following twice daily dosing on Day 1 in each cohort).

Posaconazole tablet and oral suspension safety
The safety of posaconazole oral suspension 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 reactions included nausea, vomiting, diarrhoea, pyrexia, and increased bilirubin.
The safety of posaconazole tablet has been assessed in 336 patients and healthy volunteers enrolled in clinical trials. The safety profile of tablets was similar to that of the oral suspension.

Tabulated list of adverse reactions
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known.

Table 2. Adverse reactions by body system and frequency*

Blood and lymphatic system disorders	
Common:	neutropenia
Uncommon:	thrombocytopenia, leukopenia, anaemia, eosinophilia, lymphadenopathy, splenic infarction
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, decreased appetite, hypokalaemia, hypomagnesaemia
Uncommon:	hyperglycaemia, hypoglycaemia
Psychiatric disorders	
Uncommon:	abnormal dreams, confusional state, sleep disorder
Rare:	psychotic disorder, depression

Nervous system disorders	
Common:	paresthesia, dizziness, somnolence, headache, dysgeusia
Uncommon:	convulsions, neuropathy, hypoaesthesia, tremor, aphasia, insomnia
Rare:	cerebrovascular accident, encephalopathy, peripheral neuropathy, syncope
Eye disorders	
Uncommon:	blurred vision, photophobia, visual acuity reduced
Rare:	diplopia, scotoma
Ear and labyrinth disorder	
Rare:	hearing impairment
Cardiac disorders	
Uncommon:	long QT syndrome[§], electrocardiogram abnormal[§], palpitations, bradycardia, supraventricular extrasystoles, tachycardia
Rare:	torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders	
Common:	hypertension
Uncommon:	hypotension, vasculitis
Rare:	pulmonary embolism, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	cough, epistaxis, hiccups, nasal congestion, pleuritic pain, tachypnoea
Rare:	pulmonary hypertension, interstitial pneumonia, pneumonitis
Gastrointestinal disorders	
Very Common:	nausea
Common:	vomiting, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, constipation, anorectal discomfort
Uncommon:	pancreatitis, abdominal distension, enteritis, epigastric discomfort, eructation, gastrooesophageal reflux disease, oedema mouth
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, cholestasis, hepatic toxicity, hepatic function abnormal
Rare:	hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, asterixis
Skin and subcutaneous tissue disorders	
Common:	rash, pruritis
Uncommon:	mouth ulceration, alopecia, dermatitis, erythema, petechiae
Rare:	Stevens Johnson syndrome, vesicular rash
Musculoskeletal and connective tissue disorders	
Uncommon:	back pain, neck pain, musculoskeletal pain, pain in extremity
Renal and urinary disorders	
Uncommon:	acute renal failure, renal failure, blood creatinine increased
Rare:	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, chest discomfort, drug intolerance, feeling jittery, mucosal inflammation tongue oedema, face oedema
Investigations Uncommon:	 altered medicine levels, blood phosphorus decreased, chest x-ray abnormal

* Based on adverse reactions observed with the oral suspension, gastro-resistant tablets, and concentrate for solution for infusion.

§ See section 4.4.

Description of selected adverse reactions

Hepatobiliary disorders

During post-marketing surveillance of posaconazole oral suspension, severe hepatic injury with fatal outcome has been reported (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose of posaconazole tablets.

During clinical trials, patients who received posaconazole oral suspension 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 posaconazole oral suspension 1,200 mg twice a day for 3 days. No adverse reactions were noted by the investigator.

Posaconazole is not removed by haemodialysis. There is no special treatment available in the case of overdose with posaconazole. Supportive care may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC04.

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.

Epidemiological Cut-off (ECOFF) Values for *Aspergillus spp.*
The ECOFF values for posaconazole, which distinguish the wild type population from isolates with acquired resistance have been determined by EUCAST methodology.

EUCAST ECOFF values:
- *Aspergillus flavus*: 0.5 mg/L
- *Aspergillus fumigatus*: 0.25 mg/L
- *Aspergillus nidulans*: 0.5 mg/L
- *Aspergillus niger*: 0.5 mg/L
- *Aspergillus terreus*: 0.25 mg/L

There are currently insufficient data to set clinical breakpoints for *Aspergillus* spp. ECOFF values do not equate to clinical breakpoints.

Breakpoints
EUCAST MIC breakpoints for posaconazole [susceptible (S); resistant (R)]:
- *Candida albicans*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida tropicalis*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida parapsilosis*: S ≤0.06 mg/L, R >0.06 mg/L

There are currently insufficient data to set clinical breakpoints for other Candida species.

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.

Clinical experience

Summary of posaconazole tablet bridging study
Study 5615 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole tablet. Study 5615 was conducted in a similar patient population to that previously studied in the pivotal posaconazole oral suspension clinical program. The pharmacokinetics and safety data from Study 5615 were bridged to the existing data (including efficacy data) with the oral suspension.

The subject population included: 1) patients with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia, or 2) patients who had undergone a HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. Two different dosing groups were evaluated: 200 mg twice daily on Day 1, followed by 200 mg once daily thereafter (Part IA) and 300 mg twice daily on Day 1, followed by 300 mg once daily thereafter (Part 1B and Part 2).

Serial PK samples were collected on Day 1 and at steady-state on Day 8 for all Part 1 subjects and a subset of Part 2 subjects. Moreover, sparse PK samples were collected at several days during steady state before the next dose (C_{min}) for a larger subject population. Based on average C_{min} concentrations,

a predicted average concentration (Cav) could be calculated for 186 subjects dosed with 300 mg. PK analysis in patients of Cav found that 81 % of the subjects treated with the 300 mg once daily dose attained steady state predicted Cav between 500-2,500 ng/mL. One subject (<1 %) had a predicted Cav below 500 ng/mL and 19 % of the subjects had a predicted Cav above 2,500 ng/mL. Subjects achieved a mean predicted Cav at steady state of 1,970 ng/mL.

In Table 3 a comparison is shown of exposure (Cav) after administration of posaconazole tablet and posaconazole oral suspension at therapeutic doses in patients depicted as quartile analysis. Exposures after tablet administration are generally higher than, but overlapping with, exposures after administration of posaconazole oral suspension.

Table 3. Cav quartile analyses of pivotal patient studies with posaconazole tablet and oral suspension

	Posaconazole tablet	**Posaconazole oral suspension**		
	Prophylaxis in AML and HSCT Study 5615	**Prophylaxis in GVHD Study 316**	**Prophylaxis in Neutropenia Study 1899**	**Treatment - Invasive Aspergillosis Study 0041**
	300 mg once daily (Day 1 300 mg twice daily)*	**200 mg three times daily**	**200 mg three times daily**	**200 mg four times daily (hospitalized) then 400 mg twice daily**
Quartile	**pCav Range (ng/mL)**	**Cav Range (ng/mL)**	**Cav Range (ng/mL)**	**Cav Range (ng/mL)**
Q1	442 – 1,223	22 – 557	90 – 322	55 – 277
Q2	1,240 – 1,710	557 – 915	322 – 490	290 – 544
Q3	1,719 – 2,291	915 – 1,563	490 – 734	550 – 861
Q4	2,304 – 9,523	1,563 – 3,650	734 – 2,200	877 – 2,010

pCav: predicted Cav
Cav = the average concentration when measured at steady state
*20 patients received 200 mg once daily (Day 1 200 mg twice daily)

Summary of posaconazole oral suspension studies

Invasive aspergillosis
Oral posaconazole suspension 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 (Study 0041). 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 4, 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 4. Overall efficacy of posaconazole oral suspension at the end of treatment for invasive aspergillosis in comparison to an external control group

	Posaconazole oral suspension		External control group	
Overall Response	45/107 (42 %)		22/86 (26 %)	
Success by Species All mycologically confirmed *Aspergillus* spp.[2]	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 %)

Fusarium spp.
11 of 24 patients who had proven or probable fusariosis were successfully treated with posaconazole oral suspension 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 oral suspension 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 oral suspension 800 mg/day in divided doses for a median of 296 days and up to 460 days.

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 leukaemia 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 leukaemia 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.

[2] Includes other less common species or species unknown

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 oral suspension	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 oral suspension	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).

Paediatric population
There is no paediatric experience for posaconazole tablets.

Sixteen patients 8-17 years of age were treated with posaconazole oral suspension 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 posaconazole oral suspension 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 oral suspension (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

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).

Absorption
Posaconazole tablets are absorbed with a median T_{max} of 4 to 5 hours and exhibits dose proportional pharmacokinetics after single and multiple dosing up to 300 mg.

Following a single dose administration of 300 mg posaconazole tablets after a high fat meal to healthy volunteers, the $AUC_{0\text{-}72\ hours}$ and C_{max} were higher compared to administration under fasted condition (51 % and 16 % for $AUC_{0\text{-}72\ hours}$ and C_{max} respectively).

Posaconazole plasma concentrations following administration of posaconazole tablets may increase over time in some patients. The reason for this time-dependency is not completely understood.

Distribution
Posaconazole, after administration of the tablet, has a mean apparent volume of distribution of 394 L (42 %), ranging between 294-583 L among the studies in healthy volunteers.

Posaconazole is highly protein bound (> 98 %), predominantly to serum albumin.

Biotransformation
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.

Elimination
Posaconazole after administration of the tablets, is slowly eliminated with a mean half-life ($t_{½}$) of 29 hours (range 26 to 31 hours) and a mean apparent clearance ranging from 7.5 to 11 L/hr. 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 plasma concentrations are attained by Day 6 at the 300 mg dose (once daily after twice daily loading dose at Day 1).

Pharmacokinetics in special populations

Children (< 18 years)

There is no paediatric experience with posaconazole tablets.

The pharmacokinetics of posaconazole oral suspension have been evaluated in paediatric patients. Following administration of 800 mg per day of posaconazole oral suspension 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 tablets are comparable in men and women.

Elderly

The pharmacokinetics of posaconazole tablets are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Race

There is insufficient data among different races with posaconazole tablets.

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

Weight

Pharmacokinetic modeling with an oral tablet formulation suggests that patients weighing greater than 120 kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg.

Patients, in particular those receiving posaconazole after HSCT, who have a low body weight (< 60 kg) are more likely to experience higher plasma concentrations of posaconazole and should be closely monitored for adverse events.

Renal impairment

Following single-dose administration of posaconazole oral suspension, 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.

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

Hepatic impairment
After a single oral dose of 400 mg posaconazole oral suspension to patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (six per group), the mean AUC was 1.3 to 1.6-fold higher compared to that for matched control subjects with normal hepatic function. Unbound concentrations were not determined and it cannot be excluded that there is a larger increase in unbound posaconazole exposure than the observed 60 % increase in total AUC. The elimination half-life ($t^{1/2}$) was prolonged from approximately 27 hours up to ~43 hours in respective groups. No dose adjustment is recommended for patients with mild to severe hepatic impairment but caution is advised due to the potential for higher plasma exposure.

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

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 maximal plasma concentrations 8.5-fold greater than the concentrations 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 2.1-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 2.1-fold and 8.5-fold greater, respectively, than those achieved with the human 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

Tablet core
Hypromellose acetate succinate
Cellulose, microcrystalline

Hydroxypropylcellulose (E463)
Silica dental type
Croscarmellose sodium
Magnesium stearate

Tablet coat
polyvinyl alcohol
macrogol 3350
titanium dioxide (E171)
talc
iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Noxafil 100 mg gastro-resistant tablets are packaged in a PVC/ polychlorotrifluoroethylene laminate blister with push-through aluminium lidding.

Noxafil gastro-resistant tablets are packaged in a blister in cartons of 24 (2x12) or 96 (8x12) tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/320/002	24 tablets
EU/1/05/320/003	96 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005

Date of latest renewal: 25 October 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 300 mg of posaconazole.
Each mL contains 18 mg of posaconazole.

Excipient with known effect:
Each vial contains 462 mg (20 mmol) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless to yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Noxafil concentrate for solution for infusion 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.

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.

Noxafil concentrate for solution for infusion 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 (GVHD) and who are at high risk of developing invasive fungal infections.

Please refer to the Summary of Product Characteristics of Noxafil oral suspension for use in oropharyngeal candidiasis.

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.

Posology
Noxafil is also available for oral administration (Noxafil 100 mg gastro-resistant tablets and 40 mg/mL oral suspension). A switch to oral administration is recommended as soon as the patients' condition allows (see section 4.4).

Recommended dose is shown in Table 1.

Table 1. Recommended dose according to indication

Indication	**Dose and duration of therapy** (See section 5.2)
Refractory invasive fungal infections (IFI)/patients with IFI intolerant to 1st line therapy	Loading dose of 300 mg Noxafil twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Prophylaxis of invasive fungal infections	Loading dose of 300 mg Noxafil twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with AML or MDS, prophylaxis with Noxafil 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.

Noxafil should be administered via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous infusion over approximately 90 minutes. Noxafil concentrate for solution for infusion should not be given by bolus administration. If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes (see section 4.8 and 6.6).

Special populations

Renal impairment
In patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, Betadex Sulfobutyl Ether Sodium (SBECD), is expected to occur. Oral formulations of Noxafil should be used in these patients unless an assessment of the benefit/risk to the patient justifies the use of Noxafil concentrate for solution for infusion. Serum creatinine levels should be closely monitored in these patients (see section 4.4).

Hepatic impairment
Limited data on the effect of hepatic impairment (including Child-Pugh C classification of chronic liver disease) on the pharmacokinetics of posaconazole demonstrate an increase in plasma exposure compared to subjects with normal hepatic function, but do not suggest that dose adjustment is necessary (see sections 4.4 and 5.2). It is recommended to exercise caution due to the potential for higher plasma exposure.

Paediatric population
The safety and efficacy of Noxafil concentrate for solution for infusion in children aged below 18 years have not been established.
No data are available.

Noxafil concentrate for solution for infusion should not be used in children aged below 18 years because of pre-clinical safety concerns (see section 5.3).

Method of administration
Noxafil concentrate for solution for infusion requires dilution (see section 6.6) prior to administration. Noxafil should be administered via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous (IV) infusion over approximately 90 minutes (see sections 4.2, 4.4, and 4.8).
Noxafil concentrate for solution for infusion should not be given by bolus administration.

If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes to reduce the likelihood of infusion site reactions (see section 4.8).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 Noxafil to patients with hypersensitivity to other azoles.

Hepatic toxicity
Hepatic reactions (e.g. 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 hepatic impairment due to limited clinical experience and the possibility that posaconazole plasma levels may be higher in these patients (see sections 4.2 and 5.2).

Monitoring of patients with severe renal impairment
Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see sections 4.2 and 5.2).

Monitoring of hepatic function
Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during Noxafil 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 Noxafil 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. Noxafil 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). Noxafil 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.
In patients, mean maximum plasma concentrations (C_{max}) after posaconazole concentrate for solution for infusion are 4-fold increased compared to administration of oral suspension. An increased effect on the QTc interval cannot be ruled out. Particular caution is advised in such cases where posaconazole is administered peripherally, as the recommended infusion time of 30 minutes may further increase C_{max}.

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).

Rifamycin antibacterials (rifampicin, rifabutin), certain anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), and efavirenz
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).

Midazolam and other benzodiazepines metabolised by CYP3A4
Due to the risk of prolonged sedation and possible respiratory depression co-administration of posaconazole with any benzodiazepines metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam) should only be considered if clearly necessary. Dose adjustment of benzodiazepines metabolised by CYP3A4 should be considered (see section 4.5).

Plasma exposure
Plasma concentrations following administration of posaconazole intravenous concentrate for solution for infusion are generally higher than those obtained with posaconazole oral suspension.
Posaconazole plasma concentrations following administration of posaconazole may increase over time in some patients (see section 5.2). Safety data at higher exposure levels achieved with posaconazole concentrate for solution for infusion are at present limited.

Thromboembolic events
Thromboembolic events have been identified as a potential risk for posaconazole intravenous concentrate for solution for infusion but were not observed in the clinical studies. Thrombophlebitis was observed in clinical trials. Caution is warranted on any sign or symptom of thromboembolic events (see sections 4.8 and 5.3).

Sodium content
Each vial of Noxafil contains 462 mg (20 mmol) of sodium. This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

The following information was derived from data with posaconazole oral suspension or early tablet formulation. All drug interactions with posaconazole oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility) are considered relevant to posaconazole concentrate for solution for infusion as well.

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

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

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 twice daily x 10 days) decreased the C_{max} and AUC of posaconazole oral suspension (200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days) by 21 % and 23 %, respectively. The effect of posaconazole on fosamprenavir levels when fosamprenavir is given with ritonavir is unknown.

Phenytoin

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.

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 reactions, plasma concentrations of the CYP3A4 substrate and/or adverse reactions should be closely monitored and the dose adjusted as needed.

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
After oral administration, 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 reactions related to increased rifabutin levels (e.g. uveitis) is recommended.

Sirolimus
Repeat dose administration of oral posaconazole oral suspension (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 targeted and careful attention should be paid to clinical signs and symptoms, laboratory parameters and tissue biopsies.

Ciclosporin
In heart transplant patients on stable doses of ciclosporin, posaconazole oral suspension 200 mg once daily increased ciclosporin concentrations requiring dose reductions. Cases of elevated ciclosporin levels resulting in serious adverse reactions, 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.

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 posaconazole oral suspension (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 posaconazole oral suspension (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 reactions 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 oral suspension (200 mg once daily for 10 days) increased the exposure (AUC) of intravenous midazolam (0.05 mg/kg) by 83 %. In another study in healthy volunteers, repeat dose administration of posaconazole oral suspension (200 mg twice daily for 7 days) increased the C_{max} and AUC of intravenous 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 oral suspension 400 mg twice daily for 7 days increased the intravenous 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, posaconazole oral suspension (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) (see section 4.4).

Calcium channel blockers metabolised through CYP3A4 (e.g. diltiazem, verapamil, nifedipine, nisoldipine)
Frequent monitoring for adverse reactions 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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding
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.

Fertility
Posaconazole had no effect on fertility of male rats at doses up to 180 mg/kg (2.8 times the exposure achieved from a 300 mg intravenous dose in human) or female rats at a dose up to 45 mg/kg (3.4 times the exposure from a 300 mg intravenous dose in patients). There is no clinical experience assessing the impact of posaconazole on fertility in humans.

4.7 Effects on ability to drive and use machines

Since certain adverse reactions (e.g. dizziness, somnolence, etc.) have been reported with posaconazole use, which potentially may affect driving/operating machinery, caution needs to be used.

4.8 Undesirable effects

Safety data mainly derive from studies with the oral suspension.

Noxafil concentrate for solution for infusion was investigated in AML and MDS patients and those after HSCT with or at risk for GVHD only. Maximum duration of exposure to the concentrate for solution for infusion was shorter than with the oral suspension. Plasma exposure resulting from the solution for infusion was higher than observed with the oral suspension. A higher incidence of adverse reactions cannot be ruled out.

Summary of the safety profile

Posaconazole concentrate for solution for infusion safety
In initial studies of healthy volunteers, administration of a single dose of posaconazole infused over 30 minutes via a peripheral venous catheter was associated with a 12 % incidence of infusion site reactions (4 % incidence of thrombophlebitis). Multiple doses of posaconazole administered via a peripheral venous catheter were associated with thrombophlebitis (60 % incidence). Therefore, in subsequent studies posaconazole was administered via central venous catheter. If a central venous catheter was not readily available, patients could receive a single infusion over 30 minutes via a peripheral venous catheter. Peripheral infusion time longer than 30 minutes, leads to a higher incidence of infusion site reactions and thrombophlebitis.

The safety of posaconazole concentrate for solution for infusion has been assessed in 268 patients in clinical trials. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole concentrate for solution for infusion when given as antifungal prophylaxis (Study 5520). Eleven patients received a single dose of 200 mg posaconazole concentrate for solution for infusion, 21 patients received 200 mg daily dose for a median of 14 days, and 237 patients received 300 mg daily dose for a median of 9 days. No safety data are available for administration > 28 days. Safety data in the elderly are limited.

The most frequently reported adverse reaction (>25 %) with an onset during the posaconazole intravenous phase of dosing with 300 mg once daily was diarrhoea (32 %).

The most common adverse reaction (>1 %) leading to discontinuation of posaconazole concentrate for solution for infusion 300 mg once daily was AML (1 %).

Tabulated list of adverse reactions
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known.

Table 2. Adverse reactions by body system and frequency*

Blood and lymphatic system disorders	
Common:	neutropenia
Uncommon:	thrombocytopenia, leukopenia, anaemia, eosinophilia, lymphadenopathy, splenic infarction
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, decreased appetite, hypokalaemia, hypomagnesaemia
Uncommon:	Hyperglycaemia, hypoglycaemia
Psychiatric disorders	
Uncommon:	abnormal dreams, confusional state, sleep disorder
Rare:	psychotic disorder, depression
Nervous system disorders	
Common:	paresthesia, dizziness, somnolence, headache, dysgeusia
Uncommon:	convulsions, neuropathy, hypoaesthesia, tremor, aphasia, insomnia
Rare:	cerebrovascular accident, encephalopathy, peripheral neuropathy, syncope
Eye disorders	
Uncommon:	blurred vision, photophobia, visual acuity reduced
Rare:	diplopia, scotoma
Ear and labyrinth disorder	
Rare:	hearing impairment
Cardiac disorders	
Uncommon:	long QT syndrome[§], electrocardiogram abnormal[§], palpitations, bradycardia, supraventricular extrasystoles, tachycardia
Rare:	torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders	
Common:	hypertension
Uncommon:	hypotension, thrombophlebitis, vasculitis

Rare:	pulmonary embolism, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	cough, epistaxis, hiccups, nasal congestion, pleuritic pain, tachypnoea
Rare:	pulmonary hypertension, interstitial pneumonia, pneumonitis
Gastrointestinal disorders	
Very Common	nausea
Common:	vomiting, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, constipation, anorectal discomfort
Uncommon:	pancreatitis, abdominal distension, enteritis, epigastric discomfort, eructation, gastrooesophageal reflux disease, oedema mouth
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, cholestasis, hepatic toxicity, hepatic function abnormal
Rare:	hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, asterixis
Skin and subcutaneous tissue disorders	
Common:	rash, pruritis
Uncommon:	mouth ulceration, alopecia, dermatitis, erythema, petechiae
Rare:	Stevens Johnson syndrome, vesicular rash
Musculoskeletal and connective tissue disorders	
Uncommon:	back pain, neck pain, musculoskeletal pain, pain in extremity
Renal and urinary disorders	
Uncommon:	acute renal failure, renal failure, blood creatinine increased
Rare:	renal tubular acidosis, 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, pain, chills, malaise, chest discomfort, drug intolerance, feeling jittery, infusion site pain, infusion site phlebitis, infusion site thrombosis, mucosal inflammation
Rare:	tongue oedema, face oedema
Investigations	
Uncommon:	altered medicine levels, blood phosphorus decreased, chest x-ray abnormal

***** Based on adverse reactions observed with the oral suspension, gastro-resistant tablets, and concentrate for solution for infusion.

[§] See section 4.4.

Description of selected adverse reactions

Hepatobiliary disorders

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no experience with overdose of posaconazole concentrate for solution for infusion.

During clinical trials, patients who received posaconazole oral suspension 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 posaconazole oral suspension 1,200 mg twice a day for 3 days. No adverse reactions were noted by the investigator.

Posaconazole is not removed by haemodialysis. There is no special treatment available in the case of overdose with posaconazole. Supportive care may be considered.

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.

Epidemiological Cut-off (ECOFF) values for *Aspergillus spp.*
The ECOFF values for posaconazole, which distinguish the wild type population from isolates with acquired resistance, have been determined by EUCAST methodology.

EUCAST ECOFF values:
- *Aspergillus flavus*: 0.5 mg/L
- *Aspergillus fumigatus*: 0.25 mg/L
- *Aspergillus nidulans*: 0.5 mg/L
- *Aspergillus niger*: 0.5 mg/L
- *Aspergillus terreus*: 0.25 mg/L

There are currently insufficient data to set clinical breakpoints for *Aspergillus* spp. ECOFF values do not equate to clinical breakpoints.

Breakpoints
EUCAST MIC breakpoints for posaconazole [susceptible (S); resistant (R)]:

- *Candida albicans*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida tropicalis*: S ≤0.06 mg/L, R >0.06 mg/L
- *Candida parapsilosis*: S ≤0.06 mg/L, R >0.06 mg/L

There are currently insufficient data to set clinical breakpoints for other Candida species.

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.

Clinical experience

Summary of posaconazole concentrate for solution for infusion bridging study
Study 5520 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole concentrate for solution for infusion.

Study 5520 enrolled a total of 279 subjects, including 268 receiving at least one dose of posaconazole concentrate for solution for infusion. Cohort 0 was designed to evaluate the tolerability of a single dose of posaconazole concentrate for solution for infusion when administered via a central line. The subject population for Cohorts 1 and 2 included subjects with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia. Two different dosing groups were evaluated in Cohorts 1 and 2: 200 mg twice daily on Day 1, followed by 200 mg once daily thereafter (Cohort 1) and 300 mg twice daily on Day 1, followed by 300 mg once daily thereafter (Cohort 2).

The subject population in Cohort 3 included: 1) patients with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia, or 2) patients who had undergone a HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. These types of patients had been previously studied in a pivotal controlled trial of posaconazole oral suspension. Based on the pharmacokinetics and safety results of Cohorts 1 and 2, all subjects in Cohort 3 received 300 mg twice daily on Day 1, followed by 300 mg once daily thereafter.

The total subject population had a mean age of 51 years (range = 18-82 years), 95 % were White, the major ethnicity was not Hispanic or Latino (92 %), and 55 % were male. The study treated 155 (65 %) subjects with AML or MDS, and 82 (35 %) subjects with HSCT, as the primary diseases at study entry.
Serial pharmacokinetic samples were collected on Day 1 and at steady-state on Day 14 for all Cohort 1 and 2 subjects and on Day 10 for a subset of Cohort 3 subjects. This serial pharmacokinetic analysis demonstrated that 94 % of the subjects treated with the 300 mg once daily dose attained steady state Cav between 500-2500 ng/mL [Cav was the average concentration of posaconazole at steady state, calculated as AUC/dosing interval (24 hours).]. This exposure was selected based on pharmacokinetic/pharmacodymanic considerations with posaconazole oral suspension. Subjects who received 300 mg once daily achieved a mean Cav at steady state of 1500 ng/mL.

Summary of posaconazole oral suspension studies

Invasive aspergillosis
Oral posaconazole suspension 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 oral suspension at the end of treatment for invasive aspergillosis in comparison to an external control group

	Posaconazole oral suspension		External control group	
Overall Response	45/107 (42 %)		22/86 (26 %)	
Success by Species All mycologically confirmed *Aspergillus* spp.[3]	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 %)

Fusarium spp.
11 of 24 patients who had proven or probable fusariosis were successfully treated with posaconazole oral suspension 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 oral suspension 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 oral suspension 800 mg/day in divided doses for a median of 296 days and up to 460 days.

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

[3] Includes other less common species or species unknown

(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 leukaemia 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 leukaemia 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 4 and 5 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 oral suspension	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 oral suspension	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).

Paediatric population
There is no paediatric experience for posaconazole concentrate for solution for infusion.

Sixteen patients 8-17 years of age were treated with posaconazole oral suspension 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 posaconazole oral suspension 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 oral suspension (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

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).

Distribution
Following administration of 300 mg posaconazole concentrate for solution for infusion over 90 minutes, mean peak plasma concentration at the end of infusion was 3280 ng/mL (74 % CV). Posaconazole exhibits dose proportional pharmacokinetics after single and multiple dosing in the therapeutic dose range (200-300 mg). Posaconazole has a distribution volume of 261 L, indicating extravascular distribution.

Posaconazole is highly protein bound (> 98 %), predominantly to serum albumin.

Biotransformation
Posaconazole does not have any major circulating metabolites. 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 of posaconazole oral suspension.

Elimination

Posaconazole, after administration of 300 mg of posaconazole concentrate for solution for infusion, is slowly eliminated with a mean half-life ($t_{½}$) of 27 hours and a mean clearance of 7.3 L/hr. After administration of ^{14}C-posaconazole as oral suspension, 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 plasma concentrations are attained by Day 6 at the 300 mg dose (once daily after twice daily loading dose at Day 1).

Posaconazole plasma concentrations following administration of posaconazole concentrate for solution for infusion single dose increased in a greater than dose proportional manner over the range of 50-200 mg; by comparison, dose-dependent increases were observed over a range of 200-300 mg.

Pharmacokinetics in special populations

Children (< 18 years)

There is no paediatric experience with posaconazole concentrate for solution for infusion (see sections 4.2 and 5.3).

Gender

The pharmacokinetics of posaconazole concentration for solution for infusion are comparable in men and women.

Elderly

The pharmacokinetics of posaconazole concentrate for solution for infusion are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Race

There is insufficient data among different races with posaconazole concentrate for solution for infusion.

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

Weight

Pharmacokinetic modeling with an oral tablet formulation suggests that patients weighing greater than 120 kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg. Patients with a low body weight (< 60 kg) are more likely to experience higher plasma concentrations of posaconazole and should be closely monitored for adverse events.

Renal impairment

Following single-dose administration of posaconazole oral suspension, 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. Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see section 4.2).

Similar recommendations apply to posaconazole concentrate for solution for infusion; however, a specific study has not been conducted with posaconazole concentrate for solution for infusion.

Hepatic impairment
After a single oral dose of 400 mg posaconazole oral suspension to patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (six per group), the mean AUC was 1.3 to 1.6-fold higher compared to that for matched control subjects with normal hepatic function. Unbound concentrations were not determined and it cannot be excluded that there is a larger increase in unbound posaconazole exposure than the observed 60 % increase in total AUC. The elimination half-life ($t^{1/2}$) was prolonged from approximately 27 hours up to ~43 hours in respective groups. No dose adjustment is recommended for patients with mild to severe hepatic impairment but caution is advised due to the potential for higher plasma exposure.

Similar recommendations apply to posaconazole concentrate for solution for infusion; however, a specific study has not been conducted with posaconazole concentrate for solution for infusion.

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 maximal plasma concentrations 8.9-fold greater than the concentrations obtained at therapeutic doses in humans with 300 mg intravenous infusion administration. Echocardiography revealed no indication of cardiac decompensation in a repeat dose safety pharmacology study in rats at a systemic exposure 2.2-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 2.2-fold and 8.9-fold greater, respectively, than those achieved with the human therapeutic doses.

A non-dose related incidence of thrombus/emboli in the lung was seen in the 1 month repeated dose study in the monkey. The clinical significance of this finding is unknown.

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.

In a nonclinical study using intravenous administration of posaconazole in very young dogs (dosed from 2-8 weeks of age) an increase in the incidence of brain ventricle enlargement was observed in treated animals as compared with concurrent control animals. No difference in the incidence of brain

ventricle enlargement between control and treated animals was observed following the subsequent 5-month treatment-free period. There were no neurologic, behavioural or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to juvenile dogs (4 days to 9 months of age). The clinical significance of this finding is unknown; therefore, the use of posaconazole concentrate for solution for infusion to patients under 18 years of age is not recommended (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex Sulfobutyl Ether Sodium (SBECD)
Disodium edetate
Hydrochloric acid [for pH adjustment]
Sodium hydroxide [for pH adjustment]
Water for injections

6.2 Incompatibilities

Noxafil must not be diluted with:

Lactated Ringer's solution
5 % dextrose with Lactated Ringer's solution
4.2 % sodium bicarbonate

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

From a microbiological point of view, once admixed, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2°C-8°C. This medicinal product is for single use only.

6.4 Special precautions for storage

Store in a refrigerator at 2°C-8°C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial closed with bromobutyl rubber stopper and aluminium seal containing 16.7 mL of solution.
Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Administration instructions for Noxafil concentrate for solution for infusion

- Equilibrate the refrigerated vial of Noxafil to room temperature.
- Aseptically transfer 16.7 mL of posaconazole to an intravenous bag (or bottle) containing a compatible admixture diluent (see below for list of diluents) using the volume ranging from

150 mL to 283 mL depending on the final concentration to be achieved (not less than 1 mg/mL and not greater than 2 mg/mL).

- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous infusion over approximately 90 minutes. Noxafil concentrate for solution for infusion should not be given by bolus administration.
- If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter with a volume to achieve a dilution of approximately 2 mg/mL. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes.
  Note: In clinical trials, multiple peripheral infusions given through the same vein resulted in infusion site reactions (see section 4.8).
- Noxafil is for single use.

The following medicinal products can be infused at the same time through the same intravenous line (or cannula) as Noxafil concentrate for solution for infusion:

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

Any products not listed in the table above should not be coadministered with Noxafil through the same intravenous line (or cannula).

Noxafil concentrate for solution for infusion should be inspected visually for particulate matter prior to administration. The solution of Noxafil ranges from colourless to pale yellow. Variations of colour within this range do not affect the quality of the product.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Noxafil must not be diluted with:

Lactated Ringer’s solution
5 % dextrose with Lactated Ringer’s solution
4.2 % sodium bicarbonate

This medicinal product must not be mixed with other medicinal products except those mentioned below:

5 % dextrose in water
0.9 % sodium chloride
0.45 % sodium chloride

5 % dextrose and 0.45 % sodium chloride
5 % dextrose and 0.9 % sodium chloride
5 % dextrose and 20 mEq KCl

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/320/004 1 vial

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2005
Date of latest renewal: 25 October 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Cenexi HSC, 2, rue Louis Pasteur; 14200 Hérouville St Clair, France

Schering-Plough Labo N.V., Industriepark 30, Zone A, BE-2220 Heist-op-den-Berg, Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 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

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Noxafil oral suspension and tablets are NOT interchangeable.

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/320/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Noxafil

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 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

105 mL
oral suspension

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach 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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/320/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 100 mg gastro-resistant tablets
posaconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 100 mg of posaconazole.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

24 gastro-resistant tablets
96 gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Noxafil oral suspension and tablets are NOT interchangeable.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/320/002 24 tablets
EU/1/05/320/003 96 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

noxafil tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 100 mg gastro-resistant tablets
posaconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Noxafil 300 mg concentrate for solution for infusion
posaconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 300 mg of posaconazole.
Each mL contains 18 mg of posaconazole.

3. LIST OF EXCIPIENTS

Excipients: Betadex Sulfobutyl Ether Sodium (SBECD), disodium edetate, hydrochloric acid and sodium hydroxide (for pH adjustment), water for injections.
Contains sodium. See package leaflet for information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
Single use vial.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/320/004 1 vial

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Noxafil 300 mg sterile concentrate
posaconazole
Intravenous use after dilution

2. METHOD OF ADMINISTRATION

See leaflet

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Noxafil 40 mg/mL oral suspension
posaconazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Noxafil is and what it is used for

Noxafil contains a medicine called posaconazole. This belongs to a group of medicines called "antifungals". It is used to prevent and treat many different fungal infections.

This medicine works by killing or stopping the growth of some types of fungi that can cause infections.

Noxafil can be used in adults to treat the following types of fungal infections when other antifungal medicines have not worked or you have had to stop taking them:
- 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 caused by a fungus 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 were not previously treated.

This medicine can also be used to prevent fungal infections in adults who are at high risk of getting a fungal infection, such as:
- patients who have a weak immune system due to having chemotherapy for "acute myelogenous leukemia" (AML) or "myelodysplastic syndromes" (MDS)
- patients having "high-dose immunosuppressive therapy" after "hematopoietic stem cell transplant" (HSCT).

2. What you need to know before you take Noxafil

Do not take Noxafil if:
- you are allergic to posaconazole or any of the other ingredients of this medicine (listed in section 6).
- you are taking: terfenadine, astemizole, cisapride, pimozide, halofantrine, quinidine, any medicines that contain "ergot alkaloids" such as ergotamine or dihydroergotamine, or a "statin" such as simvastatin, atorvastatin or lovastatin.

Do not take Noxafil if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Noxafil.

See "Other medicines and Noxafil" below for more information including information on other medicines which may interact with Noxafil.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Noxafil if you:
- have had an allergic reaction to another antifungal medicine such as ketoconazole, fluconazole, itraconazole or voriconazole.
- have or have ever had liver problems. You may need to have blood tests while you are taking this medicine.
- develop severe diarrhoea or vomiting, as these conditions may limit the effectiveness of this medicine.
- have an abnormal heart rhythm tracing (ECG) that shows a problem called long QTc interval
- have a weakness of the heart muscle or heart failure
- have a very slow heartbeat
- have heart rhythm disturbance
- have any problem with potassium, magnesium or calcium levels in your blood.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking Noxafil.

If you develop severe diarrhoea or vomiting (being sick) while taking Noxafil, talk to your doctor, pharmacist or nurse straight away, as this may stop it from working properly. See Section 4 for more information.

Children
Noxafil should not be used in children (17 years of age and younger).

Other medicines and Noxafil
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Noxafil if you are taking any of the following:
- terfenadine (used to treat allergies)
- astemizole (used to treat allergies)
- cisapride (used to treat stomach problems)
- pimozide (used to treat symptoms of Tourette's and mental illness)
- halofantrine (used to treat malaria)
- quinidine (used to treat abnormal heart rhythms).

Noxafil can increase the amount of these medicines in the blood which may lead to very serious changes to your heart rhythm:

- any medicines that contain "ergot alkaloids" such as ergotamine or dihydroergotamine used to treat migraines. Noxafil can increase the amount of these medicines in the blood which may lead to a severe decrease in blood flow to your fingers or toes and could cause damage to them.
- a "statin" such as simvastatin, atorvastatin or lovastatin used to treat high cholesterol.

Do not take Noxafil if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Other medicines

Look at the list of medicines given above that must not be taken while you are taking Noxafil. In addition to the medicines named above there are other medicines that carry a risk of rhythm problems that may be greater when they are taken with Noxafil. Please make sure you tell your doctor about all the medicines you are taking (prescribed or non-prescribed).

Certain medicines may increase the risk of side effects of Noxafil by increasing the amount of Noxafil in the blood.

The following medicines may decrease the effectiveness of Noxafil by decreasing the amount of Noxafil in the blood:

- rifabutin and rifampicin (used to treat certain infections). If you are already taking rifabutin, you will need a blood test and you will need to look out for some possible side effects of rifabutin.
- some medicines used to treat or prevent fits including; phenytoin, carbamazepine, phenobarbital or primidone).
- efavirenz and fosamprenavir 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.

Noxafil may possibly increase the risk of side effects of some other medicines by increasing the amount of these medicines in the blood. These medicines include:

- vincristine, vinblastine and other "vinca alkaloids" (used to treat cancer)
- ciclosporin (used during or after transplant surgery)
- tacrolimus and sirolimus (used during or after 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)
- midazolam, triazolam, alprazolam or other "benzodiazepines" (used as sedatives or muscle relaxants)
- diltiazem, verapamil, nifedipine, nisoldipine or other "calcium channel blockers" (used to treat high blood pressure)
- digoxin (used to treat heart failure)
- Glipizide or other "sulfonylureas" (used to treat high blood sugar).

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Noxafil.

Noxafil with food and drink

To improve absorption of posaconazole, whenever possible it should be taken during or immediately after food or a nutritional drink (see section 3 "How to take Noxafil"). There is no information on the effect of alcohol on posaconazole.

Pregnancy and breast-feeding

Tell your doctor if you are or think you are pregnant before you start to take Noxafil.
Do not take Noxafil if you are pregnant unless you are told to by your doctor.

If you are a woman who could become pregnant you should use effective contraception while you are taking this medicine. If you become pregnant while you are taking Noxafil, contact your doctor straight away.

Do not breast-feed while taking Noxafil. This is because small amounts may pass into breast milk.

Driving and using machines
You may feel dizzy, sleepy, or have blurred vision while taking Noxafil, which may affect your ability to drive or use tools or machines. If this happens, do not drive or use any tools or machines and contact your doctor.

Noxafil contains glucose
Noxafil 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 Noxafil

Do not switch between taking Noxafil tablets and Noxafil oral suspension without talking to your doctor or pharmacist because it may result in a lack of efficacy or an increased risk of adverse reactions.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Your doctor will monitor your response and condition to determine how long Noxafil needs to be given and whether any change is needed to your daily dose.

The table below shows the recommended dose and length of treatment which depend on the type of infection that you have and may be individually adapted for you by your doctor. Do not adapt your dose yourself before consulting your doctor or change your treatment regime.

Whenever possible you should take posaconazole during or immediately after food or a nutritional drink.

Indication	**Recommended dose and length of treatment**
Treatment of refractory Fungal Infections (*Invasive aspergillosis, Fusariosis, Chromoblastomycosis/Mycetoma, Coccidioidomycosis)*	The recommended dose is 200 mg (one 5 mL spoonful) taken four times daily. Alternatively, if recommended by your doctor, you may take 400 mg (two 5 mL spoonfuls) twice a day provided that you are able to take both doses during or after food or a nutritional drink.
First time 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.
Prevention of serious Fungal Infections	Take 200 mg (one 5 mL spoonful) three times a day.

If you take more Noxafil 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 Noxafil
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.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor, pharmacist or nurse straight away if you notice any of the following serious side effects – you may need urgent medical treatment:
- nausea or vomit (feeling or being sick), diarrhoea
- signs of liver problems - these include yellowing of your skin or whites of the eyes, unusually dark urine or pale faeces, feeling sick for no reason, stomach problems, loss of appetite or unusual tiredness or weakness, an increase in liver enzymes shown up in blood tests
- allergic reaction

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common: the following may affect up to 1 in 10 people
- a change in the salt level in your blood shown in blood tests - signs include feeling confused or weak
- abnormal skin sensations, such as numbness, tingling, itching, creeping, pricking or burning
- headache
- low potassium levels – shown up in blood tests
- low magnesium levels – shown up in blood tests
- high blood pressure
- loss of appetite, stomach pain or upset stomach, passing wind, dry mouth, changes in your taste
- heartburn (a burning sensation in the chest rising up to the throat)
- low levels of "neutrophils" a type of white blood cell (neutropenia) –this can make you more likely to get infections and be shown up in blood tests
- fever
- feeling weak, dizzy, tired or sleepy
- rash
- itching
- constipation
- rectal discomfort

Uncommon: the following may affect up to 1 in 100 people
- anaemia - signs include headaches, feeling tired or dizzy, being short of breath or looking pale and a low level of haemoglobin shown up in blood tests
- low level of platelets (thrombocytopenia) shown in blood tests – this may lead to bleeding
- low level of "leukocytes" a type of white blood cell (leukopenia) shown in blood tests – this can make you more likely to get infections
- high level of "eosinophils" a type of white blood cell (eosinophilia) – this can happen if you have inflammation
- inflammation of the blood vessels
- heart rhythm problems
- fits (convulsions)
- nerve damage (neuropathy)
- abnormal heart rhythm – shown up on a heart trace (ECG), palpitations, slow or fast heartbeat, high or low blood pressure
- low blood pressure
- inflammation of the pancreas (pancreatitis) – this may cause severe stomach pain

- oxygen supply to the spleen is interrupted (splenic infarction) - this may cause severe stomach pain
- severe kidney problems – signs include passing more or less urine, that is a different colour than usual
- high blood levels of creatinine – shown in blood tests
- cough, hiccups
- nose bleeds
- severe sharp chest pain when breathing in (pleurritic pain)
- swelling of lymph glands (lymphadenopathy)
- reduced feeling of sensitivity especially on the skin
- tremor
- high or low blood sugar levels
- blurred vision, sensitivity to light
- hair loss (alopecia)
- mouth ulcers
- shivering, feeling generally unwell
- pain, back or neck pain, pain in arms or legs
- water retention (oedema)
- menstrual problems (abnormal vaginal bleeding)
- inability to sleep (insomnia)
- being completely or partially unable to talk
- swelling of the mouth
- abnormal dreams, or difficulty sleeping
- problems with co-ordination or balance
- mucosal inflammation
- stuffy nose
- difficulty breathing
- chest discomfort
- feeling bloated
- mild to severe nausea, vomiting, cramps and diarrhoea, usually caused by a virus, stomach pain
- belching
- feeling jittery

<u>Rare: the following may affect up to 1 in 1,000 people</u>
- pneumonia – signs include feeling short of breath and producing discoloured phlegm
- high blood pressure in the blood vessels in the lungs (pulmonary hypertension) this can cause serious damage to your lungs and heart
- blood problems such as unusual blood clotting or prolonged bleeding
- severe allergic reactions, including widespread blistering rash and skin peeling
- mental problems such as hearing voices or seeing things that are not there
- fainting
- having problems thinking or talking, having jerking movements, especially in your hands that you cannot control
- stroke – signs include pain, weakness, numbness, or tingling in the limbs
- having a blind or dark spot in your field of vision
- heart failure or heart attack which could lead to the heart stopping beating and death, heart rhythm problems, with sudden death
- blood clots in your legs (deep vein thrombosis) – signs include intense pain or swelling of the legs
- blood clots in your lungs (pulmonary embolism) – signs include feeling short of breath or pain while breathing
- bleeding into your stomach or gut – signs include vomiting blood or passing blood in your stool

- a blockage in your gut (intestinal obstruction) especially in the “ileum”. The blockage will prevent the contents of your intestine from passing through to the lower bowel signs include feeling bloated, vomiting, severe constipation, loss of appetite, and cramps
- “haemolytic uraemic syndrome” when red blood cells breakup (hemolysis) which may happen with or without kidney failure
- “pancytopenia” low level of all blood cells (red and white blood cells and platelets) shown in blood tests
- large purple discolourations on the skin (thrombotic thrombocytopenic purpura)
- swelling of the face or tongue
- depression
- double vision
- breast pain
- adrenal glands not working properly – this may cause weakness, tiredness, loss of appetite, skin discolouration
- pituitary gland not working properly – this may cause low blood levels of some hormones that affect the function of the male or female sex organs
- hearing problems

Some patients have also reported feeling confused after taking Noxafil, the frequency of this is not known.

Tell your doctor, pharmacist or nurse if you notice any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Noxafil

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Do not freeze.
- 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.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Noxafil contains

- The active substance in Noxafil 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 Noxafil looks like and contents of the pack

Noxafil 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
Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer
Cenexi HSC
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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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Noxafil 100 mg gastro-resistant tablets
posaconazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Noxafil is and what it is used for

Noxafil contains a medicine called posaconazole. This belongs to a group of medicines called "antifungals". It is used to prevent and treat many different fungal infections.

This medicine works by killing or stopping the growth of some types of fungi that can cause infections.

Noxafil can be used in adults to treat the following types of fungal infections when other antifungal medicines have not worked or you have had to stop taking them:
- 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 caused by a fungus 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.

This medicine can also be used to prevent fungal infections in adults who are at high risk of getting a fungal infection, such as:
- patients who have a weak immune system due to having chemotherapy for "acute myelogenous leukemia" (AML) or "myelodysplastic syndromes" (MDS)
- patients having "high-dose immunosuppressive therapy" after "hematopoietic stem cell transplant" (HSCT).

2. What you need to know before you take Noxafil

Do not take Noxafil if:
- you are allergic to posaconazole or any of the other ingredients of this medicine (listed in section 6).
- you are taking: terfenadine, astemizole, cisapride, pimozide, halofantrine, quinidine, any medicines that contain "ergot alkaloids" such as ergotamine or dihydroergotamine, or a "statin" such as simvastatin, atorvastatin or lovastatin.

Do not take Noxafil if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Noxafil.

See "Other medicines and Noxafil" below for more information including information on other medicines which may interact with Noxafil.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Noxafil if you:
- have had an allergic reaction to another antifungal medicine such as ketoconazole, fluconazole, itraconazole or voriconazole.
- have or have ever had liver problems. You may need to have blood tests while you are taking this medicine.
- develop severe diarrhoea or vomiting, as these conditions may limit the effectiveness of this medicine.
- have an abnormal heart rhythm tracing (ECG) that shows a problem called long QTc interval
- have a weakness of the heart muscle or heart failure
- have a very slow heartbeat
- have heart rhythm disturbance
- have any problem with potassium, magnesium or calcium levels in your blood.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking Noxafil.

If you develop severe diarrhoea or vomiting (being sick) while taking Noxafil, talk to your doctor, pharmacist or nurse straight away, as this may stop it from working properly. See Section 4 for more information.

Children
Noxafil should not be used in children (17 years of age and younger).

Other medicines and Noxafil

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Noxafil if you are taking any of the following:
- terfenadine (used to treat allergies)
- astemizole (used to treat allergies)
- cisapride (used to treat stomach problems)
- pimozide (used to treat symptoms of Tourette's and mental illness)
- halofantrine (used to treat malaria)
- quinidine (used to treat abnormal heart rhythms).

Noxafil can increase the amount of these medicines in the blood which may lead to very serious changes to your heart rhythm:

- any medicines that contain "ergot alkaloids" such as ergotamine or dihydroergotamine used to treat migraines. Noxafil can increase the amount of these medicines in the blood which may lead to a severe decrease in blood flow to your fingers or toes and could cause damage to them.
- a "statin" such as simvastatin, atorvastatin or lovastatin used to treat high cholesterol.

Do not take Noxafil if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Other medicines

Look at the list of medicines given above that must not be taken while you are taking Noxafil. In addition to the medicines named above there are other medicines that carry a risk of rhythm problems that may be greater when they are taken with Noxafil. Please make sure you tell your doctor about all the medicines you are taking (prescribed or non-prescribed).

Certain medicines may increase the risk of side effects of Noxafil by increasing the amount of Noxafil in the blood.

The following medicines may decrease the effectiveness of Noxafil by decreasing the amount of Noxafil in the blood:

- rifabutin and rifampicin (used to treat certain infections). If you are already taking rifabutin, you will need a blood test and you will need to look out for some possible side effects of rifabutin.
- some medicines used to treat or prevent fits including; phenytoin, carbamazepine, phenobarbital or primidone).
- efavirenz and fosamprenavir used to treat HIV infection.

Noxafil may possibly increase the risk of side effects of some other medicines by increasing the amount of these medicines in the blood. These medicines include:

- vincristine, vinblastine and other "vinca alkaloids" (used to treat cancer)
- ciclosporin (used during or after transplant surgery)
- tacrolimus and sirolimus (used during or after 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)
- midazolam, triazolam, alprazolam or other "benzodiazepines" (used as sedatives or muscle relaxants)
- diltiazem, verapamil, nifedipine, nisoldipine or other "calcium channel blockers" (used to treat high blood pressure)
- digoxin (used to treat heart failure)
- Glipizide or other "sulfonylureas" (used to treat high blood sugar).

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Noxafil.

Pregnancy and breast-feeding

Tell your doctor if you are or think you are pregnant before you start to take Noxafil.
Do not take Noxafil if you are pregnant unless you are told to by your doctor.
If you are a woman who could become pregnant you should use effective contraception while you are taking this medicine. If you become pregnant while you are taking Noxafil, contact your doctor straight away.

Do not breast-feed while taking Noxafil. This is because small amounts may pass into breast milk.

Driving and using machines
You may feel dizzy, sleepy, or have blurred vision while taking Noxafil, which may affect your ability to drive or use tools or machines. If this happens, do not drive or use any tools or machines and contact your doctor.

3. How to take Noxafil

Do not switch between taking Noxafil tablets and Noxafil oral suspension without talking to your doctor or pharmacist because it may result in a lack of efficacy or an increased risk of adverse reactions.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The usual dose is 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day, thereafter.

The length of treatment may depend on the type of infection that you have and may be individually adapted for you by your doctor. Do not adapt your dose yourself before consulting your doctor or change your treatment regimen.

Taking this medicine
- Swallow the tablet whole with some water.
- Do not crush, chew, break or dissolve the tablet.
- Tablets may be taken with or without food.

If you take more Noxafil than you should
If you think that you may have taken too much Noxafil, talk to a doctor or go to the hospital straight away.

If you forget to take Noxafil
- If you forget a dose, take it as soon as you remember it.
- However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule.
- Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor, pharmacist or nurse straight away if you notice any of the following serious side effects – you may need urgent medical treatment:
- nausea or vomit (feeling or being sick), diarrhoea
- signs of liver problems - these include yellowing of your skin or whites of the eyes, unusually dark urine or pale faeces, feeling sick for no reason, stomach problems, loss of appetite or unusual tiredness or weakness, an increase in liver enzymes shown up in blood tests
- allergic reaction

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common: the following may affect up to 1 in 10 people
- a change in the salt level in your blood shown in blood tests - signs include feeling confused or weak
- abnormal skin sensations, such as numbness, tingling, itching, creeping, pricking or burning
- headache
- low potassium levels – shown up in blood tests
- low magnesium levels – shown up in blood tests
- high blood pressure
- loss of appetite, stomach pain or upset stomach, passing wind, dry mouth, changes in your taste
- heartburn (a burning sensation in the chest rising up to the throat)
- low levels of "neutrophils" a type of white blood cell (neutropenia) –this can make you more likely to get infections and be shown up in blood tests
- fever
- feeling weak, dizzy, tired or sleepy
- rash
- itching
- constipation
- rectal discomfort

Uncommon: the following may affect up to 1 in 100 people
- anaemia - signs include headaches, feeling tired or dizzy, being short of breath or looking pale and a low level of haemoglobin shown up in blood tests
- low level of platelets (thrombocytopenia) shown in blood tests – this may lead to bleeding
- low level of "leukocytes" a type of white blood cell (leukopenia) shown in blood tests – this can make you more likely to get infections
- high level of "eosinophils" a type of white blood cell (eosinophilia) – this can happen if you have inflammation
- inflammation of the blood vessels
- heart rhythm problems
- fits (convulsions)
- nerve damage (neuropathy)
- abnormal heart rhythm – shown up on a heart trace (ECG), palpitations, slow or fast heartbeat, high or low blood pressure
- low blood pressure
- inflammation of the pancreas (pancreatitis) – this may cause severe stomach pain
- oxygen supply to the spleen is interrupted (splenic infarction) - this may cause severe stomach pain
- severe kidney problems – signs include passing more or less urine, that is a different colour than usual
- high blood levels of creatinine – shown in blood tests
- cough, hiccups
- nose bleeds
- severe sharp chest pain when breathing in (pleurritic pain)
- swelling of lymph glands (lymphadenopathy)
- reduced feeling of sensitivity especially on the skin
- tremor
- high or low blood sugar levels
- blurred vision, sensitivity to light
- hair loss (alopecia)
- mouth ulcers

- shivering, feeling generally unwell
- pain, back or neck pain, pain in arms or legs
- water retention (oedema)
- menstrual problems (abnormal vaginal bleeding)
- inability to sleep (insomnia)
- being completely or partially unable to talk
- swelling of the mouth
- abnormal dreams, or difficulty sleeping
- problems with co-ordination or balance
- mucosal inflammation
- stuffy nose
- difficulty breathing
- chest discomfort
- feeling bloated
- mild to severe nausea, vomiting, cramps and diarrhoea, usually caused by a virus, stomach pain
- belching
- feeling jittery

Rare: the following may affect up to 1 in 1,000 people

- pneumonia – signs include feeling short of breath and producing discoloured phlegm
- high blood pressure in the blood vessels in the lungs (pulmonary hypertension) this can cause serious damage to your lungs and heart
- blood problems such as unusual blood clotting or prolonged bleeding
- severe allergic reactions, including widespread blistering rash and skin peeling
- mental problems such as hearing voices or seeing things that are not there
- fainting
- having problems thinking or talking, having jerking movements, especially in your hands that you cannot control
- stroke – signs include pain, weakness, numbness, or tingling in the limbs
- having a blind or dark spot in your field of vision
- heart failure or heart attack which could lead to the heart stopping beating and death, heart rhythm problems, with sudden death
- blood clots in your legs (deep vein thrombosis) – signs include intense pain or swelling of the legs
- blood clots in your lungs (pulmonary embolism) – signs include feeling short of breath or pain while breathing
- bleeding into your stomach or gut – signs include vomiting blood or passing blood in your stool
- a blockage in your gut (intestinal obstruction) especially in the “ileum”. The blockage will prevent the contents of your intestine from passing through to the lower bowel signs include feeling bloated, vomiting, severe constipation, loss of appetite, and cramps
- “haemolytic uraemic syndrome” when red blood cells breakup (hemolysis) which may happen with or without kidney failure
- “pancytopenia” low level of all blood cells (red and white blood cells and platelets) shown in blood tests
- large purple discolourations on the skin (thrombotic thrombocytopenic purpura)
- swelling of the face or tongue
- depression
- double vision
- breast pain
- adrenal glands not working properly – this may cause weakness, tiredness, loss of appetite, skin discolouration
- pituitary gland not working properly – this may cause low blood levels of some hormones that affect the function of the male or female sex organs

- hearing problems

Some patients have also reported feeling confused after taking Noxafil, the frequency of this is not known.

Tell your doctor, pharmacist or nurse if you notice any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Noxafil

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Noxafil contains
The active substance in Noxafil is posaconazole. Each tablet contains 100 mg of posaconazole.

The other ingredients are: hypromellose acetate succinate; cellulose, microcrystalline; hydroxypropylcellulose (E463); silica dental type; croscarmellose sodium; magnesium stearate, polyvinyl alcohol, macrogol 3350 , titanium dioxide (E171), talc, iron oxide yellow (E172).

What Noxafil looks like and contents of the pack

Noxafil gastro-resistant tablets are yellow-coated and capsule-shaped, debossed “100” on one side packaged in a blister in cartons of 24 (2x12) or 96 (8x12) tablets.

Not all pack sizes may be marketed.

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Other sources of information
Detailed information on this medicinal product is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Noxafil 300 mg concentrate for solution for infusion
posaconazole

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Noxafil is and what it is used for

Noxafil contains a medicine called posaconazole. This belongs to a group of medicines called "antifungals". Noxafil is used to prevent and treat many different fungal infections.

Noxafil works by killing or stopping the growth of some types of fungi that can cause infections.

Noxafil can be used in adults to treat the following types of fungal infections when other antifungal medicines have not worked or you have had to stop taking them:
- 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 caused by a fungus 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.

Noxafil can also be used to prevent fungal infections in adults who are at high risk of getting a fungal infection, such as:
- patients who have a weak immune system due to having chemotherapy for "acute myelogenous leukemia" (AML) or "myelodysplastic syndromes" (MDS)
- patients having "high-dose immunosuppressive therapy" after "hematopoietic stem cell transplant" (HSCT).

2. What you need to know before you use Noxafil

Do not use Noxafil if:
- you are allergic to posaconazole or any of the other ingredients of this medicine (listed in section 6).
- you are taking: terfenadine, astemizole, cisapride, pimozide, halofantrine, quinidine, any medicines that contain "ergot alkaloids" such as ergotamine or dihydroergotamine, or a "statin" such as simvastatin, atorvastatin or lovastatin.

Do not use Noxafil if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Noxafil.

See "Other medicines and Noxafil" below for information on other medicines which may interact with Noxafil.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Noxafil if you:
- have had an allergic reaction to another antifungal medicine such as ketoconazole, fluconazole, itraconazole or voriconazole.
- have or have ever had liver problems. You may need to have blood tests while you are taking Noxafil.
- have an abnormal heart rhythm tracing (ECG) that shows a problem called long QTc interval
- have a weakness of the heart muscle or heart failure
- have a very slow heartbeat
- have heart rhythm disturbance
- have any problem with potassium, magnesium or calcium levels in your blood.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before using Noxafil.

Children
Noxafil should not be used in children (17 years of age and younger).

Other medicines and Noxafil
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take Noxafil if you are taking any of the following:
- 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).

Noxafil can increase the amount of these medicines in the blood which may lead to very serious changes to your heart rhythm:
- any medicines that contain "ergot alkaloids" such as ergotamine or dihydroergotamine used to treat migraines. Noxafil can increase the amount of these medicines in the blood which may lead to a severe decrease in blood flow to your fingers or toes and could cause damage to them.
- a "statin" such as simvastatin, atorvastatin or lovastatin used to treat high cholesterol.

Do not take Noxafil if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Noxafil.

Other medicines
Look at the list of medicines given above that must not be taken while you are taking Noxafil. In addition to the medicines named above 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).

Certain medicines may increase the risk of side effects of Noxafil by increasing the amount of Noxafil in the blood.

The following medicines may decrease the effectiveness of Noxafil by decreasing the amount of Noxafil in the blood:
- rifabutin and rifampicin (used to treat certain infections). If you are already taking rifabutin, you will need a blood test and you will need to look out for some possible side effects of rifabutin.
- some medicines used to treat or prevent fits including: phenytoin, carbamazepine, phenobarbital or primidone.
- efavirenz and fosamprenavir used to treat HIV infection.

Noxafil may possibly increase the risk of side effects of some other medicines by increasing the amount of these medicines in the blood. These medicines include:
- vincristine, vinblastine and other "vinca alkaloids" (used to treat cancer)
- ciclosporin (used during or after transplant surgery)
- tacrolimus and sirolimus (used during or after 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)
- midazolam, triazolam, alprazolam or other "benzodiazepines" (used as sedatives or muscle relaxants)
- diltiazem, verapamil, nifedipine, nisoldipine or other "calcium channel blockers" (used to treat high blood pressure)
- digoxin (used to treat heart failure)
- Glipizide or other "sulfonylureas" (used to treat high blood sugar)

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Noxafil.

Pregnancy and breast-feeding
Tell your doctor if you are or think you are pregnant before you start to take Noxafil.
Do not use Noxafil if you are pregnant unless you are told to by your doctor.
If you are a woman who could become pregnant you should use effective contraception while you are using Noxafil. If you become pregnant while you are using Noxafil, contact your doctor straight away.

Do not breast-feed while using Noxafil. This is because small amounts may pass into breast milk.

Driving and using machines
You may feel dizzy, sleepy, or have blurred vision while taking Noxafil, which may affect your ability to drive or use tools or machines. If this happens, do not drive or use any tools or machines and contact your doctor.

Noxafil contains sodium
This medicinal product contains 462 mg (20 mmol) sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

3. How to use Noxafil

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 300 mg twice a day on the first day, then 300 mg once a day, thereafter.

Noxafil concentrate for solution for infusion will be diluted to the correct concentration by your pharmacist or nurse.

Noxafil concentrate for solution for infusion will always be prepared and given to you by a healthcare professional.
You will be given Noxafil:

- through a plastic tube placed in your vein (intravenous infusion)
- usually over 90 minutes

The length of treatment may depend on the type of infection that you have or the length of time your immune system is not working properly and may be individually adapted for you by your doctor. Do not adapt your dose yourself before consulting your doctor or change your treatment regimen.

If a dose of Noxafil has been forgotten
As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However, tell your doctor or pharmacist if you think that a dose has been forgotten.

When Noxafil treatment is stopped by your doctor you should not experience any effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor, pharmacist or nurse straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- nausea or vomit (feeling or being sick), diarrhoea,
- signs of liver problems, these include yellowing of your skin or whites of the eyes, unusually dark urine or pale faeces, feeling sick for no reason, stomach problems, loss of appetite or unusual tiredness or weakness, an increase in liver enzymes shown up in blood tests
- allergic reaction

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

<u>Common: the following may affect up to 1 in 10 people</u>

- a change in the salt level in your blood shown in blood tests signs include feeling confused or weak
- abnormal skin sensations, such as numbness, tingling, itching, creeping, pricking, or burning
- swelling, redness, and tenderness along the vein in which Noxafil was given
- headache
- low potassium levels – shown up in blood tests
- low magnesium levels – shown up in blood tests
- high blood pressure
- loss of appetite, stomach pain or upset stomach, passing wind, dry mouth, changes in your taste

- heartburn (a burning sensation in the chest rising up to the throat)
- low levels of "neutrophils" a type of white blood cell (neutropenia) – this can make you more likely to get infections and be shown up in blood tests
- fever
- feeling weak, dizzy, tired, or sleepy
- rash
- itching
- constipation
- rectal discomfort

Uncommon: the following may affect up to 1 in 100 people

- anaemia- signs include headaches, feeling tired or dizzy, being short of breath or looking pale and a low level of haemoglobin shown up in blood tests
- low level of platelets (thrombocytopenia) shown in blood tests – this may lead to bleeding
- low level of "leukocytes" a type of white blood cell (leukopenia) shown in blood tests – this can make you more likely to get infections
- high level of "eosinophils" a type of white blood cell (eosinophilia) – this can happen if you have inflammation
- inflammation of the blood vessels
- heart rhythm problems
- fits (convulsions)
- nerve damage (neuropathy)
- abnormal heart rhythm – shown up on a heart trace (ECG), palpitations, slow or fast heartbeat, high or low blood pressure
- low blood pressure
- inflammation of the pancreas (pancreatitis) – this may cause severe stomach pain
- oxygen supply to the spleen is interrupted (splenic infarction) - this may cause severe stomach pain
- severe kidney problems – signs include passing more or less urine that is a different colour than usual
- high blood levels of creatinine – shown in blood tests
- cough, hiccups
- nose bleeds
- severe sharp chest pain when breathing in (pleurritic pain)
- swelling of lymph glands (lymphadenopathy)
- reduced feeling of sensitivity especially on the skin
- tremor
- high or low blood sugar levels
- blurred vision, sensitivity to light
- hair loss (alopecia)
- mouth ulcers
- shivering, feeling generally unwell
- pain, back or neck pain, pain in arms or legs
- water retention (oedema)
- menstrual problems (abnormal vaginal bleeding)
- inability to sleep (insomnia)
- being completely or partially unable to talk
- swelling of the mouth
- abnormal dreams, or difficulty sleeping
- problems with co-ordination or balance
- mucosal inflammation
- stuffy nose
- difficulty breathing

- chest discomfort
- feeling bloated
- mild to severe nausea, vomiting, cramps and diarrhoea, usually caused by a virus, stomach pain
- belching
- feeling jittery
- inflammation or pain at injection site

Rare: the following may affect up to 1 in 1,000 people
- pneumonia – signs include feeling short of breath and producing discoloured phlegm
- high blood pressure in the blood vessels in the lungs (pulmonary hypertension) this can cause serious damage to your lungs and heart
- blood problems such as unusual blood clotting or prolonged bleeding
- severe allergic reactions, including widespread blistering rash and skin peeling
- mental problems such as hearing voices or seeing things that are not there
- fainting
- having problems thinking or talking, having jerking movements, especially in your hands that you cannot control
- stroke – signs include pain, weakness, numbness, or tingling in the limbs
- having a blind or dark spot in your field of vision
- heart failure or heart attack which could lead to the heart stopping beating and death, heart rhythm problems, with sudden death
- blood clots in your legs (deep vein thrombosis) – signs include intense pain or swelling of the legs
- blood clots in your lungs (pulmonary embolism) – signs include feeling short of breath or pain while breathing
- bleeding into your stomach or gut – signs include vomiting blood or passing blood in your stool
- a blockage in your gut (intestinal obstruction) especially in the "ileum". The blockage will prevent the contents of your intestine from passing through to the lower bowel signs include feeling bloated, vomiting, severe constipation, loss of appetite, and cramps
- "haemolytic uraemic syndrome" when red blood cells breakup (hemolysis) which may happen with or without kidney failure
- "pancytopenia" low level of all blood cells (red and white blood cells and platelets) shown in blood tests
- large purple discolourations on the skin (thrombotic thrombocytopenic purpura)
- swelling of the face or tongue
- depression
- double vision
- breast pain
- adrenal glands not working properly – this may cause weakness, tiredness, loss of appetite, skin discolouration
- pituitary gland not working properly – this may cause low blood levels of some hormones that affect the function of the male or female sex organs
- hearing problems

Some patients have also reported feeling confused after using Noxafil, the frequency of this is not known.

Tell your doctor, pharmacist or nurse if you notice any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Noxafil

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C–8°C).
- Once prepared, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours at 2°C-8°C (in a refrigerator). This medicinal product is for single use only and any unused solution should be discarded.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Noxafil contains
The active substance is posaconazole. Each vial contains 300 mg of posaconazole.

The other ingredients are: Betadex Sulfobutyl Ether Sodium (SBECD), disodium edetate, hydrochloric acid (concentrated), sodium hydroxide, water for injections.

What Noxafil looks like and contents of the pack
Noxafil concentrate for solution for infusion is a clear, colourless to yellow liquid. Variations of colour within this range do not affect the quality of the product.

This medicine is available in a single use glass vial closed with bromobutyl rubber stopper and aluminium seal.

Marketing Authorisation Holder and Manufacturer

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Administration instructions for Noxafil concentrate for solution for infusion

- Equilibrate the refrigerated vial of Noxafil to room temperature.
- Aseptically transfer 16.7 mL of posaconazole to an intravenous bag (or bottle) containing a compatible admixture diluent (see below for list of diluents) using the volume ranging from 150 mL to 283 mL depending on the final concentration to be achieved (not less than 1 mg/mL and not greater than 2 mg/mL).
- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous infusion over approximately 90 minutes. Noxafil concentrate for solution for infusion should not be given by bolus administration.
- If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter with a volume to achieve a dilution of approximately 2 mg/mL. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes.
  Note: In clinical trials, multiple peripheral infusions given through the same vein resulted in infusion site reactions (see section 4.8).
- Noxafil is for single use.

The following medicinal products can be infused at the same time through the same intravenous line (or cannula) as Noxafil concentrate for solution for infusion:

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

Any products not listed in the table above should not be coadministered with Noxafil through the same intravenous line (or cannula).

The infusion solution should be inspected visually for particulate matter prior to administration. The solution of Noxafil ranges from colourless to pale yellow. Variations of colour within this range do not affect the quality of the product.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Noxafil must not be diluted with:

Lactated Ringer’s solution
5 % dextrose with Lactated Ringer’s solution
4.2 % sodium bicarbonate

This medicinal product must not be mixed with other medicinal products except those mentioned below:

5 % dextrose in water
0.9 % sodium chloride
0.45 % sodium chloride
5 % dextrose and 0.45 % sodium chloride
5 % dextrose and 0.9 % sodium chloride
5 % dextrose and 20 mEq KCl