AUSTRALIAN PRODUCT INFORMATION

NOXAFIL®

(posaconazole)
Concentrated Injection

1 NAME OF THE MEDICINE

Posaconazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Posaconazole is a white to off-white crystalline powder.

Each vial of NOXAFIL concentrated injection contains 300 mg of posaconazole (18 mg per mL).

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

NOXAFIL (posaconazole) concentrated injection is a clear, colourless to yellow liquid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NOXAFIL (posaconazole) concentrated injection is indicated for use in the treatment of the following invasive fungal infections in adults:

- Invasive aspergillosis in patients intolerant of, or with disease that is refractory to, alternative therapy.
- Fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis, and mycetoma in patients intolerant of, or with disease that is refractory to, alternative therapy.

NOXAFIL is also indicated for the:

- Prophylaxis of invasive fungal infections among adults, who are at high risk of developing these infections, such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Recommended dose is shown in Table 1.

TABLE 1. Recommended dose according to indication

Indication	Dose and duration of therapy
Refractory invasive fungal infections (IFI)/intolerant to alternative therapy	Loading dose of 300 mg NOXAFIL twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Prophylaxis of invasive fungal infections	Loading dose of 300 mg NOXAFIL twice a day on the first day, then 300 mg once a day thereafter. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with AML or MDS, prophylaxis with NOXAFIL should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3.

Method of administration
NOXAFIL concentrated injection must be diluted before administration. Not for bolus injection.

- Equilibrate the refrigerated vial of NOXAFIL to room temperature.
- Aseptically transfer 16.7 mL of posaconazole to an IV bag (or bottle) containing a compatible infusion solution (see below for list of diluents) using a volume ranging from 150 mL to 283 mL depending on the final concentration to be achieved (not less than 1 mg/mL and not greater than 2 mg/mL).
- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC) by slow intravenous (IV) infusion over approximately 90 minutes. Not for IV bolus administration.
- If a central venous catheter is not available, a single infusion may be administered through a peripheral venous catheter. When administered through a peripheral venous catheter, the infusion should be administered over approximately 30 minutes.
  Note: In clinical trials, multiple peripheral infusions given through the same vein were not well tolerated (see Section 4.8 Adverse Effects (Undesirable Effects)).
- NOXAFIL is a single dose unpreserved sterile solution. Therefore, from a microbiological point of view, once admixed, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2°-8°C. NOXAFIL is for single use only and any unused solution should be discarded.

NOXAFIL concentrated injection can be diluted with:

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

NOXAFIL concentrated injection should only be administered with these diluents.

NOXAFIL concentrated injection must not be diluted with Lactated Ringer's solution, 5% dextrose with Lactated Ringer's solution, 4.2% sodium bicarbonate.

Intravenous line compatibility

A study was conducted to evaluate physical compatibility of NOXAFIL concentrated injection with injectable drug products and commonly used intravenous diluents during simulated Y-site infusion. Compatibility was determined through visual observations, measurement of particulate matter and turbidity.

Based on the results of the study, the following drug products can be infused at the same time through the same intravenous line (or cannula) as NOXAFIL concentrated injection:

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

Any products not listed in the table above should not be co-administered with NOXAFIL through the same intravenous line (or cannula).

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

Use in renal impairment: In patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2), receiving the NOXAFIL concentrated injection, accumulation of the intravenous vehicle, Sulfobutyl Betadex Sodium (SBECD), is expected to occur. NOXAFIL concentrated injection for IV infusion should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), unless an assessment of the benefit/risk to the patient justifies the use of NOXAFIL concentrated injection. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to NOXAFIL oral suspension therapy. Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see **Section 5.2 Pharmacokinetic Properties** and **Section 4.4 Special Warnings and Precautions for Use**).

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 Pharmacokinetic Properties, Pharmacokinetics in special populations).**

Use in paediatrics: Safety and efficacy in children below the age of 18 years have not been established.

NOXAFIL concentrated injection should not be used in children because of pre-clinical safety concerns (see **Section 4.4 Special Warnings and Precautions for Use, Pre-clinicalsafety**).

Use in the elderly: No dosage adjustment is recommended for elderly patients (see **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations**).

4.3 CONTRAINDICATIONS

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

Coadministration 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 Interactions with Other Medicines and Other Forms of Interactions**).

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*, coadministration 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 Interactions with Other Medicines and Other Forms of Interactions**).

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. Subjects with severe or serious reactions to azoles were excluded from key studies of posaconazole.

Hepatic toxicity

Hepatic reactions (e.g., mild to moderate elevations in alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase, total bilirubin, and/or clinical hepatitis) have been reported in clinical trials. 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. In the clinical pharmacology program, no healthy subject had CTC Grade 3 or Grade 4 (>5 x ULN) elevations in their liver function test results. Most of these LFT changes were mild in severity and all were transient in nature, returned to baseline after the cessation of dosing, and rarely led to study discontinuation. See Table 2 for hepatic enzyme abnormalities in healthy volunteers.

Liver function tests should be evaluated at the start of and during the course of posaconazole therapy, particularly in treatment beyond 14 days with posaconazole concentrated injection. 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. Patients who develop abnormal liver function tests during posaconazole therapy should be 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.

TABLE 2. Summary of Hepatic Enzyme Abnormalities in the Healthy Volunteers

CTC Grade	AST		ALT		GGT	
	POS n=444	Placebo n=48	POS n=444	Placebo n=48	POS n=431	Placebo n=47
0 (≤1 x ULN)	417 (94%)	48 (100%)	388 (87%)	46 (96%)	408 (95%)	46 (98%)
1 (>1 - 2.5 x ULN)	26 (6%)	0 (0%)	50 (11%)	1 (2%)	20 (5%)	1 (2%)
2 (>2.5 - 5 x ULN)	1 (<1%)	0 (0%)	6 (1%)	1 (2%)	3 (1%)	0 (0%)

CTC=Common Toxicity Criteria; ULN=upper limit of normal
Note: The majority of subjects had CTC Grade 0 liver function test (LFTs) at baseline. This table summarizes the worst CTC grade observed during the treatment phase per subject per laboratory test. Only subjects with at least one treatment value for a given laboratory test are included in the summary.

QT prolongation

Some azoles have been associated with prolongation of the QT_c interval on the electrocardiogram (ECG). Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions and should not be administered with medicines that are known to prolong the QT_c interval and are metabolised through the CYP3A4 (See **Section 5.2 Pharmacokinetic Properties, Electrocardiogram evaluation**, **Section 4.3 Contraindications**, **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Electrolyte disturbances

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

Midazolam and other benzodiazepines metabolised by CYP3A4

Due to the risk of prolonged sedation it is recommended that dose adjustments should be considered when posaconazole is administered with any benzodiazepine that is metabolised by CYP3A4 (e.g. midazolam, triazolam, alprazolam).

Dose adjustment of benzodiazepine metabolised by CYP3A4 should be considered (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

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 Interactions with Other Medicines and Other Forms of Interactions).**

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 Interactions with Other Medicines and Other Forms of Interactions).** Refer to the venetoclax prescribing information for the medical management of patients concomitantly administered venetoclax and posaconazole.

Effects on adrenal steroid hormones

As observed with other azole antifungal agents, effects related to inhibition of adrenal steroid hormone synthesis were seen in repeat-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.

Use in hepatic impairment

See **Section 4.4. Special Warnings and Precautions for Use, Hepatic toxicity** and **Section Section 4.2 Dose and Method of Administration, Use in hepatic impairment**.

Use in renal impairment

In patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2), receiving the NOXAFIL concentrated injection, accumulation of the intravenous vehicle, Sulfobutyl Betadex Sodium (SBECD), is expected to occur. NOXAFIL concentrated injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), unless an assessment of the benefit/risk to the patient justifies the use of NOXAFIL concentrated injection. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to NOXAFIL oral suspension therapy.

Due to the variability in exposure, patients with severe renal impairment (eGFR: <20 mL/min/1.73 m^2) should be monitored closely for breakthrough fungal infections (see **Section 5.2 Pharmacokinetic Properties** and **Section 4.2 Dose and Method of Administration).**

A specific study has not been conducted with posaconazole concentrated injection.

Following single-dose administration of 400 mg of the oral suspension, there was no effect of mild and moderate renal impairment (n=18, eGFR ≥20 mL/min/1.73 m^2) on posaconazole pharmacokinetics, therefore, no dose adjustment is required. In subjects with severe renal insufficiency (n=6, eGFR < 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). However, as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected. Posaconazole is not removed by haemodialysis.

Use in the elderly

Of the 279 patients treated with posaconazole concentrated injection, 52 (19%) were greater than 65 years of age. The pharmacokinetics of posaconazole concentrated injection are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients and age was not a significant covariate in the population PK model; therefore, no dosage adjustment is recommended for NOXAFIL concentrated injection in geriatric patients.

Paediatric use

(See **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations, Children (<18 years)**). Safety and effectiveness in paediatric patients below the age of 18 years have not been established.

NOXAFIL concentrated injection should not be used in children because of pre-clinical safety concerns (see **Section 5.3 Preclinical Safety Data, Pre-clinical safety**).

Effects on laboratory tests

See **Section 4.8 Adverse Effects (Undesirable Effects), Clinical laboratory values**.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Summary of drug interactions

Contraindicated	Avoid concomitant use unless the benefit outweighs the risk	Dose adjustment of other medications and/or monitoring of adverse events	No dose adjustment required
Ergotamine or dihydroergotamine	Rifabutin	Rifabutin	Antacids
Terfenadine, astemizole	Phenytoin	Cyclosporine	Zidovudine, ritonavir, lamivudine, indinavir
Cisapride	Cimetidine	Tacrolimus	Glipizide
Pimozide	Efavirenz	Sirolimus	
Quinidine	Vinca alkaloids		
Halofantrine		Midazolam	
HMG-CoA reductase inhibitors primarily metabolized through CYP3A4		Atazanavir/ritonavir Fosamprenavir	
		Calcium channel blockers metabolized through CYP3A4	
		Sulfonylureas	
		Digoxin	

Note that the majority of the interaction studies were carried out in healthy volunteers with repeat dose regimens of posaconazole 400 mg (oral suspension) twice daily administered with a meal or nutritional supplement. All drug interactions with posaconazole oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility) are considered relevant to posaconazole concentrated injection as well. See below for further information.

Effect of other drugs on posaconazole

Posaconazole is metabolized 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 (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 (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.

Cimetidine (400 mg twice a day) decreased the C_{max} and AUC of posaconazole 200 mg once a day each by 39 %. Concomitant use of posaconazole and cimetidine should be avoided unless the benefit outweighs the risk. The effect of other H_2 receptor antagonists and proton pump inhibitors that may suppress gastric acidity has not been studied. Reduction in bioavailability may occur, therefore co-administration of posaconazole with H_2 receptor antagonists and proton pump inhibitors should be avoided if possible.

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

Gastrointestinal Motility Agents: No clinically meaningful effect on the pharmacokinetics of posaconazole was observed when oral posaconazole was concomitantly administered with metoclopramide. No dosage adjustment is required when given concomitantly with metoclopramide.

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

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

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. A study conducted in 20 healthy volunteers, 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. The GMRs of posaconazole C_{max} and AUC when taken as posaconazole versus posaconazole/fosamprenavir were 0.79 (0.71-0.89) and 0.77 (0.68-0.87), respectively.

Effects of posaconazole 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, metabolized 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 Contraindications**).

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. Coadministration of posaconazole and ergot alkaloids is contraindicated (see **Section 4.3 Contraindications**).

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 Special Warnings and Precautions for Use**). 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 once daily increased cyclosporine concentrations requiring dose reductions. Cases of

elevated cyclosporine levels resulting in serious adverse events, including nephrotoxicity and one fatal case of leukoencephalopathy, were reported in clinical efficacy studies. When initiating treatment with posaconazole in patients already receiving 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. Clinically significant interactions resulting in hospitalisation and/or posaconazole discontinuation were reported in clinical efficacy studies. When initiating posaconazole treatment in patients already receiving tacrolimus, the dose of tacrolimus should be reduced (e.g. to about one third of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during co-administration, and upon discontinuation of posaconazole, and the dose of tacrolimus should be adjusted as necessary.

Sirolimus: Repeat dose administration of oral posaconazole (400 mg twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9 fold, 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 coadministration, 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 coadministered, careful monitoring of full blood counts and adverse effects related to increased rifabutin levels (e.g., uveitis) is recommended.

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 coadministration.

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 Special Warnings and Precautions for Use**).

Zidovudine (AZT), lamivudine (3TC), ritonavir, 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), ritonavir (600 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. Although not considered clinically significant, ritonavir exposure was increased by 30% with the addition of posaconazole.

HMG-CoA reductase inhibitors primarily metabolized through CYP3A4: Repeat dose administration of oral posaconazole (50, 100, and 200 mg 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 statins concentrations in plasma can be associated with rhabdomyolysis. Co-administration of posaconazole and HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 is contraindicated.

Interactions with HMG-CoA reductase inhibitors that are not metabolized by CYP3A4 have not been investigated but clinically relevant drug interactions are not expected as posaconazole does not inhibit other CYP isoenzymes at relevant concentrations.

Calcium channel blockers metabolized 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 coadministration with posaconazole. Dose adjustment of calcium channel blockers may be required.

Digoxin: Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and posaconazole. Therefore, 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.

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 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 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.

Fosamprenavir: The effect of posaconazole on fosamprenavir levels when fosamprenavir is given with ritonavir is unknown. A study conducted in 20 healthy subjects, administration 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) with fosamprenavir (700 mg twice a day for 10 days) resulted in a 36 % and 65 % lower C_{max} and AUC for amprenavir compared to when fosamprenavir was administered with ritonavir. The GMRs of amprenavir C_{max} and AUC when taken as fosamprenavir and posaconazole versus fosamprenavir/ritonavir were 0.64 (0.55-0.76) and 0.35 (0.32-0.39), respectively.

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 Special Warnings and Precautions for Use).**

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Posaconazole administered by the oral route had no effect on the fertility of male rats at doses up to 180 mg/kg/day (2.8 times the exposure achieved from a 300 mg IV dose in humans). Posaconazole administered by the oral route to female rats at doses up to 45 mg/kg/day (3.4 times the exposure from a 300 mg IV dose in patients) for 2 weeks prior to mating did not affect fertility, but disruption of oestrus cycling was seen in female rats treated for 4 weeks.

Use in pregnancy

Pregnancy Category B3

There are no adequate studies in pregnant women. A total of three pregnancies have been reported in female subjects treated with posaconazole oral suspension. Two pregnancies were electively terminated; no examination was reported on the foetuses. Another pregnancywas diagnosed at a follow-up visit approximately 1 month after the completion of a full 16- week prophylactic treatment with POS oral suspension 200 mg TDS in a patient who had received an allogeneic haematopoietic stem cell transplant. The subject delivered a healthy full-term male infant via caesarean section.

Studies in rats with posaconazole administered by the oral route have shown reproductive toxicity including post implantation loss, increased skeletal variations, teratogenicity (craniofacial malformations), increased gestation length, dystocia, and reduced postnatal viability at exposure levels lower than those expected at the recommended doses in humans. An increase in post implantation loss and increased skeletal variations were seen in rabbits at plasma exposure levels greater than those of humans receiving therapeutic doses of posaconazole oral suspension.

NOXAFIL must not be used during pregnancy unless the benefit to the mother clearly outweighs the risk to the foetus. Women of childbearing potential must be advised to always use effective contraceptive measure during treatment and for at least 2 weeks after completing therapy.

Use in lactation

Posaconazole administered by the oral route is excreted in milk of lactating rats. The excretion of posaconazole in human breast milk has not been investigated. Women taking posaconazole should not breastfeed.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Posaconazole concentrated injection
In clinical trials, the type and frequency of adverse effects reported for posaconzole concentrated injection were generally similar to that reported in trials of posaconazole oral suspension.

In initial studies of healthy volunteers, administration of a single dose of posaconazole concentrated injection infused over 30 minutes via a peripheral venous catheter was well tolerated. However, multiple doses of posaconazole concentrated injection administered via a peripheral venous catheter were associated with thrombophlebitis (60% incidence). Therefore, in subsequent studies, posaconazole concentrated injection was administered via central venous catheter. If a central venous catheter was not readily available, patients could receive a single infusion over 30 minutes via a peripheral venous catheter.

The safety of posaconazole concentrated injection has been assessed in 268 patients in a clinical trial. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole concentrated injection when given as antifungal prophylaxis (Study 5520). Patients were immunocompromised with underlying conditions including haematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 55% male, had a mean age of 51 years (range 18-82 years, 19% of patients were ≥65

years of age), and were 95% white and 8% Hispanic. Ten patients received a single dose of 200 mg posaconazole concentrated injection, 21 patients received 200 mg daily dose for a median of 14 days, and 237 patients received 300 mg daily dose for a median of 9 days. Each patient in the multiple dose cohorts received BD dosing on Day 1. In each cohort, following posaconazole IV therapy, patients received posaconazole oral suspension to complete 28 days of total posaconazole therapy. Safety and efficacy of posaconazole concentrated injection at the recommended dose has not been assessed beyond 14 days in clinical trials.

Table 3 presents treatment-emergent adverse reactions observed in patients treated with posaconazole IV solution 300 mg daily dose at an incidence of ≥10% in the posaconazole concentrated injection study.

TABLE 3. **Posaconazole concentrated injection (Study 5520): Number (%) of Subjects Treated with Posaconazole IV Solution 300 mg Daily Dose Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10%**

Body System **Preferred Term**	**Posaconazole IV Solution Treatment Phase n=237 (%)***		**Posaconazole IV Solution Treatment Phase or Subsequent Oral Suspension Treatment Phase n=237(%)†**	
Subjects Reporting any Adverse Reaction	220	(93)	235	(99)
Blood and Lymphatic System Disorder				
Anemia	16	(7)	23	(10)
Febrile Neutropenia	44	(19)	54	(23)
Thrombocytopenia	17	(7)	25	(11)
Gastrointestinal Disorder				
Abdominal Pain Upper	15	(6)	25	(11)
Abdominal Pain	30	(13)	41	(17)
Constipation	18	(8)	31	(13)
Diarrhoea	75	(32)	93	(39)
Nausea	46	(19)	70	(30)
Vomiting	29	(12)	45	(19)
General Disorders and Administration Site Conditions				
Fatigue	19	(8)	24	(10)
Chills	28	(12)	38	(16)
Mucosal Inflammation	37	(16)	44	(19)
Edema Peripheral	28	(12)	35	(15)
Pyrexia	49	(21)	73	(31)
Metabolism and Nutrition Disorders				
Decreased appetite	23	(10)	29	(12)
Hypokalemia	51	(22)	67	(28)

Hypomagnesemia	25	(11)	30	(13)
Nervous System Disorders				
Headache	33	(14)	49	(21)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	21	(9)	31	(13)
Dyspnea	16	(7)	24	(10)
Epistaxis	34	(14)	40	(17)
Skin and Subcutaneous Tissue Disorders				
Petechiae	20	(8)	24	(10)
Rash	35	(15)	56	(24)
Vascular Disorders				
Hypertension	20	(8)	26	(11)
*Adverse reactions reported in patients with an onset during the posaconazole IV dosing phase of the study. †Adverse reactions reported with an onset at any time during the study in patients who were treated for up to 28 days of posaconazole therapy.				

The most frequently reported adverse effect (>30%) with an onset during the posaconazole IV phase of dosing with 300 mg once daily was diarrhoea (32%).

The most common adverse effect (>1%) leading to discontinuation of posaconazole IV solution 300 mg once daily was acute myelogenous leukemia (AML) (1%).

Posaconazole oral suspension
Drug-related, adverse reactions observed in 2400 subjects dosed with posaconazole oral suspension are shown in Table 4. 172 patients received posaconazole oral suspension therapy for ≥ 6 months; 58 of these received posaconazole oral suspension therapy for ≥ 12 months.

The most frequently reported adverse reactions reported across the whole population of healthy volunteers and patients were nausea (6%) and headache (6%).

TABLE 4. Treatment-related adverse reactions reported in posaconazole dosed subjects by body system and frequency n=2400
Common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000)

Infections and infestations	
Uncommon:	oral candidiasis, sinusitis
Rare:	catheter related infection, non herpetic cold sores, oesophageal candidiasis, pneumonia, upper respiratory tract infection, urinary tract infection

Blood and lymphatic system disorders	
Common:	neutropenia
Uncommon:	anaemia, thrombocytopenia, leukopenia, eosinophilia, lymphadenopathy
Rare:	abnormal blood gases, haemolytic uraemic syndrome, neutrophilia, pancytopenia, coagulation disorder, haemorrhage NOS, platelet count increased, prothrombin decreased, prothrombin time prolonged, purpura, thrombotic thrombocytopenic purpura
Immune system disorders	
Uncommon:	allergic reaction
Rare:	hypersensitivity reaction, Stevens Johnson syndrome
Endocrine disorders	
Rare:	adrenal insufficiency, gonadotropins decreased
Metabolism and nutrition disorders	
Common:	anorexia, electrolyte imbalance
Uncommon:	hyperglycaemia, hypertriglyceridaemia, hyperuricaemia, weight decrease, LDH increased, dehydration
Rare:	amylase increased, hypercholesterolemia, hyperlipaemia, hyperproteinaemia, hypoalbuminaemia, lipase increased, metabolic acidosis, renal tubular acidosis, vitamin K deficiency, weight increase
Psychiatric disorders	
Uncommon:	altered mental status, anxiety, confusion, insomnia
Rare:	amnesia, depression, abnormal dreaming, emotional lability, libido decreased, paroniria, psychosis
Nervous system disorders	
Common:	dizziness, headache, paresthesia, somnolence
Uncommon:	neuropathy, hypoesthesia, convulsions, tremor
Rare:	peripheral neuropathy, areflexia, ataxia, cognition impaired, delirium, dysphonia, dystonia, encephalopathy, hemiparesis, hyperkinesia, hyperreflexia, hyporeflexia, hypotonia, impaired concentration, memory impairment, meningism, mononeuritis, restless leg syndrome, sciatica, syncope
Eye disorders	
Uncommon:	conjunctivitis, blurred vision
Rare:	eye pain, eyes dry, periorbital oedema, diplopia, photophobia, scotoma
Ear and labyrinth disorder	
Uncommon:	earache, vertigo
Rare:	hearing impairment, tinnitus
Cardiac disorders	
Uncommon:	abnormal ECG, QTc/QT prolongation, atrial flutter, atrial fibrillation, bundle branch block, tachycardia, extrasystoles, palpitation, ventricular hypertrophy
Rare:	

	bradycardia, cardiac failure, cardio-respiratory arrest, sudden death, ventricular tachycardia, aortic valve sclerosis, cardiomegaly, ejection fraction decreased, mitral valve disease NOS, myocardial infarction, supraventricular tachycardia, premature atrial contractions, premature ventricular contractions, AV block, torsades de pointes
Vascular disorders Uncommon: Rare:	 flushing, hot flushes, hypertension, hypotension atherosclerosis, cerebrovascular accident, deep venous thrombosis NOS, pulmonary embolism, ischemia, haematoma
Respiratory, thoracic and mediastinal disorders Uncommon: Rare:	 chest pain, coughing, dyspnoea, epistaxis, pharyngitis, nasal congestion atelectasis, dry throat, pulmonary hypertension, interstitial pneumonia, nasal irritation, pneumonitis, postnasal drip, pulmonary infiltration, rales, rhinitis, rhinorrhoea
Gastrointestinal disorders Common: Uncommon: Rare:	 abdominal pain, diarrhoea, dyspepsia, flatulence, dry mouth, nausea, vomiting taste perversion, constipation, loose stools, abdominal distention, dysphagia, ascites, eructation, thirst, gastritis, gastroesophageal reflux, mucositis NOS, oesophagitis, pancreatitis, tongue discolouration gastrointestinal tract haemorrhage, ileus, abdominal tenderness, cheilitis, haemorrhagic diarrhoea, oesophagus ulceration, haemorrhagic gastritis, odynophagia, pancreatic enzymes NOS increased, proctalgia, retching, aphthous stomatitis, tenesmus, melena, gingivitis, glossitis
Hepatobiliary disorders Common: Uncommon: Rare:	 elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, bilirubin) hepatitis, hepatocellular damage, hepatomegaly, jaundice asterixis, cholestasis, hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, splenomegaly
Skin and subcutaneous tissue disorders Common: Uncommon: Rare:	 rash alopecia, dry skin, maculopapular rash, urticaria, furunculosis, acne, mouth ulceration, pruritus, pruritic rash stomatitis, dermatitis, erythema, erythematous rash, follicular rash, macular rash, night sweats, seborrhoea, skin nodule, vesicular rash
Musculoskeletal and connective tissue disorders Uncommon:	

Rare:	myalgia, arthralgia, back pain, musculoskeletal pain, flank pain, muscle weakness bone pain, chest wall pain, fasciitis, neck stiffness, cramps extremities, muscle cramps
Renal and urinary disorders Uncommon: Rare:	 albuminuria, altered micturition frequency, dysuria, increased blood creatinine, acute renal failure, renal failure, haematuria, renal impairment, nocturia increased BUN, interstitial nephritis, micturition disorder, renal calculus, urinary tract obstruction NOS
Reproductive system and breast disorders Uncommon: Rare:	 menstrual disorder leukorrhoea, breast pain
General disorders and administration site conditions Common: Uncommon: Rare:	 asthenia, fatigue, fever increased sweating, pain, rigors, malaise, weakness, oedema, tooth discolouration face oedema, tongue oedema
Investigations Uncommon:	 altered drug levels
Injury, poisoning and procedural complications Uncommon: Rare:	 drug toxicity (NOS) ecchymoses

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 605patients 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 oral suspension.

In addition, rare cases of haemolytic uremic 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.

TABLE 5. Treatment-related adverse events reported in ≥ 1% of patients treated for invasive fungal infections with posaconazole oral suspension
(Severity as classified by the investigator)

Disorder	Total (All) n=330 Number (%)	Total (Mild/Moderate) n=330 Number (%)	Total (Severe/Life-Threatening) n=330 Number (%)
Body as a Whole-General			
anorexia	8 (2)	8 (2)	0
asthenia	4 (1)	4 (1)	0
chest pain	2 (1)	2 (1)	0
dizziness	7 (2)	6 (2)	1 (<1)
drug level altered	7 (2)	4 (1)	3 (1)
fatigue	7 (2)	6 (2)	1 (<1)
fever	3 (1)	3 (1)	0
headache	15 (5)	13 (4)	2 (1)
weakness	2 (1)	2 (1)	0
Cardiovascular, general			
cardio-respiratory arrest	2 (1)	0	2 (1)
ventricular hypertrophy	2 (1)	1 (<1)	1 (<1)
Central and Peripheral Nervous System			
confusion	3 (1)	3 (1)	0
convulsions	2 (1)	0	2 (1)
hyperreflexia	2 (1)	2 (1)	0
hypoesthesia	2 (1)	2 (1)	0
mental status, altered	2 (1)	2 (1)	0
paresthesia	6 (2)	6 (2)	0
somnolence	3 (1)	3 (1)	0
tremor	2 (1)	2 (1)	0
Blood and lymphatic system	6 (2)	4 (1)	2 (1)
anaemia	4 (1)	3 (1)	1 (<1)
Eye	4 (1)	3 (1)	1 (<1)
vision blurred	2 (1)	2 (1)	0
Reproductive system and breast			
breast pain	1 (<1)	1 (<1)	0
menstrual disorder (based on females only)	2 (2)	2 (2)	0
Gastro-intestinal system			
abdominal distension	2 (1)	2 (1)	0
abdominal pain	16 (5)	13 (4)	3 (1)
constipation	2 (1)	2 (1)	0
diarrhoea	11 (3)	10 (3)	1 (<1)
dyspepsia	2 (1)	2 (1)	0
flatulence	3 (1)	3 (1)	0
mouth dry	5 (2)	5 (2)	0
nausea	31 (9)	2 (1)	29 (9)
vomiting	19 (6)	18 (5)	1 (<1)
Heart Rate and Rhythm			
atrial flutter	2 (1)	1 (<1)	1 (<1)

ECG abnormal specific	2 (1)	2 (1)	0
extrasystoles	2 (1)	1 (<1)	1 (<1)
fibrillation atrial	3 (1)	2 (1)	1 (<1)
QTc/QT prolongation	6 (2)	6 (2)	0
tachycardia	2 (1)	2 (1)	0
tachycardia supraventricular	2 (1)	1 (<1)	1 (<1)
Injury and poisoning			
drug toxicity (NOS)	2 (1)	0	2 (1)
Liver and biliary system			
bilirubinemia	4 (1)	3 (1)	1 (<1)
gamma-GT increased	2 (1)	0	2 (2)
hepatic enzymes increased	7 (2)	6 (2)	1 (<1)
hepatic function abnormal	2 (1)	2 (1)	0
jaundice	2 (1)	1 (<1)	1 (<1)
AST increased	9 (3)	6 (2)	3 (1)
ALT increased	11 (3)	9 (3)	2 (1)
Metabolic and nutritional			
phosphatase alkaline increased	6 (2)	5 (2)	1 (<1)
thirst	2 (1)	2 (1)	0
Musculo-skeletal system			
musculo-skeletal pain	2 (1)	2 (1)	0
Platelet, bleeding and clotting			
thrombocytopenia	2 (1)	2 (1)	0
Renal & Urinary System			
blood creatinine decreased	5 (2)	4 (2)	1 (<1)
nocturia	2 (1)	2 (1)	0
renal failure	2 (1)	1 (<1)	1 (<1)
renal failure acute	2 (1)	0	2 (1)
Skin / subcutaneous tissue			
alopecia	4 (1)	4 (1)	0
dry skin	3 (1)	3 (1)	0
pruritus	3 (1)	3 (1)	0
rash	9 (3)	7 (2)	2 (1)
rash maculopapular	4 (1)	3 (1)	1 (<1)
rash vesicular	2 (1)	2 (1)	0

TABLE 6. Treatment-related, treatment-emergent adverse events (any grade): ≥ 2% of subjects (OPC) with posaconazole oral suspension

Adverse event	**Number (%) of subjects**		
	Controlled OPC pool		**Refractory OPC pool**
	POS n = 557	**FLU n = 262**	**POS n = 239**
Subjects reporting any adverse event[a]	**150 (27)**	**70 (27)**	**135 (56)**
Body as a whole – general disorders			

Anorexia	6 (1)	1 (< 1)	7 (3)
Asthenia	4 (1)	2 (1)	6 (3)
Dizziness	9 (2)	5 (2)	8 (3)
Fatigue	8 (1)	5 (2)	7 (3)
Fever	10 (2)	1 (<1)	6 (3)
Headache	16 (3)	5 (2)	18 (8)
Central and peripheral nervous system disorders			
Somnolence	4 (1)	5 (2)	3 (1)
Disorders of blood and lymphatic system	2 (< 1)	0 (0)	6 (3)
Anaemia	10 (2)	4 (2)	20 (8)
Neutropenia			
Gastro-intestinal system disorders			
Abdominal pain	10 (2)	8 (3)	12 (5)
Diarrhoea	19 (3)	13 (5)	26 (11)
Flatulence	6 (1)	0 (0)	11 (5)
Mouth dry	7 (1)	6 (2)	5 (2)
Nausea	27 (5)	18 (7)	20 (8)
Vomiting	20 (4)	4 (2)	16 (7)
Liver and biliary system disorders			
Hepatic enzymes increased	1 (< 1)	0 (0)	5 (2)
Hepatic function abnormal	3 (1)	4 (2)	0 (0)
Metabolic and nutritional disorders			
Phosphatase alkaline increased	3 (1)	3 (1)	5 (2)
Musculo-skeletal system disorders			
Myalgia	1 (< 1)	0 (0)	4 (2)
Platelet, bleeding and clotting disorders			
Thrombocytopenia	3 (1)	0 (0)	4 (2)
Psychiatric disorders			
Insomnia	3 (1)	0 (0)	6 (3)
Skin and subcutaneous tissue disorders			
Pruritus	6 (1)	2 (1)	5 (2)
Rash	8 (1)	4 (2)	10 (4)

[a] number of subjects reporting treatment-emergent adverse events at least once during the study. Subjects may have reported more than one event.

TABLE 7. Studies 316 and 1899, Treatment-related, treatment-emergent adverse events: All (≥ 2% incidence) and Severe/Life Threatening Number (%) of Subjects (Prophylaxis) in the posaconazole oral suspension or fluconazole treatment groups.

	POS n=605		FLU n=539		ITC n=58	
	All	**Severe/LT**	**All**	**Severe/LT**	**All**	**Severe/LT**
Subjects reporting any adverse event[a]	209 (35)	81 (13)	186 (35)	53 (10)	30 (52)	6 (10)
Gastro-Intestinal System Disorders						
Abdominal Pain	13 (2)	1 (< 1)	15 (3)	2 (< 1)	1 (2)	0
Constipation	4 (1)	0	12 (2)	0	0	0
Diarrhoea	28 (5)	4 (1)	24 (4)	1 (<1)	9 (16)	0
Dyspepsia	8 (1)	1 (<1)	9 (2)	0	0	0
Nausea	44 (7)	5 (1)	45 (8)	1 (<1)	8 (14)	0
Vomiting	27 (4)	4 (1)	29 (5)	3 (1)	6 (10)	0
Heart Rate and Rhythm Disorders						
QTc/QT Prolongation	14 (2)	1 (<1)	6 (1)	0	4 (7)	0
Liver and Biliary System Disorders						
Bilirubinemia	15 (2)	10 (2)	10 (2)	6 (1)	3 (5)	2 (3)
GGT Increased	14 (2)	10 (2)	8 (1)	4 (1)	1 (2)	0
Hepatic Enzymes Increased	15 (2)	11 (2)	10 (2)	3 (1)	0	0

SGOT Increased SGPT Increased	14 (2) 16 (3)	2 (<1) 7 (1)	7 (1) 8 (1)	3 (1) 7 (1)	1 (2) 1 (2)	0 1 (2)
Metabolic and Nutritional Disorders Hypokalemia	11 (2)	2 (<1)	6 (1)	1 (<1)	1 (2)	1 (2)
Skin and Subcutaneous Tissue Disorders Rash	12 (2)	1 (<1)	10 (2)	0	1 (2)	0

GGT = gamma glutamyl transpeptidase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase

[a] number of subjects reporting treatment-emergent advserse events at least once during the study. Subjects may have reported more than one event.

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 oftherapy.

In the comparative trials of patients infected with HIV 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 %.

The number of patients with changes in liver function tests from Common Toxicity Criteria (CTC) Grade 0, 1, or 2 at Baseline to Grade 3 or 4 during the study are presented in Table 8 for the prophylaxis studies 316 and 1899.

TABLE 8. Posaconazole oral suspension studies 316 and 1899, Changes in Liver Function Test Results from CTC Grade 0, 1 or 2 at Baseline to Grade 3 or 4.

	Number (%) of Patients With Change[a]	
Study 316		
Laboratory Parameter	Posaconazole N=301	Fluconazole N=299
AST	11/266 (4)	13/266 (5)
ALT	47/271 (17)	39/272 (14)
Bilirubin	24/271 (9)	20/275 (7)
Alkaline Phosphatase	9/271 (3)	8/271 (3)
Study 1899		
	Posaconazole (n=304)	Fluconazole/Itraconazole (n=298)
AST	9/286 (3)	5/280 (2)
ALT	18/289 (6)	13/284 (5)
Bilirubin	20/290 (7)	25/285 (9)
Alkaline Phosphatase	4/281 (1)	1/276 (<1)

a: Change from Grade 0 to 2 at Baseline to Grade 3 or 4 during the study. These data are presented in the form X/Y, where X represents the number of patients who met the criterion as indicated, and Y represents the number of patients who had a baseline observation and at least one post-baseline observation.

CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase.

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

Endocrine Disorders: pseudoaldosteronism

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no experience with overdosage of posaconazole concentrated injection.

During clinical trials, patients who received posaconazole oral suspension doses up to 1600 mg/day had no noted adverse reactions different from those reported with patients at 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} < 20mL/min), posaconazole was not removed by haemodialysis. Thus, haemodialysis is unlikely to be effective in removing posaconazole from the systemic circulation.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Antiinfective for systemic use, triazole derivative, J02AC04

Mechanism of action

Posaconazole is a triazole antifungal agent. It is an 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 Therapeutic Indications):** *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*. While posaconazole has been used in a clinical setting against these microorganisms, sufficient evidence for efficacy has not been collected for all the listed microorganisms (see **Section 5.1 Pharmacodynamic Properties, Clinical trials**).

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 microorganisms have not been established in clinical trials.

NOXAFIL 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 NOXAFIL 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 NOXAFIL 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. Clinical studies of posaconazole in combination with antifungal drugs including amphotericin B-based drugs and caspofungin have not been conducted.

Clinical trials

Posaconazole concentrated injection

Study 5520 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole concentrated injection.

Study 5520 enrolled a total of 279 subjects, including 268 receiving at least one dose of posaconazole concentrated injection. Cohort 0 was designed to evaluate the tolerability of a single dose of posaconazole concentrated injection when administered via a central line. Cohorts 1 and 2 of the study were designed to select a dose for further evaluation in Cohort 3, after first evaluating pharmacokinetics, safety, and tolerability in the neutropenic patient population at high risk of a fungal infection. Cohort 3 of the study was designed to evaluate posaconazole concentrated injection in a more diverse patient population, and to confirm the exposure of posaconazole concentrated injection in additional subjects at risk of a fungal infection.

The subject population for Cohorts 0, 1, and 2 included subjects with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia. Two different dosing groups were evaluated in Cohorts 1 and 2: 200 mg BD on Day 1, followed by 200 mg QD thereafter (Cohort 1) and 300 mg BD on Day 1, followed by 300 mg QD thereafter (Cohort 2).

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

The total subject population had a mean age of 51 years (range = 18-82 years), 95 % were White, the major ethnicity was not Hispanic or Latino (92 %), and 55 % were male. The study treated 155 (65 %) subjects with AML or MDS, and 82 (35 %) subjects with HSCT, as the primary diseases at study entry.

Serial pharmacokinetic samples were collected on Day 1 and at steady-state on Day 14 for all Cohort 1 and 2 subjects and on Day 10 for a subset of Cohort 3 subjects. This serial pharmacokinetic analysis demonstrated that 94 % of the subjects treated with the 300 mg QD dose attained steady state C_{av} between 500-2500 ng/mL. [C_{av} was the average concentration of posaconazole at steady state, calculated as AUC/dosing interval (24 hours)]. This exposure was selected based on pharmacokinetic/pharmacodynamic considerations with posaconazole oral suspension. 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 1500 ng/mL. The PK findings from the pivotal study (Study 5520) support a 300-mg daily dose of posaconazole concentrated injection for use in prophylaxis.

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, in a small number of cases, voriconazole or echinocandins, and/or with intolerance to amphotericin B (including liposomal formulations) or itraconazole 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 median duration of posaconazole therapy was 56 days (1-585 days).

The majority of patients were severely immunocompromised with underlying conditions such as haematologic 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 salvage therapy (e.g. amphotericin B including liposomal formulations, and/or itraconazole) 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 %) while the remaining patients were intolerant to prior antifungal therapy (12 % posaconazole; 21 % external control group).

As shown in Table 9, 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).

TABLE 9. Overall efficacy of posaconazole at the end of treatment* for invasive aspergillosis in comparison to an external control group

	Posaconazole		**External Control Group**	
Overall Response	45/107 (42 %)		22/86 (26 %)	
	Adjusted Odds Ratio ** 4.06 (95 % CI: 1.50, 11.04) P=0.006			
	Unadjusted Odds ratio 2.11 (95 % CI: 1.14, 3.92) P=0.018			
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 %)

* end of all study drug therapy plus 7 days within 372 days of the start of salvage therapy
** adjusted odds ratio was obtained using a logistic regression model adjusting for major covariates
*** includes other less common species or species unknown

Other serious fungal pathogens
Posaconazole 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 theprior therapy.

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.*: Successful responses to posaconazole 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.

Chromoblastomycosis/mycetoma: Successful responses to posaconazole 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 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) in HIV-infected patients

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 10 below. Posaconazole and fluconazole demonstrated equivalent clinical success rates at Day 14 as well as 4 weeks after the end of treatment. However, posaconazole demonstrated a significantly better mycological response rate than fluconazole 4 weeks after the end of treatment.

TABLE 10. Clinical Success Rates and Mycological Response 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)
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 oropharyngeal candidiasis refractory to itraconazole and fluconazole (rOPC) in HIV-infected patients

The primary efficacy parameter in the short-term treatment study was the clinical success rate (cure or improvement) after 4 weeks of treatment. HIV-infected patients were treated with posaconazole 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.*

In the long-term treatment study 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.

Prophylaxis of invasive fungal infections (IFIs) (Studies 316 and 1899):
Two large, randomised, controlled studies were conducted using posaconazole 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-randomization as determined by an independent, blinded external expert panel. A key secondary endpoint was the incidence of proven/probable IFIs during the on-treatment period (first dose to last dose of study 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-randomization. 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 11 for results from both studies.

TABLE 11. Results from Clinical Studies in Prophylaxis of Invasive Fungal Infections

Study 316: Allogeneic Hematopoietic Stem Cell Transplant Recipients with Graft vs. Host Disease			
	Posaconazole n =301	**Fluconazole n = 299**	**P-Value**
On therapy plus 7 days			
Clinical Failure	50 (17%)	55 (18%)	
Failure due to:			
Proven/Probable IFI	7 (2%)	22 (7%)	0.0038
(*Aspergillus*)	3 (1%)	17 (6%)	0.0059
(*Candida*)	1 (<1%)	3 (1%)	
(Other)	3 (1%)	2 (1%)	

Through 16 weeks			
Clinical Failure	99 (33%)	110 (37%)	
Failure due to:			
Proven/Probable IFI	16 (5%)	27 (9%)	0.0740
(*Aspergillus*)	7 (2%)	21 (7%)	0.0013
(*Candida*)	4 (1%)	4 (1%)	
(Other)	5 (2%)	2 (1%)	
Study 1899: Neutropenic Patients with Acute Myelogenous Leukaemia/Myelodysplastic Syndromes			
	Posaconazole n =304	**Fluconazole/Itraconazole n = 298**	**P-Value**
On therapy plus 7 days			
Clinical Failure	82 (27%)	126 (42%)	
Failure due to:			
Proven/Probable IFI	7 (2%)	25 (8%)	0.0009
(*Aspergillus*)	2 (1%)	20 (7%)	0.0001
(*Candida*)	3 (1%)	2 (1%)	
(Other)	2 (1%)	3 (1%)	
Through 100 days post-randomization			
Clinical Failure	158 (52%)	191 (64%)	
Failure due to:			
Proven/Probable IFI	14 (5%)	33 (11%)	0.0031
(*Aspergillus*)	2 (1%)	26 (9%)	<0.0001
(*Candida*)	10 (3%)	4 (1%)	
(Other)	2 (1%)	3 (1%)	

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).

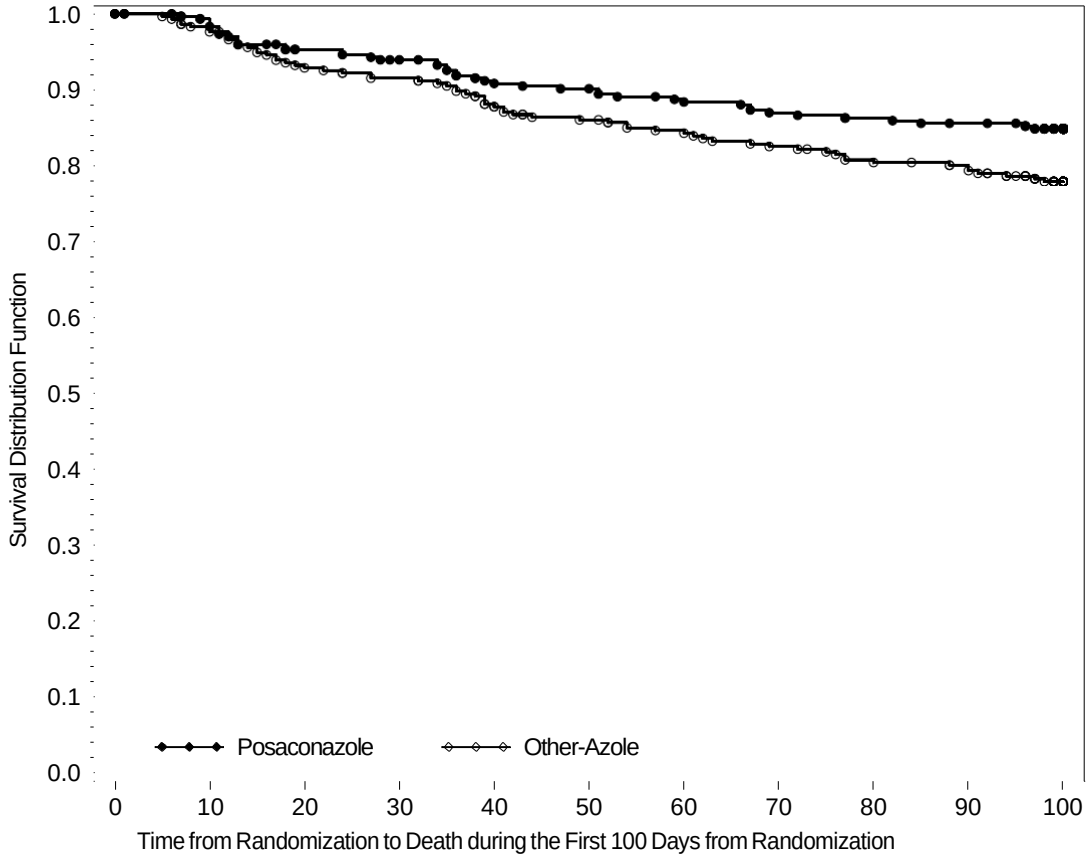


Figure 1. All cause mortality in Study 1899 (POS vs FLU/ITZ; P= 0.0354)

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:
There is no paediatric experience for posaconazole concentrated injection.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetic / pharmacodynamic relationships
A correlation between total medicinal product exposure divided by MIC (AUC/MIC) and clinical outcome was observed. The critical ratio for subjects with *Aspergillus* infections was ~200. It is particularly important to try to ensure that maximal plasma levels are achieved in patients infected with *Aspergillus* (see **Section 4.2 Dose and Method of Administration** on recommended dose regimens).

Distribution

Posaconazole exhibits dose proportional pharmacokinetics after single dosing in healthy volunteers and multiple dosing in patients in the therapeutic dose range (200-300 mg).

Following administration of 300 mg posaconazole concentrated injection, posaconazole has a distribution volume of 261 L, indicating extravascular distribution.

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

Metabolism

Posaconazole does not have any major circulating metabolites. Of the circulating metabolites, the majority are glucuronide conjugates of posaconazole with only minor amounts of oxidative (CYP450 mediated) metabolites observed. The excreted metabolites in urine and faeces account for approximately 17 % of the administered radio-labelled dose of posaconazole oral suspension.

Excretion

Posaconazole, after administration of 300 mg of posaconazole concentrated injection, is slowly eliminated with a mean half-life ($t_{1/2}$) of 27 hours and a mean clearance of 7.3 L/hr.

Posaconazole, after oral suspension administration, is slowly eliminated with a mean half-life ($t_{1/2}$) of 35 hours (range 20 to 66 hours) and an apparent total body clearance (Cl/F) of 32 L/hr. After administration of ^{14}C-posaconazole as oral suspension, 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). Steady-state is attained following 7 to 10 days of multiple-dose administration.

Summary of the mean pharmacokinetic parameters in patients
The pharmacokinetic parameters of posaconazole in patients following administration of posaconazole concentrated injection 300 mg once a day for 10 or 14 days following BD dosing on Day 1 are shown in Table 12.

TABLE 12. Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Patients Following Dosing of Posaconazole Concentrated injection (300 mg)*

Day	n	C_{max} (ng/mL)	T_{max}† (hr)	$AUC_{interval}$ (ng*hr/mL)	C_{av} (ng/mL)	C_{min} (ng/mL)
10/14	49	3280 (74)	1.5 (0.98-4.0)	36100 (35)	1500 (35)	1090 (44)

$AUC_{interval}$ = area under the concentration-time curve over the dosing interval (i.e 24 hours);
C_{av}= $AUC_{interval;}$
C_{min} = POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; C_{max}=observed maximum plasma concentration; CV=coefficient of variation, expressed as a percent (%); Day=study day on treatment; T_{max}=time of observed maximum plasma concentration.
*300 mg dose administered over 90 minutes once a day following BD dosing on Day 1
†Median (minimum-maximum)

Pharmacokinetics in special populations
Children (< 18 years)
There is no paediatric experience with posaconazole concentrated injection (see **Section 5.3 Preclinical Safety Data, Pre-clinical safety** and **Section 4.2 Dose and Method of Administration**).

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

Elderly
The pharmacokinetics of posaconazole concentrated injection are comparable in young and elderly subjects. No overall differences in safety were observed between geriatric patients and younger patients and age was not a significant covariant in the population PK model; therefore no dosage adjustment is recommended for geriatric patients.

Race

There is insufficient data among different races with posaconazole concentrated injection.

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.

Renal impairment
In patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2), receiving the NOXAFIL concentrated injection, accumulation of the intravenous vehicle, Sulfobutyl Betadex Sodium (SBECD), is expected to occur. NOXAFIL concentrated injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), unless an assessment of the benefit/risk to the patient justifies the use of NOXAFIL concentrated injection (see **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.2 Dose and Method of Administration**). A specific study has not been conducted with posaconazole concentrated injection.

Following single-dose administration of 400 mg of the oral suspension, there was no effect of mild and moderate renal impairment (n=18, eGFR ≥20 mL/min/1.73 m^2) on posaconazole pharmacokinetics, therefore, no dose adjustment is required. In subjects with severe renal insufficiency (n=6, eGFR < 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). However, as posaconazole is not significantly renally eliminated, an effect of severe renal impairment on the pharmacokinetics of posaconazole is not expected. Posaconazole is not removed by haemodialysis (see **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.2 Dose and Method of Administration**).

Hepatic impairment
A specific study has not been conducted with posaconazole concentrated injection.

In a small number of subjects (n=12) studied with hepatic impairment (Child-Pugh class A, B or C) administered 200 mg posaconazole oral suspension, C_{max} values generally decreased with the severity of hepatic dysfunction (545, 414 and 347 ng/mL for the mild, moderate, and severe groups, respectively), even though the C_{max} values (mean 508 ng/mL) for the normal subjects were consistent with previous trials in healthy volunteers. In addition, an increase in half-life was also associated with a decrease in hepatic function (26.6, 35.3, and 46.1 hours for the mild, moderate, and severe groups, respectively), as all groups had longer half-life values than subjects with normal hepatic function (22.1 hours). Due to the limited pharmacokinetic data in patients with hepatic impairment; no recommendation for dose adjustment can be made.

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

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. No subject administered posaconazole oral suspension had a QT_c (F) interval of ≥ 500 msec or an increase ≥ 60 msec in their QT_c (F) interval from baseline.

5.3 PRECLINICAL SAFETY DATA

Pre-clinical safety

In a nonclinical study using intravenous administration of posaconazole in very young dogs (dosed from 2-8 weeks of age) an increase in the incidence of brain ventricle enlargement was observed in treated animals as compared with concurrent control animals. No difference in the incidence of brain ventricle enlargement between control and treated animals wasobserved following the subsequent 5-month treatment-free period. There were no neurologic, behavioural or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to juvenile dogs (4 days to 9 months of age). The clinical significance of this finding is unknown; therefore, the use of posaconazole concentrated injection in patients under 18 years of age is not recommended (see **Section 4.2 Dose and Method of Administration**).

Genotoxicity

Posaconazole has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, mammalian mutation and human lymphocyte chromosomal aberration) and an *in vivo* mouse micronucleus test. Under the conditions of these assays, posaconazole did not cause genetic damage.

Carcinogenicity

Posaconazole administered by the oral route caused an increase in hepatocellular adenomas in mice at plasma exposure levels ~7-times higher than anticipated in humans at the maximum recommended clinical dose. This finding is considered to have occurred secondary to liver toxicity in the species, and mice are known to be particularly susceptible to this neoplastic change.

Rats treated with posaconazole administered by the oral route at exposure levels ≥ 2.4-times that of humans developed adrenal cortical cell adenomas and/or carcinomas and phaeochromocytomas. The cortical tumours are consistent with endocrinological disruption following chronic impairment of adrenal steroidogenesis. The increase in phaeochromocytomas is considered to be a rat-specific phenomenon that follows changes in calcium homeostasis. Altered calcium homeostasis has not been observed in humans receiving posaconazole. The results of animal studies indicate little carcinogenic risk for posaconazole in clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each vial of NOXAFIL concentrated injection contains the following inactive ingredients: sulfobutyl betadex sodium (SBECD), disodium edetate, hydrochloric acid, sodium hydroxide and Water for Injections.

6.2 INCOMPATIBILITIES

NOXAFIL concentrated injection must not be diluted with Lactated Ringer’s solution, 5% dextrose with Lactated Ringer’s solution, 4.2% sodium bicarbonate.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C - 8°C (Refrigerate. Do not freeze).

6.5 NATURE AND CONTENTS OF CONTAINER

NOXAFIL concentrated injection is available in a Type I glass vial closed with bromobutyl rubber stopper and aluminium seal containing 16.7 mL of solution (18 mg of posaconazole per mL).

NOXAFIL Concentrated Injection: AUST R 218702

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

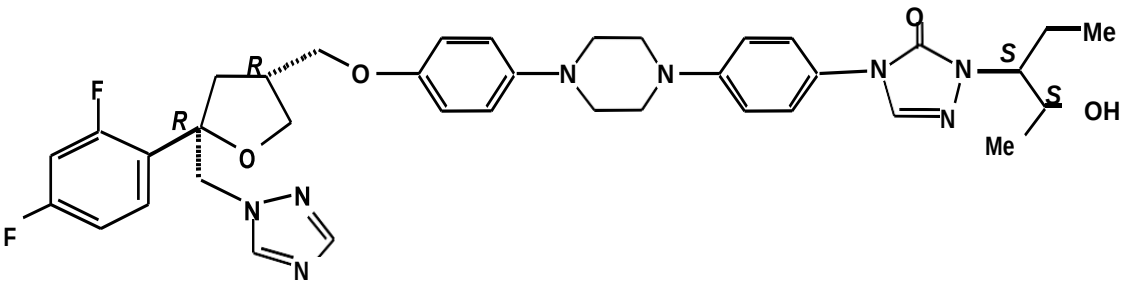
6.7 PHYSICOCHEMICAL PROPERTIES

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:

Chemical structure

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).

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.

CAS number
The CAS Registry Number is 171228-49-2.

Posaconazole has a melting range of 164°C - 165°C and is insoluble in water.

7 MEDICINE SCHEDULE (POISONS STANDARD)

All states and ACT – Schedule 4

8 SPONSOR

Merck Sharpe & Dohme (Australia) Pty Limited
Level 1, Building A, 26 Talavera Road
Macquarie Park NSW 2113
Australia

www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

27 January 2015

10 DATE OF REVISION

19 November 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4, 4.5	Updated sections to include information regarding interaction with venetoclax

NOXAFIL® is a registered trademark.

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