1 NOXAFIL (posaconazole)
NOXAFIL (posaconazole) 40 mg/mL ORAL SUSPENSION
NOXAFIL (posaconazole) MODIFIED RELEASE 100 mg TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each mL of oral suspension contains 40 mg of posaconazole.

Each modified-release tablet contains 100 mg of posaconazole.

For the full list of excipients for each product, see section 6.1.

3 PHARMACEUTICAL FORM
NOXAFIL oral suspension
White, cherry flavoured immediate-release oral suspension.

NOXAFIL modified release tablet
Yellow, coated, capsule-shaped tablet, debossed with “100” on one side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
NOXAFIL (posaconazole) modified release tablets and oral suspension are indicated for use in the treatment of the following invasive fungal infections in patients 18 years of age or older:

- Invasive aspergillosis in patients with disease that is refractory to, or are intolerant of, amphotericin B, itraconazole or voriconazole.
- Oesophageal candidiasis or candidemia in patients with disease that is refractory to, or who are intolerant of, amphotericin B, fluconazole or itraconazole.
- Fusariosis, zygomycosis, cryptococcosis, chromoblastomycosis, and mycetoma in patients with disease refractory to other therapy, or patients who are intolerant of other therapy.
- Coccidioidomycosis.

NOXAFIL (posaconazole) modified release tablets and oral suspension are also indicated for use as:

- Prophylaxis of invasive fungal infections, including both yeasts and moulds, in patients 13 years of age and older who are at high risk of developing these infections, such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients.

NOXAFIL oral suspension is also indicated for the use in the treatment of the following fungal infections in patients 18 years of age or older:

- Treatment of oropharyngeal candidiasis in immunocompromised adults, including patients with disease that is refractory to itraconazole and fluconazole.

4.2 Dose and method of administration
Coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections (see section 4.5).

Non-Interchangeability between NOXAFIL Modified Release Tablets and NOXAFIL Oral Suspension
The prescriber should follow the specific dosing instructions for each formulation. The modified release tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations.

Dose
Recommended dose for NOXAFIL Oral Suspension and NOXAFIL Modified Release Tablets are shown in Tables 1 and 2, respectively.

Table 1: Recommended Dose for NOXAFIL Oral Suspension According to Indication

Indication	Dose and Duration of Therapy
Refractory Invasive Fungal infections (IFI)/Intolerant Patients with IFI	400 mg (10 mL) twice a day* with food or a nutritional supplement. Dividing the dose further to 200 mg (5 mL) four times a day has been shown to enhance exposure to posaconazole, particularly in patients who have limited oral intake. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Coccidioidomycosis	NOXAFIL should be administered at a dose of 400 mg (10 mL) twice a day* with food or a nutritional supplement. Dividing the dose further to 200 mg (5 mL) four times a day has been shown to enhance exposure to posaconazole, particularly in patients who have limited oral intake. 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.
Refractory Oropharyngeal or Oesophageal Candidiasis	400 mg (10 mL) twice a day*. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response.
Prophylaxis of Invasive Fungal Infections	200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.

* Increasing the total daily dose above 800 mg does not further enhance the exposure to posaconazole (see section 5.2).

Table 2: Recommended Dose for NOXAFIL Modified Release Tablets According to Indication

Indication	Dose and Duration of therapy
Prophylaxis of Invasive Fungal Infections	Loading dose of 300 mg (three 100 mg modified release tablets) twice a day on the first day, then 300 mg (three 100 mg modified release tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous 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.
Refractory Invasive Fungal Infections (IFI)/Patients with IFI intolerant to 1st line therapy	Loading dose of 300 mg (three 100 mg modified release tablets) twice a day on the first day, then 300 mg (three 100 mg modified release tablets) once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Coccidioidomycosis	
Refractory Oesophageal Candidiasis	Loading dose of 300 mg (three 100 mg modified release tablets) twice a day on the first day, then 300 mg (three 100 mg modified release tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

Special Populations

Use in renal impairment: No dose adjustment is required for renal dysfunction and as posaconazole is not significantly renally eliminated, an effect of severe renal insufficiency on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended (see section 5.2).

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

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

Use in the Elderly: No dosage adjustment is recommended for elderly patients (see section 5.2).

Method of Administration

NOXAFIL Modified Release Tablets and Oral Suspension are intended for oral administration only.

NOXAFIL Oral Suspension should be administered with a meal, or with 240 mL of a nutritional supplement. Shake well before use.

NOXAFIL Modified Release Tablets should be swallowed whole, and not be divided, crushed, or chewed. NOXAFIL Modified Release Tablets may be taken without regard to food intake.

4.3 Contraindications

NOXAFIL is contraindicated in patients with known hypersensitivity to posaconazole or to any of the excipients.

Co-administration of posaconazole and ergot alkaloids (ergotamine, dihydroergotamine) is contraindicated as posaconazole may increase the plasma concentration of ergot alkaloids, which may lead to ergotism (see section 4.5).

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

Although not studied *in vitro or in vivo,* co-administration of posaconazole and certain drugs metabolised through the CYP3A4 system: terfenadine, astemizole, cisapride, pimozide, and quinidine may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life threatening adverse events, such as QT prolongation and rare occurrences of torsade de pointes (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity

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

Hepatic toxicity

In clinical trials, there were infrequent cases of hepatic reactions (e.g., mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis) during treatment with posaconazole. Elevated liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalized without interruption of therapy and rarely required drug discontinuation. Rarely, more severe hepatic reactions (including cases that have progressed to fatal outcomes) were reported in patients with serious underlying medical conditions (e.g. haematological malignancy) during treatment with posaconazole.

QT prolongation

Some azoles have been associated with prolongation of the QT_c interval on the electrocardiogram (ECG). Results from a multiple time-matched ECG analysis in healthy volunteers did not show an increase in the mean QT_c interval. Nevertheless, posaconazole should not be administered with medications that are known to prolong the QT_c interval and are metabolised through the CYP3A4 system (see sections 4.3, 4.5 and 5.2).

Electrolyte disturbances:

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

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 posaconazole with venetoclax (a CYP3A4 substrate) may increase venetoclax toxicities, including the risk of tumor lysis syndrome (TLS) and neutropenia (see section 4.5). Refer to the venetoclax prescribing information for detailed guidance.

Paediatric Use
(See section 5.2). Safety and effectiveness in paediatric patients below the age of 13 years have not been established.

Use in the Elderly
No dosage adjustment is recommended for geriatric patients (see section 5.2).

4.5 Interaction with other medicines and other forms of interaction

The interactions described in the following subsections apply to posaconazole modified release tablets and oral suspension unless otherwise specified.

Effect of Other Drugs on Posaconazole modified release tablets and oral suspension
Posaconazole is metabolised via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations.

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 by 43 % and 49 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk.

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 should be avoided unless the benefit to the patient outweighs the risk.

H_2 receptor antagonists, proton pump inhibitors and antacids
Posaconazole Oral Suspension
Posaconazole plasma concentrations (C_{max} and AUC) were reduced by 39 % when posaconazole oral suspension 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 oral suspension with H_2 receptor antagonists should be avoided if possible.

A 20 mL single dose of liquid antacid, equivalent to 25.4 mEq acid neutralizing capacity/5mL, had no clinically significant effect on posaconazole oral suspension C_{max} and AUC. No dosage adjustments are required.

Similarly, administration of 400 mg posaconazole oral suspension 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 oral suspension with proton pump inhibitors should be avoided if possible.

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

Gastrointestinal Motility Agents
Posaconazole Oral Suspension
Metoclopramide, when given with posaconazole oral suspension, decreases posaconazole plasma concentrations. If metoclopramide is concomitantly administered with posaconazole oral suspension, it is recommended to closely monitor for breakthrough fungal infections.

Loperamide does not affect posaconazole plasma concentrations. No dosage adjustment of posaconazole is required when loperamide and posaconazole are used concomitantly.

Posaconazole Modified Release Tablets
No clinically meaningful effect on the pharmacokinetics of posaconazole was observed when posaconazole modified release tablets were concomitantly administered with metoclopramide. No dosage adjustment of posaconazole modified release tablets is required when given concomitantly with metoclopramide.

Glipizide
Glipizide (10 mg single dose) had no clinically significant effect on posaconazole C_{max} and AUC. No posaconazole dosage adjustments are required.

Ritonavir
Ritonavir (600 mg twice a day) had no clinically significant effect on posaconazole C_{max} and AUC. No posaconazole dosage adjustments are required.

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 a day for 10 days) decreased the C_{max} and AUC of posaconazole (200 mg once a day on the 1st day, 200 mg twice a day on the 2nd day, then 400 mg twice a day for 8 days) by 21 % and 23 %, respectively.

Effects of Posaconazole modified release tablets and oral suspension on Other Drugs
Posaconazole is not metabolised to a clinically significant extent through the cytochrome P450 system. However, posaconazole is an inhibitor of CYP3A4 and thus the plasma levels of drugs that are metabolised through this enzyme pathway may increase when administered with posaconazole.

Terfenadine, astemizole, cisapride, pimozide, and quinidine
Although not studied *in vitro or in vivo,* co-administration of posaconazole and certain drugs such as terfenadine, astemizole, cisapride, pimozide, and quinidine, metabolised through the CYP3A4 system may result in increased plasma concentrations of these drugs, leading to potentially serious and/or life threatening adverse events (QT prolongation and rare

occurrences of torsade de pointes). Therefore, co-administration of these drugs with posaconazole is contraindicated (see section 4.3).

Ergot alkaloids
Although not studied *in vitro* or *in vivo*, 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).

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.

Cyclosporine
In heart transplant patients on stable doses of cyclosporine, posaconazole 200 mg oral suspension once daily increased cyclosporine concentrations requiring dose reductions. When initiating treatment with posaconazole in patients already receiving cyclosporine, the dose of cyclosporine should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of cyclosporine should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of cyclosporine should be adjusted as necessary.

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

Sirolimus
Repeat dose administration of oral posaconazole (400 mg oral suspension 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, respectively, in healthy subjects. When initiating therapy in patients already taking sirolimus, the dose of sirolimus should be reduced (e.g., to about 1/10 of the current dose) with frequent monitoring of sirolimus whole blood trough concentrations. Sirolimus concentrations should be performed upon initiation, during co-administration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly.

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. If the drugs are co-administered, careful monitoring of full blood counts and adverse effects related to increased rifabutin levels (e.g., uveitis) is recommended.

Midazolam
Repeat dose administration of oral posaconazole (200 mg oral suspension twice daily for 7 days) increased the C_{max} and AUC of IV midazolam (0.4 mg single dose) an average of 1.3- and 4.6-fold, respectively. Posaconazole 400 mg oral suspension twice daily for 7 days

increased the IV midazolam C_{max} and AUC by 1.6- and 6.2-fold, respectively. Both doses of posaconazole increased C_{max} and AUC of oral midazolam (2 mg single oral dose) by 2.2- and 4.5-fold, respectively. In addition, oral posaconazole (200 mg or 400 mg oral suspension) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-10 hours during co-administration. It is recommended that dose adjustments of benzodiazepines, metabolised by CYP3A4, be considered during co-administration with posaconazole.

Zidovudine (AZT), lamivudine (3TC), indinavir
In HIV infected patients on stable doses of zidovudine (300 mg twice a day or 200 mg every 8 hours), lamivudine (150 mg twice a day), and/or indinavir (800 mg every 8 hours), posaconazole had no clinically significant effect on the C_{max} and AUC of these medicinal products.

HMG-CoA reductase inhibitors primarily metabolised through CYP3A4
Repeat dose administration of oral posaconazole (50, 100, and 200 mg oral suspension once daily for 13 days) increased the C_{max} and AUC of simvastatin (40 mg single dose) an average of 7.4- to 11.4-fold, and 5.7- to 10.6-fold, respectively. Increased HMG-CoA reductase inhibitor concentrations in plasma can be associated with rhabdomyolysis. Co-administration of posaconazole and HMG-CoA reductase inhibitors primarily metabolised through CYP3A4 is contraindicated.

Calcium channel blockers metabolised through CYP3A4
Although not studied *in vitro or in vivo*, frequent monitoring for adverse effects and toxicity related to calcium channel blockers is recommended during co-administration with posaconazole. Dose adjustment of calcium channel blockers may be required.

HIV protease inhibitors
As HIV protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these antiretroviral agents. Repeat dose administration of oral posaconazole (400 mg oral suspension twice daily for 7 days) increased the C_{max} and AUC of atazanavir (300 mg once a day for 7 days) an average of 2.6-fold and 3.7-fold, respectively, in healthy subjects. Repeat dose administration of oral posaconazole (400 mg oral suspension twice daily for 7 days) increased the C_{max} and AUC of atazanavir to a lesser extent when administered as a boosted regimen with ritonavir (300 mg atazanavir plus ritonavir 100 mg once a day for 7 days) with an average of 1.5-fold and 2.5-fold, respectively, in healthy subjects. Frequent monitoring for adverse events and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with posaconazole.

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.

Venetoclax
Concomitant use of venetoclax (a CYP3A4 substrate) with posaconazole increases venetoclax C_{max} and $AUC_{0\text{-}INF}$, which may increase venetoclax toxicities (see Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Category B3. There is insufficient information on the use of NOXAFIL in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Posaconazole has been shown to cause skeletal malformations in rats at exposures lower than those obtained

at therapeutic doses in humans. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. The potential risk to humans is unknown. Posaconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Pregnancy categorisation definition
Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Women of childbearing potential
Women of childbearing potential must always use effective contraceptive measures during treatment with posaconazole.

Breast-feeding
Posaconazole is excreted in milk of lactating rats. The excretion of posaconazole in human breast milk has not been investigated. Posaconazole should not be used by nursing mothers unless the benefit to the mother clearly outweighs the potential risk to the infant.

Fertility
Posaconazole had no effect on fertility of male and female rats.

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
Posaconazole Oral Suspension
The safety of posaconazole oral suspension has been assessed in 2,400 patients and healthy volunteers enrolled in clinical trials and from post-marketing experience. One hundred and seventy-two patients received posaconazole oral suspension therapy for ≥ 6 months; 58 of these received posaconazole oral suspension therapy for ≥ 12 months.

Serious adverse events that were considered treatment related were reported in 8 % (35/428) of patients in the refractory invasive fungal infection pool. Most individual treatment related serious adverse events were reported by <1 % of patients and are largely reflective of the serious underlying conditions that predisposed to the development of the invasive fungal infection. Treatment related serious adverse events reported in 1 % of subjects (3 or 4 subjects each) included altered concentration of other medicinal products, increased hepatic enzymes, nausea, rash, and vomiting. Treatment-related serious adverse events reported in 605 patients treated with posaconazole oral suspension for prophylaxis (1 % each) included bilirubinaemia, increased hepatic enzymes, hepatocellular damage, nausea, and vomiting.

Uncommon and rare treatment related medically significant adverse events reported during clinical trials with posaconazole oral suspension have included adrenal insufficiency, pancreatitis, allergic and/or hypersensitivity reactions.

Some azoles have been associated with prolongation of the QT interval on the electrocardiogram. A pooled analysis of 173 posaconazole oral suspension-dosed healthy volunteers utilizing time matched ECGs did not show a potential to prolong the QT interval.

In addition, rare cases of torsade de pointes have been reported in patients taking posaconazole.

In addition, rare cases of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura have been reported primarily among patients who had been receiving concomitant cyclosporine or tacrolimus for management of transplant rejection or graft vs. host disease.

Posaconazole Modified Release Tablets Safety

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

The most frequently reported treatment-related adverse reactions (≥5%) with posaconazole modified release tablets (300 mg tablets once daily) were nausea and diarrhoea.

The most frequently reported adverse reaction leading to discontinuation of posaconazole modified release tablets 300 mg once daily was nausea.

Treatment-related adverse reactions (TRAEs) reported in posaconazole modified release tablets and oral suspension studies

The most common treatment-related adverse reactions reported in posaconazole modified release tablets and oral suspension studies across the whole population of healthy volunteers and patients are shown in Table 3.

Table 3: Treatment-related adverse reactions reported in posaconazole modified release tablets and oral suspension dosed subjects by body system. *Common (>1/100, <1/10)*

Blood and lymphatic system disorders Common	Neutropenia
Metabolism and nutrition disorders Common	Anorexia, electrolyte imbalance, hypokalaemia
Nervous system disorders Common	Dizziness, headache, paraesthesia, somnolence
Gastrointestinal disorders Common	Abdominal pain, diarrhoea, dyspepsia, flatulence, dry mouth, nausea, vomiting, constipation
Hepatobiliary disorders Common	Elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, bilirubin)
Skin and subcutaneous tissue disorders Common	Rash, pruritus
General disorders and administration site conditions Common	Asthenia, fatigue, pyrexia (fever)

Clinical Laboratory Values
In (uncontrolled) trials of patients with invasive fungal infections treated with NOXAFIL oral suspension doses of 800 mg/day, the incidence of clinically significant liver function test abnormalities was ; ALT and AST (> 3 X Upper Limit Normal {ULN}) 11 % and 10 %, respectively; total bilirubin (> 1.5 X ULN) 22 %; and alkaline phosphatase (> 3 X ULN) 14 %. In healthy volunteers, elevation of hepatic enzymes did not appear to be associated with higher plasma concentrations of posaconazole. In patients, the majority of abnormal liver function tests results showed minor and transient changes and rarely led to discontinuation of therapy.
In the comparative trials of patients infected with HIV (or another indication) treated with NOXAFIL at doses up to 400 mg, the incidence of clinically significant liver function test abnormalities was as follows; ALT and AST (> 3 X ULN), 3 % and 6 %, respectively: total bilirubin (> 1.5 X ULN), 3 %; and alkaline phosphatase (> 3 X ULN), 3 %.

Post-marketing Experience
The following post-marketing adverse experience has been reported:

Endocrine Disorders: pseudoaldosteronism

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose
During the clinical trials, some patients received posaconazole oral suspension doses up to 1600 mg/day with no adverse reactions noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg posaconazole oral suspension twice a day for 3 days. No adverse reactions were noted by the investigator.

In a trial of patients with severe haemodialysis-dependent renal dysfunction (Cl_{cr} < 20 mL/min), posaconazole was not removed by haemodialysis. Thus, haemodialysis is unlikely to be effective in removing posaconazole from the systemic circulation.

Posaconazole is not removed by haemodialysis.

There is no experience with overdosage of posaconazole modified release tablets.

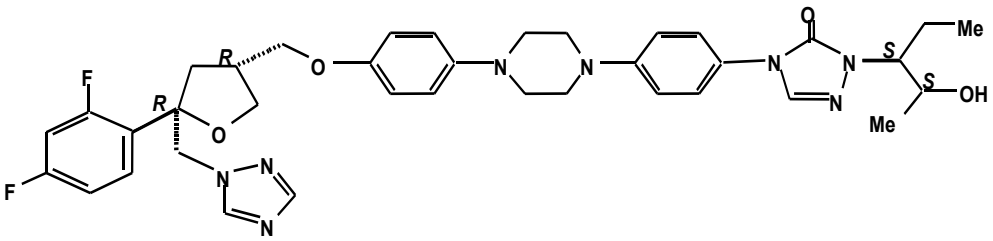
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anti-infective for systemic use, triazole derivative, ATC code: J02A C04

Posaconazole is a broad spectrum triazole antifungal compound with a molecular formula of $C_{37}H_{42}F_2N_8O_4$ yielding a molecular weight of 700.8.

The chemical structure, which possesses four chiral centres, two R and two S, and chemical name are illustrated below:

SCH 56592 (Posaconazole)



CAS INDEX NAME: D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydropropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)
CAS RN 171228-49-2.
IUPAC NAME: 4-4-[4-(4-{(3R, 5R)-5-(2,4-difluorophenyl)-5-(1H-1,2,4-triazol-1-ylmethyl)tetrahydro-3-furanyl]methoxyphenyl)piperazino]phenyl-1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-5-one.

Mechanism of action
Posaconazole is a triazole antifungal agent. It is a potent inhibitor of the enzyme lanosterol 14α-demethylase, which catalyses an essential step in ergosterol biosynthesis. Ergosterol depletion, coupled with the accumulation of methylated sterol precursors, is thought to impair membrane integrity and the function of some membrane-associated proteins. This results in the inhibition of cell growth and/or cell death.

Microbiology
Posaconazole has been shown *in vitro* and in clinical infections to be active against the following micro-organisms: (see section 4.1): *Aspergillus* species (*Aspergillus fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, *A. niger*, *A. ustus, A.ochraceus*), *Candida* species (*Candida albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*), *Cryptococcus neoformans*, *Coccidioides immitis*, *Fonsecaea pedrosoi*, *Histoplasma capsulatum, Pseudallescheria boydii* and species of *Alternaria*, *Exophiala*, *Fusarium*, *Ramichloridium, Rhizomucor*, *Mucor*, and *Rhizopus.*

Posaconazole also exhibits *in vitro* activity against the following yeasts and moulds: *Candida dubliniensis*, *C. famata, C. guilliermondii, C. lusitaniae, C. kefyr, C. rugosa, C. tropicalis, C. zeylanoides, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis, Cryptococcus laurentii, Kluyveromyces marxianus, Saccharomyces cerevisiae, Yarrowia lipolytica*, species of *Pichia*, and *Trichosporon, Aspergillus sydowii, Bjerkandera adusta, Blastomyces dermatitidis, Epidermophyton floccosum, Paracoccidioides brasiliensis, Scedosporium apiospermum, Sporothrix schenckii, Wangiella dermatitidis* and species of *Absidia, Apophysomyces, Bipolaris, Curvularia, Microsporum, Paecilomyces, Penicillium,* and *Trichophyton.* However, the safety and effectiveness of posaconazole in treating clinical infections due to these micro-organisms have not been established in clinical trials.

Posaconazole exhibits broad-spectrum antifungal activity against some yeasts and moulds not generally responsive to azoles, or resistant to other azoles:

- species of *Candida* (including *C. albicans* isolates resistant to fluconazole, voriconazole and itraconazole,
- *C. krusei* and *C. glabrata* which are inherently less susceptible to fluconazole,
- *C. lusitaniae* which is inherently less susceptible to amphotericin B),
- *Aspergillus* (including isolates resistant to fluconazole, voriconazole, itraconazole and amphotericin B)

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

In vitro posaconazole exhibited fungicidal activity against species of:

- *Aspergillus*,
- dimorphic fungi (*Blastomyces dermatitidis, Histoplasma capsulatum, Penicillium marneffei,*
- *Coccidioides immitis*)
- some species of *Candida*

In animal infection models posaconazole was active against a wide variety of fungal infections caused by moulds or yeasts. However, there was no consistent correlation between minimum inhibitory concentration and efficacy.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Drug Resistance

C. albicans strains resistant to posaconazole could not be generated in the laboratory; spontaneous laboratory *Aspergillus fumigatus* mutants exhibiting a decrease in susceptibility to posaconazole arose at a frequency of $1x10^{-8}$ to $1x10^{-9}$. Clinical isolates of *Candida albicans* and *Aspergillus fumigatus* exhibiting significant decreases in posaconazole susceptibility are rare. In those rare instances where decreased susceptibility was noted, there was no clear correlation between decreased susceptibility and clinical failure. Clinical success has been observed in patients infected with organisms resistant to other azoles; consistent with these observations posaconazole was active in vitro against many *Aspergillus* and *Candida* strains that developed resistance to other azoles and/or amphotericin B. Breakpoints for posaconazole have not been established for any fungi.

Antifungal drug combinations

When combinations of posaconazole with either amphotericin B or caspofungin were tested *in vitro* and *in vivo* there was little or no antagonism and in some instances there was an additive effect. The clinical significance of these results is unknown.

Clinical efficacy and safety

Summary of Posaconazole Oral Suspension studies

Invasive Aspergillosis

Efficacy in patients with refractory disease or intolerance to prior therapy: The efficacy and survival benefit of oral posaconazole for the treatment of invasive aspergillosis in patients with disease refractory to amphotericin B (including liposomal formulations), itraconazole or voriconazole or in patients who were intolerant of these medicinal products, was demonstrated in 107 patients enrolled in a salvage therapy trial. Patients were administered posaconazole 800 mg/day in divided doses for up to 585 days.

The majority of patients were severely immunocompromised with underlying conditions such as haematological malignancies, including bone marrow transplantation; solid organ transplantation; solid tumours and/or AIDS. An independent expert panel reviewed all patient data, including diagnosis of invasive aspergillosis, refractoriness and intolerance to previous therapy, and clinical outcome in a parallel and blinded fashion with an external control group of 86 patients treated with standard therapy mostly at the same time and at the same sites

as the patients enrolled in the posaconazole trial. A success was defined as either complete resolution (complete response) or a clinically meaningful improvement (partial response) of all signs, symptoms and radiographic findings attributable to the fungal infection. Stable, non-progressive disease and failure were considered to be a non-success. Most of the cases of aspergillosis were considered to be refractory in both the posaconazole group (88 %) and in the external control group (79 %). As shown in Table 4, a successful global response at end of treatment was seen in 42 % of posaconazole-treated patients compared to 26 % of the external group (P=0.006).

At one year, the survival rate for posaconazole was 38 % compared to 22 % for the external control group. However, this was not a prospective, randomised controlled study and so all comparisons with the external control group must be viewed in this context.

Table 4: Overall efficacy of posaconazole oral suspension at the end of treatment* for invasive aspergillosis in comparison to an external control group

	Posaconazole Oral Suspension		External Control Group	
Overall Response	45/107 (42 %)		22/86 (26 %)	
	Odds Ratio 4.06 (95 % CI: 1.50, 11.04) P=0.006			
Survival at day 365	(38 %)		(22 %)	
Success by Species				
All mycologically confirmed Aspergillus spp.*	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 %)

* includes other less common species or species unknown

Other Serious Fungal Pathogens
Posaconazole oral suspension has been shown to be effective against the following additional pathogens when other therapy had been ineffective or when the patient had developed intolerance of the prior therapy:

Candida*:* 11 of 23 (48 %) patients were successfully treated with posaconazole. Of the responders, 5 were HIV infected patients with oesophageal disease and 4 were patients with candidemia. Furthermore, in fluconazole-resistant non *albicans* species a successful outcome was noted in 4/5 cases with *C. krusei* infection.

Zygomycosis: Successful responses to posaconazole oral suspension 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.*:** Successful responses to posaconazole oral suspension therapy were seen in 11 of 24 (46 %) of patients with fusariosis. Four of the responders had disseminated disease and one patient had disease localized to the eye; the remainder had a variety of sites of infection. Seven of 24 patients had profound neutropenia at baseline. In addition, 3/5

patients with infection due to *F. solani* which is typically resistant to most antifungal agents, were successfully treated.

Cryptococcus: Successful responses to posaconazole oral suspension therapy were seen in 15 of 31 (48 %) of patients with cryptococcus. Most of the patients were HIV infected with refractory cryptococcal meningitis.

Chromoblastomycosis/Mycetoma: Successful responses to posaconazole oral suspension therapy were seen in 9 of 11 (82 %) of patients with chromoblastomycosis or mycetoma. Five of these patients had chromoblastomycosis due to Fonsecaea pedrosoi and 4 had mycetoma, mostly due to Madurella species.

Coccidioidomycosis: The efficacy of posaconazole oral suspension in the primary treatment of non-meningeal coccidioidomycosis was demonstrated in 15 clinically evaluable patients enrolled in an open-label, non-comparative trial to receive posaconazole 400 mg daily for 6 months. Most patients were otherwise healthy and had infections at a variety of sites. A satisfactory response (defined as an improvement of at least 50 % of the Cocci score as defined by the BAMSG Coccidioidomycosis trial group) was seen in 12 of 15 patients (80 %) after an average of 4 months of posaconazole treatment. In a separate open-label, non-comparative trial, the safety and efficacy of posaconazole 400 mg twice a day was assessed in 16 patients with coccidioidomycosis infection refractory to standard treatment. Most had been treated with amphotericin B (including lipid formulations) and/or itraconazole or fluconazole for months to years prior to posaconazole treatment. At the end of treatment with posaconazole, a satisfactory response (complete or partial resolution of signs and symptoms present at baseline) as determined by an independent panel was achieved for 11/16 (69 %) of patients. One patient with CNS disease that had failed fluconazole therapy had a successful outcome following 12 months of posaconazole therapy.

Treatment of Azole-susceptible Oropharyngeal Candidiasis (OPC)
A randomised, double-blind, controlled study was completed in HIV-infected patients with azole-susceptible oropharyngeal candidiasis. The primary efficacy variable was the clinical success rate (defined as cure or improvement) after 14 days of treatment. Patients were treated with posaconazole or fluconazole oral suspension (both posaconazole and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

The clinical and mycological response rates from the above study are shown in Table 5 below. Posaconazole and fluconazole demonstrated equivalent clinical success rates at Day 14 as well as 4 weeks after the end of treatment. However, posaconazole oral suspension demonstrated a significantly better sustained mycological response rate than fluconazole.

Table 5: Clinical Success Rates and Mycological Response Rates in Oropharyngeal Candidiasis

Endpoint	Posaconazole Oral Suspension	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)
Mycological Response Rate 4 Weeks After End of Treatment*	40.6 % (41/101)	26.4 % (24/91)

*Statistically significant (P=0.0376)

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.

Mycological response rate was defined as mycological success (≤ 20 CFU/ml) divided by the total number of cases eligible for analysis.

Treatment of Azole-refractory Oropharyngeal Candidiasis (rOPC) (Studies 330 and 298)
The primary efficacy parameter in Study 330 was the clinical success rate (cure or improvement) after 4 weeks of treatment. HIV-infected patients were treated with posaconazole oral suspension 400 mg twice a day with an option for further treatment during a 3-month maintenance period. A 75 % (132/176) clinical success rate and a 36.5 % (46/126) mycological response rate (≤ 20 CFU/ml) were achieved after 4 weeks of posaconazole treatment. Clinical success rates ranged from 71 % to 100 %, inclusive, for all azole-resistant *Candida* species identified at Baseline, including *C. glabrata* and *C. krusei*.

Of the total patients treated in this study, 43 had azole-refractory oesophageal candidiasis (EC), either alone or in combination with OPC. All patients with azole-refractory EC had endoscopically confirmed EC at baseline. The clinical success rate after 4 weeks was 74.4 %.

In Study 298 the primary efficacy endpoint was the clinical success rate (cure or improvement) after 3 months of treatment. A total of 100 HIV-infected patients with OPC and/or EC were treated with posaconazole 400 mg twice a day for up to 15 months. Sixty of these patients had been previously treated in Study 330. An 85.6 % (77/90) clinical success rate overall (cure or improvement) was achieved after 3 months of posaconazole treatment; 80.6 % (25/31) for previously untreated subjects.

The mean exposure to posaconazole based on the actual days dosed was 102 days (range: 1-544 days). Sixty-seven percent (67 %, 10/15) of patients treated with posaconazole for at least 12 months had continued clinical success at the last assessment.

Of the patients treated in Study 298, 15 with azole-refractory EC had been previously treated in Study 330. Sixty-seven percent (67 %, 10/15) were considered cured by the end of treatment and 33 % (5/15) were considered improved. For those patients, treatment durations ranged from 81 to 651 days.

Prophylaxis of Invasive Fungal Infections (IFIs) (Studies 316 and 1899)
Two large, randomised, controlled studies were conducted using posaconazole oral suspension as prophylaxis for the prevention of IFIs among patients at high risk.

Study 316 was a randomised, double-blind trial that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic HSCT 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 medication + 7 days). The mean duration of therapy was comparable between the two treatment groups (80 days, posaconazole; 77 days, fluconazole).

Study 1899 was a randomised, evaluator-blinded study that compared posaconazole oral suspension (200 mg three times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs 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. The mean duration of therapy was comparable between the two treatment groups (29 days, posaconazole; 25 days, fluconazole/itraconazole).

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

Table 6: 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]			
1,899[d]	7/304 (2)	25/298 (8)	0.0009
316[e]	7/291 (2)	22/288 (8)	0.0038
Fixed-Time Period [c]			
1,899[d]	14/304 (5)	33/298 (11)	0.0031
316 [d]	16/301 (5)	27/299 (9)	0.0740
Proportion (%) of Patients With Proven/Probable Aspergillosis			
On-Treatment Period[b]			
1,899[d]	2/304 (1)	20/298 (7)	0.0001
316[e]	3/291 (1)	17/288 (6)	0.0013
Fixed-Time Period[c]			
1,899[d]	4 /304 (1)	26 /298 (9)	< 0.0001
316 [d]	7/301 (2)	21/299 (7)	0.0059

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

In Study 1899, a significant decrease in all cause mortality in favour of posaconazole was observed [POS 49/304 (16 %) vs. FLU/ITZ 67/298 (22 %) p= 0.048]. Based on Kaplan-Meier estimates, the probability of survival up to day 100 after randomization, was significantly higher for posaconazole recipients; this survival benefit was demonstrated when the analysis considered all causes of death (P= 0.0354) (Figure 1) as well as IFI-related deaths (P = 0.0209).

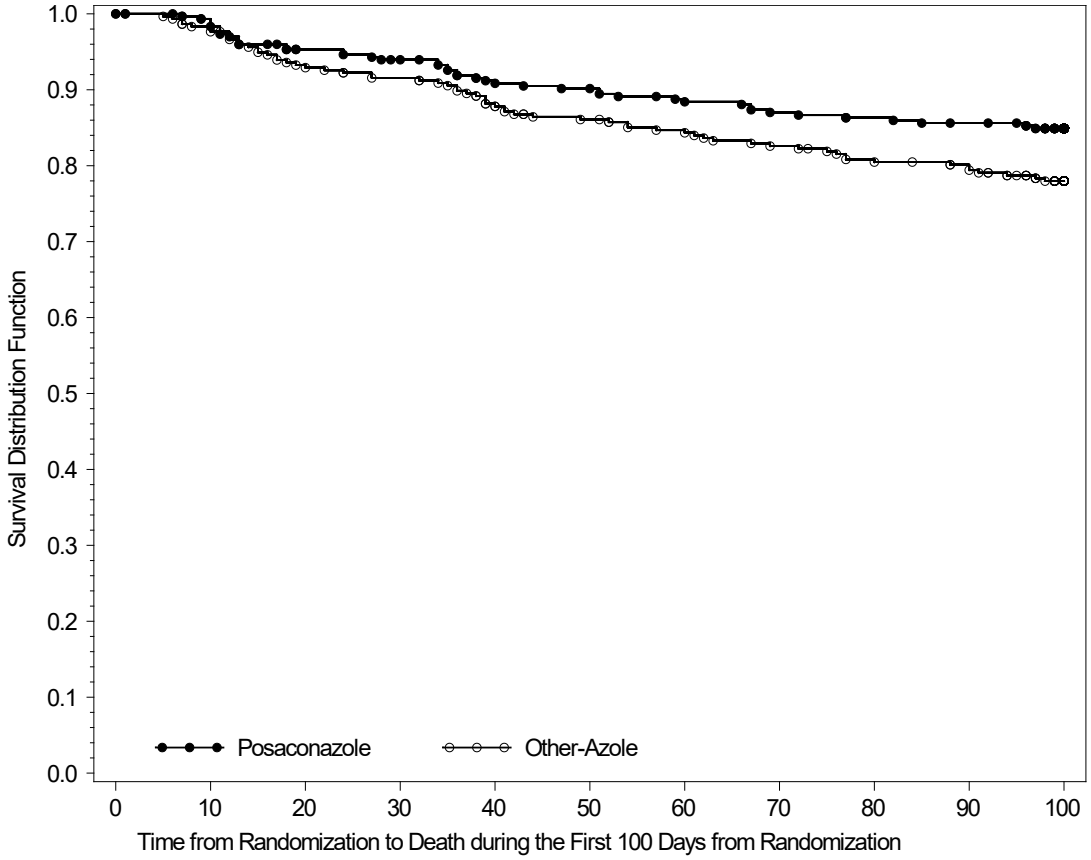


Figure 1: All cause mortality in Study 1899 (POS vs FLU/ITZ; P= 0.0354)

In Study 316, overall mortality was similar (POS, 25 %; FLU, 28 %); however, the proportion of IFI-related deaths was significantly lower in the POS group (4/301) compared with the FLU group (12/299; P= 0.0413).

Use in paediatric patients
A total of 16 patients aged 8 to 17 years were included in the posaconazole oral suspension therapeutic trials of invasive fungal infections. Five patients were < 13 years of age and 11 were 13 -17 years old. Infections included aspergillosis, candidiasis and fusariosis. Successful response after treatment with posaconazole at divided doses up to 800 mg/day was seen in 50 % (8/16) of patients. Pharmacokinetic parameters obtained from 12 of these patients were not different from those obtained from the patients in the 18 - 65 year age group, and the safety profile appeared similar.

Additionally, 12 patients aged 13 to 17 years received 600 mg/day of posaconazole oral suspension for prophylaxis of invasive fungal infections (Studies 316 and 1899). The safety profile in these patients < 18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these paediatric patients, the pharmacokinetic profile appears to be similar to patients ≥ 18 years of age.

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

Summary of Posaconazole Modified Release Tablet studies
Study 5615 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole modified release tablet. Study 5615 was conducted in a similar patient population to that previously studied in the pivotal posaconazole oral suspension clinical program. The pharmacokinetics and safety

data from Study 5615 were bridged to the existing data (including efficacy data) with the oral suspension.

Study 5615 enrolled a total of 230 subjects. Part 1 of the study was designed to select a dose for further study in Part 2, after first evaluating pharmacokinetics, safety, and tolerability in the neutropenic patient population at high risk of a fungal infection. Part 2 of the study was designed to evaluate posaconazole modified release tablet in a more diverse patient population, and to confirm the exposure of posaconazole modified release tablet in additional subjects at risk of a fungal infection. Posaconazole modified release tablet was administered without regard to food intake in both Part 1 and Part 2 of the study.

The subject population for Part 1 included subjects with acute myelogenous leukaemia (AML) or myelodysplastic syndrome (MDS) who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia. Two different dosing groups were evaluated in Part 1: 200 mg BID on Day 1, followed by 200 mg QD thereafter (Part 1A) and 300 mg BID on Day 1, followed by 300 mg QD thereafter (Part 1B).

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

The total subject population had a mean age of 51 years (range = 19-78 years), 93% were White, the major ethnicity was not Hispanic or Latino (84%), and 62% were male. The study treated 110 (48%) subjects with AML (new diagnosis), 20 (9%) subjects with AML (first relapse), 9 (4%) subjects with MDS, and 91 (40%) subjects with HSCT, as the primary diseases at study entry.

Serial PK samples were collected on Day 1 and at steady-state on Day 8 for all Part 1 subjects and a subset of Part 2 subjects. This serial PK analysis demonstrated that 90% of the subjects treated with the 300 mg QD dose attained steady state Cav between 500-2500 ng/mL. [C_{av} was the average concentration of posaconazole at steady state, calculated as AUC/dosing interval (24 hours).] Subjects with AML/MDS with neutropenia following chemotherapy or HSCT subjects receiving immunosuppressive therapy to prevent or treat GVHD who received 300 mg QD achieved a mean C_{av} at steady state of 1580 ng/mL. The PK findings from the pivotal study (Study 5615) support a 300-mg daily dose of posaconazole modified release tablet for use in prophylaxis.

5.2 Pharmacokinetic properties

Absorption

Posaconazole oral suspension is absorbed with a median T_{max} of 3 hours (patients) and ~ 5 hours (healthy volunteers). Steady-state plasma concentrations attained at 7 to 10 days following multiple-dose administration.

The pharmacokinetics of posaconazole oral suspension are linear following single and multiple dose administration of up to 800 mg. No further increases in exposure were observed when oral suspension doses above 800 mg daily were administered to patients and healthy volunteers. Dividing the total posaconazole daily dose (800 mg) as 400 mg twice a day results in a 184% higher exposure relative to once-a-day administration in patients.

When given orally in healthy volunteers, posaconazole modified release tablet is absorbed with a median T_{max} of 4 to 5 hours. Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (QD after BID loading dose at Day 1).

The absolute bioavailability of the oral modified release tablet is approximately 54%.

Relative bioavailability was investigated between the 100 mg modified release tablet under fasted conditions and the 100 mg oral suspension under fed conditions in healthy adults. Under these conditions, plasma exposure to posaconazole for the two treatments was similar. Under fasted conditions, the exposure of posaconazole after single-dose tablet administration was 3.7-fold higher than the oral suspension.

Effect of food on oral absorption in healthy volunteers
The AUC of posaconazole oral suspension is about 2.6 times greater when administered with a nonfat meal or nutritional supplement (14 g fat) and 4 times greater when administered with a high-fat meal (~ 50 g fat) relative to the fasted state. Posaconazole oral suspension should be administered with food or a nutritional supplement (see section 4.2).

Posaconazole modified release tablet 100 mg taken under fasted conditions in healthy volunteers achieved similar exposures to oral suspension 100 mg administered with a high fat meal. Posaconazole modified release tablets do not require administration with food in contrast to posaconazole oral suspension.

Distribution
Posaconazole oral suspension has a large apparent volume of distribution (1774 L) suggesting extensive penetration into the peripheral tissues.

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

Posaconazole is highly protein bound (> 98.0 %), predominantly to serum albumin.

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

Excretion
Posaconazole oral suspension is slowly eliminated with a mean half-life ($t_{½}$) of 35 hours (range 20 to 66 hours) and a total body clearance (Cl/F) of 32 L/hr. Steady state is attained following 7 to 10 days of multiple-dose administration.

Posaconazole modified release tablet is eliminated with a mean half-life ($t_{½}$) ranging between 26 and 31 hours and a mean apparent clearance ranging from 7.5 to 11 L/hr.

Posaconazole is predominantly excreted in the faeces (77 % of the radio-labelled dose) with the major component eliminated as parent drug (66 % of the radio-labelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radio-labelled dose excreted in urine (<0.2 % of the radio-labelled dose is parent drug).

Summary of the mean pharmacokinetic parameters in patients

Oral suspension
The general pharmacokinetic findings across the clinical program in both healthy volunteers and patients were consistent, in that posaconazole oral suspension was slowly absorbed and slowly eliminated with an extensive volume of distribution. In addition, the phenomenon of dose-limited absorption of posaconazole at 800 mg/day was observed both in healthy volunteers and patients. The mean pharmacokinetic parameters in patients and healthy volunteers following administration of posaconazole 400 mg twice a day for 7 days are displayed in Table 7.

Table 7: Pharmacokinetics of posaconazole oral suspension in patients and healthy volunteers

Population	Dose	Mean (%CV)		
		C_{max} (ng/mL)	T_{max}[a] (hr)	AUC(τ) (ng·hr/mL)
Healthy Volunteers	400 mg twice a day (n=174)	2850 (36)	5 (0-12)	29453 (37)
Patients	400 mg twice a day (n=24)	851 (82)	3 (0-12.5)	8619 (86)

[a] Median (range)

The exposure to posaconazole oral suspension following administration of 400 mg twice a day was ~ 3 times higher in healthy volunteers than in patients, without additional safety findings at the higher concentrations (Table 7).

Modified Release Tablet
The general pharmacokinetic findings across the clinical program in both healthy volunteers and patients were consistent, in that posaconazole modified release tablet was slowly absorbed and slowly eliminated with a large volume of distribution. The mean pharmacokinetic parameters in patients and healthy volunteers following administration of posaconazole modified release tablets 300 mg once daily (after BID on Day 1 only) for 8 days are displayed in Table 8.

Table 8: Pharmacokinetics of posaconazole modified release tablets in patients and healthy volunteers

		Mean (%CV)		
Population	Dose	Cmax (ng/mL)	Tmax[a] (hr)	AUC(τ) (ng·hr/mL)
Healthy Volunteers	300 mg/day (n=12)	2764 (21)	3.98 (3 - 6)	51618 (25)
Patients	300 mg/day (n=50)	2090 (38)	4 (1.3 - 8.1)	37900 (42)

The exposure to posaconazole modified release tablet following administration of 300 mg once daily (after BID on Day 1 only) up to steady state was 1.3 times higher in healthy volunteers than in patients, without additional safety findings at the higher concentrations (Table 8).

Pharmacokinetics in Special Populations

Paediatric

Following administration of 800 mg per day of posaconazole oral suspension as a divided dose for treatment of invasive fungal infections, mean trough plasma concentrations from 12 paediatric patients 8 -17 years of age (776 ng/mL) were similar to concentrations from 194 patients 18 - 64 years of age (817 ng/mL). No pharmacokinetic data are available from paediatric patients less than 8 years of age. Similarly, in the prophylaxis studies, the mean steady-state posaconazole average concentration (C_{avg}) was comparable among ten adolescents (13 - 17 years of age) to C_{avg} achieved in adults (≥ 18 years of age).

In a study of 136 neutropenic pediatric patients 11 months – 17 years treated with posaconazole oral suspension, at doses up to 18 mg/kg/day divided TID, approximately 50% met the prespecified target (Day 7 C_{avg} between 500 ng/mL-2500 ng/mL).

In general, exposures tended to be higher in the older patients (7 to <18 years) than in younger patients (2 to <7 years). See Table 9.

Table 9: Distribution of C_{avg} by Dose and Age Group at Day 7 in Study P03579

Dose	Age Group	N	C_{avg} (ng/mL)				
			<200	200 - <500	**500 - <2500**	2500 - <3650	>3650
12 mg/kg/day divided BID	2 to <7 years	16	19% (3/16)	44% (7/16)	**31% (5/16)**	6% (1/16)	0
	7 to <18 years	14	14% (2/14)	21% (3/14)	**65% (9/14)**	0	0
18 mg/kg/day divided BID	2 to <7 years	12	25% (3/12)	25% (3/12)	**50% (6/12)**	0	0
	7 to <18 years	12	8% (1/12)	25% (3/12)	**50% (6/12)**	8% (1/12)	8% (1/12)
18 mg/kg/day divided TID	2 to <7 years	5	20% (1/5)	20% (1/5)	**60% (3/5)**	0	0
	7 to <18 years	10	20% (2/10)	0	**80% (8/10)**	0	0
12 mg/kg/day divided TID	3 months to <2 years	1	0	100% (1/1)	**0**	0	0
Numbers in parentheses = (Number of subjects in category/Total number of subjects) Target C_{avg} range (500-<2500 ng/ml) required for ~90% of subjects to meet criteria for study success							

There is no paediatric experience with posaconazole modified release tablets.

Gender

The pharmacokinetics of posaconazole are comparable in men and women. No adjustment in the dosage of NOXAFIL is necessary based on gender.

Elderly

Results from a multiple dose study of posaconazole oral suspension in healthy volunteers (N=48) indicated that at steady state, there was an increase in C_{max} (26 %) and AUC (29 %) observed in elderly subjects (24 subjects ≥ 65 years of age) relative to younger subjects (24 subjects 18 - 45 years of age). A similar trend was observed in the clinical program based on a small proportion of elderly subjects ≥ 65 years of age (N=25 vs. 194 patients 18 – 64 years of age). However, in a population pharmacokinetic analysis (Study 1899) age did not influence the pharmacokinetics of posaconazole oral suspension. The safety profile of

posaconazole oral suspension between the young and elderly patients was similar. Therefore no dose adjustment is required for age.

Of the 230 patients treated with posaconazole modified release tablets, 38 (17%) were greater than 65 years of age. The pharmacokinetics of posaconazole modified release tablets are comparable in young and elderly subjects. No overall differences in safety were observed between geriatric patients and younger patients; therefore, no dosage adjustment is recommended for elderly subjects.

Race
Results from a multiple dose study in healthy volunteers (n = 56) indicated that there was only a slight decrease (16%) in the AUC and C_{max} of posaconazole oral suspension in Black subjects relative to Caucasian subjects, therefore, no dose adjustment for race is required.

There is insufficient data among different races with posaconazole modified release tablets.

Weight
Pharmacokinetic modeling for posaconazole 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.

Renal insufficiency
Following single-dose administration of posaconazole oral suspension, there was no effect of mild and moderate renal insufficiency (n=18, Cl_{cr} ≥20 mL/min/1.73 m^2) on posaconazole pharmacokinetics, therefore, no dose adjustment is required. In subjects with severe renal insufficiency (n=6, Cl_{cr} < 20 mL/min/1.73 m^2), the exposure of posaconazole was highly variable (96 % CV) compared to the exposure in the other renal groups (< 40 % CV). As posaconazole is not significantly renally eliminated, an effect of severe renal insufficiency on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended. However, due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections. Posaconazole is not removed by haemodialysis.

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

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

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

Electrocardiogram evaluation
Multiple, time-matched ECGs collected over a 12 hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18 to 85 years of age) administered posaconazole oral suspension 400 mg BID with a high-fat meal. In this pooled analysis, the mean QT_c (Fridericia) interval change was -5 msec following administration of

the recommended clinical dose. A decrease in the QT_c (F) interval (- 3 msec) was also observed in a small number of subjects (n=16) administered placebo. The placebo-adjusted mean maximum QT_c (F) interval change from baseline was < 0 msec (- 8 msec). No healthy subject administered posaconazole had a QT_c (F) interval of ≥ 500 msec or an increase ≥ 60 msec in their QT_c (F) interval from baseline.

Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4. Rigorous attempts to correct potassium, magnesium, and calcium should be made before starting posaconazole.

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.

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 related 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

NOXAFIL oral suspension
Polysorbate 80
Simethicone
Sodium benzoate
Sodium citrate dehydrate
Citric acid monohydrate
Glycerol
Xanthan gum
Liquid glucose
Titanium dioxide
Artificial cherry flavouring
Purified water

NOXAFIL modified release tablet
Hypromellose acetate succinate
Microcrystalline cellulose
Hydroxypropylcellulose
Silicon dioxide
Croscarmellose sodium
Magnesium stearate
Opadry® II Yellow (consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350, titanium dioxide, talc, and iron oxide yellow)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
NOXAFIL oral suspension
Unopened container: 3 years.

NOXAFIL modified release tablet
2 years.

6.4 Special precautions for storage
NOXAFIL oral suspension
Store below 25°C. Do not freeze.

NOXAFIL modified release tablet
Store below 30°C. Do not freeze.

6.5 Nature and contents of container
NOXAFIL oral suspension
NOXAFIL oral suspension 105 mL is packaged in a 123 mL amber Ph. Eur. Type IV glass bottle, closed with a plastic child-resistant closure. A measuring spoon, composed of clear polystyrene and graduated to measure 2.5 mL or 5 mL of the suspension, is provided with each bottle.

NOXAFIL modified release tablet
NOXAFIL Modified Release Tablets are available in blister packs of 24 and 96 tablets.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE
Prescription

8 SPONSOR
Merck Sharp & Dohme (NZ) Ltd
P O Box 99 851
Newmarket
Auckland 1149
New Zealand

Tel: 0800 500 673

9 DATE OF FIRST APPROVAL
Oral suspension approval date: 18 September 2008.
Modified release tablet approval date: 7 May 2015.

10 DATE OF REVISION OF THE TEXT
17 September 2021

SUMMARY TABLE OF CHANGES

Section(s) changed	Summary of new information
4.2, 4.4, 5.1	Updated sections to correct safety and efficacy age statements regarding the paediatric population to be consistent with that in the approved indications

NOXAFIL® is a registered trademark.

RCN000021612-NZ

S-CCDS-MK-5592-OS-T-042021