SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Noxafil 300 mg gastro-resistant powder and solvent for oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 300 mg of posaconazole. Following reconstitution, the gastro-resistant oral suspension has a concentration of approximately 30 mg per mL.

Excipients with known effect

This medicinal product contains 0.28 mg/mL methyl parahydroxybenzoate (E218) and 0.04 mg/mL propyl parahydroxybenzoate.

This medicinal product contains 47 mg of sorbitol (E420) per mL.

This medicinal product contains 7 mg of propylene glycol (E1520) per mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant powder and solvent for oral suspension.

Off-white to yellow powder.

The solvent is a cloudy, colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Noxafil gastro-resistant powder and solvent for oral suspension is indicated for use in the treatment of the following fungal infections in paediatric patients from 2 years of age (see sections 4.2 and 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 powder and solvent for oral suspension is indicated for prophylaxis of invasive fungal infections in the following paediatric patients from 2 years of age:

- Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high-risk of developing invasive fungal infections;
- Haematopoietic 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 concentrate for solution for infusion and the gastro-resistant tablets for use in primary treatment of invasive aspergillosis.

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 gastro-resistant powder and solvent for oral suspension and Noxafil oral suspension

Noxafil gastro-resistant powder and solvent for oral suspension is indicated for paediatric population (<18 years old) only. Another formulation (Noxafil oral suspension) is available for adult patients ≥18 years old.

The gastro-resistant powder and solvent for oral suspension is not to be used interchangeably with oral suspension due to the differences in the dosing of each formulation. Therefore, follow the specific dose recommendations for each of the formulations.

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

Posology

Noxafil is also available as 40 mg/mL oral suspension; 100 mg gastro-resistant tablet; and 300 mg concentrate for solution for infusion.

Dosing for paediatric patients 2 years to less than 18 years of age is shown in Table 1.

The maximum dose volume that can be administered with a 10 mL dosing syringe is 8 mL using one marketed sachet of Noxafil gastro-resistant powder and solvent for oral suspension, corresponding to a maximum dose of 240 mg (i.e., the recommended dose for patients weighing 40 kg). For paediatric patients weighing > 40 kg, it is recommended to use posaconazole tablets if the patient can swallow whole tablets. Refer to the tablet SmPC for additional dosing information.

Table 1. Recommended dose in paediatric patients (2 years to less than 18 years of age) and weighing 10 to 40 kg

Weight (kg)	**Dose (volume)**
10-<12 kg	90 mg (3 mL)
12-<17 kg	120 mg (4 mL)
17-<21 kg	150 mg (5 mL)
21-<26 kg	180 mg (6 mL)
26-<36 kg	210 mg (7 mL)
36-40 kg	240 mg (8 mL)

On Day 1, the recommended dose is administered twice.

After Day 1, the recommended dose is administered once daily.

Duration of therapy

For patients with refractory invasive fungal infections (IFI) or patients with IFI intolerant to 1st line therapy, the duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

For patients with acute myelogenous leukaemia or myelodysplastic syndromes, prophylaxis of invasive fungal infections 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. Duration of therapy is based on recovery from neutropenia or immunosuppression.

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 posaconazole in children aged below 2 years have not been established.

No clinical data are available.

Method of administration

For oral use

The dose should be administered orally within 30 minutes of mixing.

Noxafil gastro-resistant powder and solvent for oral suspension must be administered with the provided notched tip syringes.

For details on preparation and administration of the gastro-resistant powder and solvent for oral suspension, see section 6.6 and Instructions for Use.

Noxafil gastro-resistant powder and solvent for oral suspension may be taken with or without food (see section 5.2).

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).

Co-administration during the initiation and dose-titration phase of venetoclax in Chronic Lymphocytic Leukaemia (CLL) patients (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity

There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing posaconazole 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 posaconazole therapy must be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of posaconazole should be considered if clinical signs and symptoms are consistent with development of liver disease.

QTc prolongation

Some azoles have been associated with prolongation of the QTc interval. Posaconazole must not be administered with medicinal products that are substrates for CYP3A4 and are known to prolong the QTc interval (see sections 4.3 and 4.5). Posaconazole 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.

Drug interactions

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).

Midazolam and other benzodiazepines

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).

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

Venetoclax toxicity
Concomitant administration of strong CYP3A inhibitors, including posaconazole, with the CYP3A4 substrate venetoclax, may increase venetoclax toxicities, including the risk of tumour lysis syndrome (TLS) and neutropenia (see sections 4.3 and 4.5). Refer to the venetoclax SmPC for detailed guidance.

Rifamycin antibacterials (rifampicin, rifabutin), flucloxacillin, 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).

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).

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.

Photosensitivity reaction
Posaconazole may cause increased risk of photosensitivity reaction. Patients should be advised to
avoid sun exposure during treatment without adequate protection such as protective clothing and
sunscreen with a high sun protection factor (SPF).

Methyl parahydroxybenzoate and propyl parahydroxybenzoate
This medicinal product contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate. May cause allergic reactions (possibly delayed).

Sorbitol
This medicine contains 47 mg sorbitol (E420) per mL.
In medicinal products for oral use, sorbitol may affect the bioavailability of other medicinal products for oral use administered concomitantly.
Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Propylene glycol

This medicine contains 7 mg propylene glycol (E1520) per mL.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

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.

Flucloxacillin
Flucloxacillin (a CYP450 inducer) may decrease plasma posaconazole concentrations. Concomitant
use of posaconazole and flucloxacillin should be avoided unless the benefit to the patient outweighs the risk (see section 4.4).

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 dose 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
Most of the vinca alkaloids (e.g. vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see section 4.4). Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole

antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

Rifabutin
Posaconazole increased the C_{max} and AUC of rifabutin by 31 % and 72 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk (see also above regarding the effect of rifabutin on plasma levels of posaconazole). If these medicinal products are co-administered, careful monitoring of full blood counts and adverse 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.

All-trans retinoic acid (ATRA) or tretinoin
As ATRA is metabolised by the hepatic CYP450 enzymes, notably CYP3A4, concomitant administration with posaconazole, which is a strong inhibitor of CYP3A4, may lead to increased exposure to tretinoin resulting in an increased toxicity (especially hypercalcaemia). Serum calcium levels should be monitored and, if needed, appropriate dose adjustments of tretinoin should be considered during the treatment with posaconazole, and during the following days after treatment.

Venetoclax
Compared with venetoclax 400 mg administered alone, co-administration of 300 mg posaconazole, a strong CYP3A inhibitor, with venetoclax 50 mg and 100 mg for 7 days in 12 patients, increased venetoclax C_{max} to 1.6-fold and 1.9-fold, and AUC to 1.9-fold and 2.4-fold, respectively (see sections 4.3 and 4.4).
Refer to the venetoclax SmPC.

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

Summary of the safety profile

Safety data mainly derive from studies with the oral suspension.
The safety of posaconazole oral suspension has been assessed in > 2,400 patients and healthy volunteers enrolled in clinical studies and from post-marketing experience. The most frequently reported serious related adverse reactions included nausea, vomiting, diarrhoea, pyrexia, and increased bilirubin.

Posaconazole gastro-resistant powder and solvent for oral suspension and concentrate for solution for infusion safety
The safety of posaconazole gastro-resistant powder and solvent for oral suspension and concentrate for solution for infusion has been assessed in 115 paediatric patients aged 2 to less than 18 years for prophylaxis use.

The most frequently reported adverse reactions during treatment were alanine aminotransferase increased (2.6 %), aspartate aminotransferase increased (3.5 %) and rash (2.6 %).

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 (cannot be estimated from the available data).

Table 2. Adverse reactions by body system and frequency reported in clinical studies and/or post-marketing use*

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, pseudoaldosteronism
Metabolism and nutrition disorders Common: Uncommon:	electrolyte imbalance, anorexia, decreased appetite, hypokalaemia, hypomagnesaemia hyperglycaemia, hypoglycaemia
Psychiatric disorders Uncommon: Rare:	 abnormal dreams, confusional state, sleep disorder psychotic disorder, depression
Nervous system disorders Common: Uncommon: Rare:	 paraesthesia, dizziness, somnolence, headache, dysgeusia convulsions, neuropathy, hypoaesthesia, tremor, aphasia, insomnia cerebrovascular accident, encephalopathy, peripheral neuropathy, syncope
Eye disorders Uncommon: Rare:	 blurred vision, photophobia, visual acuity reduced diplopia, scotoma
Ear and labyrinth disorder Rare:	 hearing impairment
Cardiac disorders Uncommon: Rare:	 long QT syndrome[§], electrocardiogram abnormal[§], palpitations, bradycardia, supraventricular extrasystoles, tachycardia torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders Common: Uncommon: Rare:	 hypertension hypotension, vasculitis pulmonary embolism, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders Uncommon: Rare:	 cough, epistaxis, hiccups, nasal congestion, pleuritic pain, tachypnoea 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, gastroesophageal 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
Not known:	photosensitivity reaction[§]
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, concentrate for solution for infusion, and gastro-resistant powder and solvent for oral suspension.

§ 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no experience with overdose of posaconazole gastro-resistant powder and solvent for oral suspension.

During clinical studies, 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.

The following *in vitro* data are available, but their clinical significance is unknown. In a surveillance study of > 3,000 clinical mold isolates from 2010-2018, 90 % of non-*Aspergillus* fungi exhibited the following *in vitro* minimum inhibitory concentration (MIC): *Mucorales* spp (n=81) of 2 mg/L; *Scedosporium apiospermum/S. boydii* (n=65) of 2 mg/L; *Exophiala dermatiditis* (n=15) of 0.5 mg/L, and *Purpureocillium lilacinum* (n=21) of 1 mg/L.

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*: 0.5 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
- *Candida dubliniensis*: 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 gastro-resistant powder and solvent for oral suspension and concentrate for solution for infusion bridging study

The pharmacokinetics and safety of posaconazole concentrate for solution for infusion and gastro-resistant powder and solvent for oral suspension have been assessed in 115 paediatric subjects aged 2 to less than 18 years in a nonrandomized, multi-center, open-label, sequential dose-escalation study (Study 097). Immunocompromised paediatric subjects with known or expected neutropenia were exposed to posaconazole at 3.5 mg/kg, 4.5 mg/kg or 6.0 mg/kg daily (BID on Day 1). All 115 subjects initially received posaconazole concentrate for solution for infusion for at least 7 days, and 63 subjects were transitioned to gastro-resistant powder and solvent for oral suspension. The mean overall treatment duration (posaconazole concentrate for solution for infusion and gastro-resistant powder and solvent for oral suspension) of all treated subjects was 20.6 days (see section 5.2).

Paediatric population

The safety and efficacy of posaconazole have been established in paediatric patients 2 to less than 18 years of age. Use of posaconazole in these age groups is supported by evidence from adequate and well-controlled studies of posaconazole in adults, pharmacokinetic and safety data from paediatric studies, and by population pharmacokinetic modelling (see section 5.2). No new safety signals associated with the use of posaconazole in paediatric patients were identified in the paediatric studies (see section 4.8).

Safety and efficacy of Noxafil have not been established in paediatric patients below the age of 2 years.

No data are available.

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

The absolute bioavailability of the gastro-resistant powder and solvent for oral suspension is approximately 83 %. Administration of posaconazole gastro-resistant powder and solvent for oral suspension following consumption of a high fat meal in adults had no significant effect on AUC and resulted in a moderate (23% to 41 %) decrease in C_{max}. Based on a population pharmacokinetic model, no significant effect of a meal on posaconazole gastro-resistant powder and solvent for oral suspension bioavailability was identified in paediatric patients 2 to less than 18 years of age. Therefore, the gastro-resistant powder and solvent for oral suspension can be administered without regard to food.

Concomitant administration of posaconazole gastro-resistant powder and solvent for oral suspension with medicinal products affecting gastric pH or gastric motility would not be expected to demonstrate any significant effects on posaconazole pharmacokinetic exposure based on similarity to the gastro-resistant tablets.

An *in vitro* dissolution study was conducted to evaluate the impact of alcohol (5, 10, 20, and 40 %) on the dissolution of Noxafil gastro-resistant powder and solvent for oral suspension. Posaconazole was found to release faster from Noxafil gastro-resistant powder and solvent for oral suspension in the presence of alcohol *in vitro*, which may interfere with its delayed release characteristics.

Distribution

Posaconazole has a central volume of distribution of 112 L (5.2 % RSE) based on population PK modelling in paediatric subjects receiving IV or PFS formulations. 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 is slowly eliminated with a mean clearance 4.7 L/h (3.9%RSE) and a corresponding to half-life ($t_{½}$) of 24 hours based on population PK modelling in paediatric subjects receiving IV or PFS. 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 7 after once daily dosing (twice daily on Day 1) in paediatric subject receiving PFS.

Pharmacokinetics in special populations

Children (< 18 years)

Based on a population pharmacokinetic model evaluating posaconazole pharmacokinetics and predicting exposures in paediatric patients, the exposure target of steady-state posaconazole average concentration (C_{av}) of approximately 1,200 ng/mL and $C_{av} \geq 500$ ng/mL in approximately 90 % of patients is attained with the recommended dose of posaconazole concentrate for solution for infusion and gastro-resistant powder and solvent for oral suspension. Simulations, using the population pharmacokinetic model, predict a $C_{av} \geq 500$ ng/mL in 90% of paediatric patients weighing at least 40 kg following administration of the adult dose of posaconazole gastro-resistant tablets (300 mg twice daily on Day 1 and 300 mg once daily starting on Day 2).

The population pharmacokinetic analysis of posaconazole in paediatric patients suggests that age, sex, renal impairment and ethnicity have no clinically meaningful effect on the pharmacokinetics of posaconazole.
No dose adjustment is recommended in case of renal impairment (see section 4.2).

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.

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 either oral posaconazole administration to juvenile dogs (4 days to 9 months of age) or intravenous posaconazole administration to juvenile dogs (10 weeks to 23 weeks of age). The clinical significance of this finding is unknown.

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

Powder

Hypromellose acetate succinate

Solvent

purified water
glycerol (E422)
methyl parahydroxybenzoate (E218)
propyl parahydroxybenzoate
sodium dihydrogen phosphate monohydrate
citric acid anhydrous (E330)
xanthan gum (E415)
sodium citrate (E331)
saccharin sodium (E954)
microcrystalline cellulose
carmellose sodium
carrageenan calcium sulfate trisodium phosphate (E407)
sorbitol solution (E420)
potassium sorbate (E202)

flavour berry citrus sweet containing propylene glycol (E1520), water, natural and artificial flavour

antifoam Af emulsion containing polyethylene glycol (E1521), octamethyl cyclotetrasiloxane, decamethylcyclopentasiloxane and poly(oxy-1,2-ethanediyl), .alpha.-(1-oxooctadecyl)-.omega.-hydroxy

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After reconstitution: 30 minutes.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

Noxafil gastro-resistant powder and solvent for oral suspension is supplied as a pack containing:

Package 1: The kit contains 8 child-resistant single-use sachets (PET/aluminium/LLDPE), two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, one 473 mL solvent bottle (HDPE) with polypropylene (PP) closure with a foil induction seal liner, and one bottle adapter for the solvent bottle.

Package 2: A box of six 3 mL (green) and six 10 mL (blue) notched tip syringes.

6.6 Special precautions for disposal

Complete details on preparation and administration of the gastro-resistant powder and solvent for oral suspension can be found in the instructions for use booklet that is

included in the kit. Parents and/or caregivers should be instructed to read the instructions for use booklet before preparing and administering Noxafil gastro-resistant powder and solvent for oral suspension.

Each single-use sachet contains 300 mg of posaconazole which is suspended in 9 mL of solvent to obtain 10 mL total of suspension with a final concentration of approximately 30 mg per mL.

Note: ONLY the solvent in the kit should be used to prepare Noxafil.

Note: To ensure delivery of the correct dose, ONLY the provided notched tip syringes should be used for preparation and administration. The design of the notched tip syringe prevents aggregation of the suspension during preparation and administration.

The notch-tip syringe provided in the kit should be used to administer Noxafil with the enteral feeding tube. The enteral feeding tube size should be selected based on the patient characteristics. Use a suitable enteral feeding tube based on tube material per the following table.

Type	**Tube material**	**Tube size**
Gastric Tubing	Polyurethane	16 Fr or larger
	Silicone	14 Fr or larger
Nasogastric Tubing	PVC*	12 Fr or larger
	Polyurethane	12 Fr or larger

*PVC – polyvinyl chloride

The tube should be flushed again with at least 10 mL water to ensure Noxafil is delivered and to clear the tube.

After administration of the required volume, the remaining suspension in the mixing cup cannot be re-used and must be discarded.

The dose should be administered orally within 30 minutes of mixing.

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

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme (UK) Limited

120 Moorgate

London

EC2M 6UR

United Kingdom

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