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.

Excipients with known effect
This medicinal product contains approximately 1.75 g of glucose per 5 mL of suspension.
This medicinal product contains 10 mg of sodium benzoate per 5 mL of suspension.
This medicinal product contains up to 1.25 mg of benzyl alcohol per 5 mL of suspension.
This medicinal product contains up to 24.75 mg of propylene glycol 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.
- Zygomycosis, in patients intolerant of, or with disease that is refractory to, alternative therapy.

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

4.2 Posology and method of administration

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

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. Substitution of the tablets for the oral suspension, or vice versa, can result in inadvertent overdosing or underdosing and adverse drug reactions. Therefore, follow the specific dosage recommendations for each formulation.

Posology
Noxafil is also available as 100 mg gastro-resistant tablet. 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 leukaemia 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 posaconazole in children and adolescents aged below 18 years have not been established.

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).

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), 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).

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.

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

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

Sodium benzoate
This medicinal product contains 10 mg of sodium benzoate per 5 mL of suspension.

Benzyl alcohol
This medicinal product contains up to 1.25 mg of benzyl alcohol per 5 mL of suspension. Benzyl alcohol may cause anaphylactoid reactions.

Propylene glycol
This medicinal product contains up to 24.75 mg of propylene glycol per 5 mL of suspension.

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
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 (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 studies 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 (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:	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:	paraesthesia, 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:	torsades 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 suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

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 organisms not previously regarded as susceptible to azoles such as the *zygomycetes (e.g. species of Absidia, Mucor, Rhizopus and Rhizomucor)*.

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.

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 study (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 %)

Zygomycosis: Successful responses to posaconazole therapy were noted in 7/13 (54%) of patients with zygomycete infections. Sites of infection included the sinuses, lung, and skin. Organisms included Rhizopus, Mucor and Rhizomucor. Most of the patients had underlying haematological malignancies, half of which required a bone marrow transplant. Half of the patients were enrolled with intolerance to previous therapy and the other half as a result of disease that was refractory to prior therapy. Three patients were noted to have disseminated disease, one of which had a successful outcome after failing amphotericin B therapy.

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).

[1] Includes other less common species or species unknown

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

Table 4. Clinical success rates in Oropharyngeal Candidiasis

Endpoint	Posaconazole	Fluconazole
Clinical success rate at Day 14	91.7 % (155/169)	92.5 % (148/160)
Clinical success rate 4 weeks after end of treatment	68.5 % (98/143)	61.8 % (84/136)

Clinical success rate was defined as the number of cases assessed as having a clinical response (cure or improvement) divided by the total number of cases eligible for analysis.

Prophylaxis of Invasive Fungal Infections (IFIs) (Studies 316 and 1899)
Two randomised, controlled prophylaxis studies were conducted among patients at high risk for developing invasive fungal infections.

Study 316 was a randomised, double-blind study 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-randomisation 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-randomisation. 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 randomisation 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 randomisation to 100 days post-randomisation; in 316 it was the period from the baseline day to 111 days post-baseline.
d: All randomised
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 randomisation 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 randomisation to 100 days post-randomisation; in 316 it was the period from the baseline day to 111 days post-baseline.
d: All randomised
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 randomisation, 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
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)
Pharmacokinetics in paediatric patients below the age of 18 years have not been established.

Gender
The pharmacokinetics of posaconazole are comparable in men and women.

Elderly
An increase in C_{max} (26 %) and AUC (29 %) was observed in elderly subjects (24 subjects ≥ 65 years of age) relative to younger subjects (24 subjects 18 - 45 years of age). However, in clinical efficacy studies, 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 modelling 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 ($t_{½}$) 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

Liquid glucose (corn syrup)
Glycerol
Polysorbate 80
Artificial cherry flavour #13174 containing benzyl alcohol and propylene glycol
Titanium dioxide
Simeticone
Xanthan gum
Sodium benzoate
Citric acid monohydrate
Sodium citrate dihydrate
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened container: The expiry date of the product is indicated on the packaging materials

After first opening the container: 4 weeks.

6.4 Special precautions for storage

Store below 25˚C. Do not freeze.

6.5 Nature and contents of container

105 mL of oral suspension in a 123 ml bottle (glass amber type IV) closed with a plastic child-resistant cap (polypropylene) and a measuring spoon (polystyrene) with 2 graduations: 2.5 mL and 5 mL.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme (Israel- 1996) Company Ltd.,

P.O.Box 7121, Petah-Tikva 49170.

8. MANUFACTURER: Merck Sharp & Dohme Corp., New-Jersey, USA

9. MARKETING AUTHORISATION NUMBER

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