AUSTRALIAN PRODUCT INFORMATION

NOXAFIL®

(posaconazole)
Modified release 100 mg tablets
and 40 mg/mL oral suspension

1 NAME OF THE MEDICINE

Posaconazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Posaconazole is a white to off-white crystalline powder.

NOXAFIL Oral Suspension contains 40 mg posaconazole per mL of suspension.

List of excipients with known effect:

- sodium benzoate
- liquid glucose

NOXAFIL Modified Release Tablet contains 100 mg of posaconazole.

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

3 PHARMACEUTICAL FORM

NOXAFIL (posaconazole) Oral Suspension is a white, cherry flavoured immediate-release oral suspension containing 40 mg of posaconazole per mL.

NOXAFIL (posaconazole) Modified Release Tablet is a yellow, coated, capsule-shaped tablet containing 100 mg of posaconazole.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NOXAFIL (posaconazole) is indicated for use in the treatment of the following invasive fungal infections in patients 13 years of age or older:

- 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:

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

For patients being treated for oropharyngeal candidiasis, only the oral suspension should be used.

4.2 DOSE AND METHOD OF ADMINISTRATION

NOXAFIL Oral Suspension should be administered with a full meal or with a liquid nutritional supplement in patients who cannot eat a full meal.

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.

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

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.

Administration instructions for NOXAFIL Oral Suspension

Shake well before use.

Refractory Invasive Fungal Infections (IFI) / Intolerant Patients with IFI: NOXAFIL should be administered at a dose of 400 mg (10 mL) twice a day with a meal or 240 mL of 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. Increasing the total daily dose above 800 mg does not further enhance the exposure to posaconazole (see **Section 5 Pharmacological Properties**).

Oropharyngeal Candidiasis in HIV-infected patients: NOXAFIL should be administered as a 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.

Oropharyngeal Candidiasis refractory to Itraconazole or Fluconazole in HIV-infected patients: NOXAFIL should be administered at a dose of 400 mg (10 mL) twice a day.

Prophylaxis of Invasive Fungal Infections: NOXAFIL should be administered at a dose of 200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.

Each dose of NOXAFIL oral suspension should be administered with a meal, or with a nutritional supplement in patients who cannot tolerate food, to enhance exposure.

Duration of therapy should be based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

Administration instructions for NOXAFIL Modified Release Tablets

Refractory Invasive Fungal Infections (IFI) / Intolerant Patients with IFI: 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.

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. Duration of therapy is based on recovery from neutropenia or immunosuppression.

NOXAFIL modified release tablets can be taken without regard to food intake.

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 impairment on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended (see **Section 5.2 Pharmacokinetic Properties**). Due to variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see **Section 5.2 Pharmacokinetic Properties**).

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

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 Pharmacokinetic Properties**).

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.

Coadministration of posaconazole with rivaroxaban or apixaban is contraindicated, as posaconazole may increase the plasma concentration of these medicines, which may increase the risk of bleeding (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

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

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. 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 1 for hepatic enzyme abnormalities in healthy volunteers.

Table 1
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 QTc interval and are metabolised through the CYP3A4 (see **Section 4.3 Contraindications**, **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**, **Section 5.2 Pharmacokinetic Properties, Electrocardiogram evaluation**).

Electrolyte disturbances

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 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.

Photosensitivity Reaction

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

Use in hepatic impairment

See **Section 4.2 Dose and Method of Administration, Use in hepatic impairment** and **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations, Hepatic impairment.**

Use in renal impairment

See **Section 4.2 Dose and Method of Administration, Use in renal impairment** and **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations, Renal impairment.**

Use in the elderly

No dosage adjustment is recommended for geriatric patients (See **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations, Elderly**).

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 the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Paediatric use

(See **Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations, Paediatric**). Safety and effectiveness in paediatric patients below the age of 13 years have not been established. Clinical experience of posaconazole oral suspension in paediatric patients 13 - 17 years of age is very limited (n=16), therefore pharmacology, efficacy and safety profiles have not been completely characterised in children within this age group. Available data suggest a similar profile in children 13 - 17 years of age and adults.

Use of posaconazole modified release tablets in patients 13 to 17 years of age is supported by evidence from adequate and well-controlled studies of posaconazole oral suspension.

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

Table 2

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 metabolised through CYP3A4		Atazanavir/ritonavir Fosamprenavir	
Rivaroxaban, Apixaban		Calcium channel blockers metabolised 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. See below for further information.

Effect of Other Drugs on Posaconazole

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 (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 oral suspension 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
Posaconazole oral suspension: 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.

Posaconazole modified release tablet: 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.

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.

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

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, 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 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**).

Rivaroxaban and Apixaban: Posaconazole inhibits CYP3A4 and may have an inhibitory effect on P-gp, and therefore it may increase plasma concentrations of rivaroxaban and apixaban to a clinically relevant degree, which may lead to an increased bleeding risk (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 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: Repeat dose administration of oral posaconazole 200 mg or 400 mg twice daily with a high fat meal, significantly increased the midazolam C_{max} by 2.2 fold (~7.03 to 15.4 ng/mL): AUC by approximately 5 fold (~31.9 to 159 h.ng/mL); and prolonged the mean terminal half-life of midazolam 8 to 10 hours in healthy subjects. It is recommended that dose adjustments of benzodiazepines, including midazolam metabolised by CYP3A4, be considered during co-administration with posaconazole.

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 metabolised 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 metabolised through CYP3A4 is contraindicated.

Interactions with HMG CoA reductase inhibitors that are not metabolised 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 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 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**).

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Posaconazole had no effect on the fertility of male rats at doses up to 180 mg/kg/day (1.6 times the maximum recommended clinical dose (RCD) based on AUC at steady state in healthy volunteers fed a high fat meal). Like other azoles, male dogs administered oral posaconazole had findings consistent with reduced plasma testosterone levels, including spermatic giant cells (relative exposure 4.2). Posaconazole administered to female rats at doses up to 45 mg/kg/day (relative exposure 2.0) 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 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.

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 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 Oral Suspension

Drug-related adverse reactions observed in 2 400 subjects dosed with posaconazole oral suspension are shown in Table 3. 172 patients received posaconazole oral suspension therapy for $\geq$ 6 months; 58 of these received posaconazole oral suspension therapy for $\geq$ 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 3
Treatment-related adverse reactions reported in posaconazole oral suspension 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:	flushing, hot flushes, hypertension, hypotension
Rare:	atherosclerosis, cerebrovascular accident, deep venous thrombosis NOS, pulmonary embolism, ischemia, haematoma
Respiratory, thoracic and mediastinal disorders	
Uncommon:	chest pain, coughing, dyspnoea, epistaxis, pharyngitis, nasal congestion

Rare:	atelectasis, dry throat, pulmonary hypertension, interstitial pneumonia, nasal irritation, pneumonitis, postnasal drip, pulmonary infiltration, rales, rhinitis, rhinorrhoea
Gastrointestinal disorders	
Common:	abdominal pain, diarrhoea, dyspepsia, flatulence, dry mouth, nausea, vomiting
Uncommon:	taste perversion, constipation, loose stools, abdominal distention, dysphagia, ascites, eructation, thirst, gastritis, gastroesophageal reflux, mucositis NOS, oesophagitis, pancreatitis, tongue discolouration
Rare:	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:	elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, bilirubin)
Uncommon:	hepatitis, hepatocellular damage, hepatomegaly, jaundice
Rare:	asterixis, cholestasis, hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, splenomegaly
Skin and subcutaneous tissue disorders	
Common:	rash
Uncommon:	alopecia, dry skin, maculopapular rash, urticaria, furunculosis, acne, mouth ulceration, pruritus, pruritic rash
Rare:	stomatitis, dermatitis, erythema, erythematous rash, follicular rash, macular rash, night sweats, seborrhoea, skin nodule, vesicular rash
Musculoskeletal and connective tissue disorders	
Uncommon:	myalgia, arthralgia, back pain, musculoskeletal pain, flank pain, muscle weakness
Rare:	bone pain, chest wall pain, fasciitis, neck stiffness, cramps extremities, muscle cramps
Renal and urinary disorders	
Uncommon:	albuminuria, altered micturition frequency, dysuria, increased blood creatinine, acute renal failure, renal failure, haematuria, renal impairment, nocturia
Rare:	increased BUN, interstitial nephritis, micturition disorder, renal calculus, urinary tract obstruction NOS
Reproductive system and breast disorders	
Uncommon:	menstrual disorder
Rare:	leukorrhoea, breast pain
General disorders and administration site conditions	
Common:	asthenia, fatigue, fever
Uncommon:	increased sweating, pain, rigors, malaise, weakness, oedema, tooth discolouration
Rare:	face oedema, tongue oedema
Investigations	
Uncommon:	altered drug levels
Injury, poisoning and procedural complications	
Uncommon:	drug toxicity (NOS)
Rare:	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 4
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 5
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			
Anaemia	2 (< 1)	0 (0)	6 (3)
Neutropenia	10 (2)	4 (2)	20 (8)
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 6
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
AST Increased	14 (2)	2 (<1)	7 (1)	3 (1)	1 (2)	0
ALT Increased	16 (3)	7 (1)	8 (1)	7 (1)	1 (2)	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; ALT = serum glutamic oxaloacetic transaminase; ALT = serum glutamic pyruvic transaminase

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

Posaconazole Modified Release Tablets

In clinical trials, the type and frequency of adverse effects reported for posaconazole modified release tablets were generally similar to that reported in trials of posaconazole oral suspension.

The safety of posaconazole modified release tablets has been assessed in 230 patients in clinical trials. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole modified release tablets when given as antifungal prophylaxis (P05615). Patients were immunocompromised with underlying conditions including haematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 62% male, had a mean age of 51 years (range 19-78 years, 17% of patients were ≥65 years of age), and were 93% white and 16% Hispanic. 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 BD dosing on Day 1 in each cohort).

The most frequently reported treatment-related adverse reactions (≥5%) with posaconazole modified release tablets (300 mg 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.

Table 7 presents treatment-emergent adverse reactions observed in patients treated with 300 mg daily dose at an incidence of ≥10% in posaconazole modified release tablet study.

Table 7
Posaconazole Study 5615: Number (%) of Subjects Treated with 300 mg Daily Dose Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10%

Body System Preferred Term	Posaconazole Tablet (300 mg) (n=210)	
Subjects Reporting any Adverse Reaction	201	(99)
Blood and Lymphatic System Disorder		
Anemia	22	(10)
Febrile Neutropenia	42	(20)
Thrombocytopenia	29	(14)
Gastrointestinal Disorder		
Abdominal Pain	23	(11)
Constipation	20	(10)
Diarrhea	61	(29)
Nausea	56	(27)
Vomiting	28	(13)
General Disorders and Administration Site Conditions		
Asthenia	20	(10)
Catheter Site erythema	20	(10)
Chills	22	(10)
Mucosal inflammation	29	(14)
Edema Peripheral	33	(16)
Pyrexia	59	(28)
Metabolism and Nutrition Disorders		
Hypokalemia	46	(22)
Hypomagnesemia	20	(10)
Nervous System Disorders		
Headache	30	(14)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	35	(17)
Epistaxis	30	(14)
Skin and Subcutaneous Tissue Disorders		
Rash	34	(16)
Vascular Disorders		
Hypertension	23	(11)

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 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
Studies: 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]	
Oral suspension Study 316		
Laboratory Parameter	Posaconazole N=301	Fluconazole N=299
AST ALT Bilirubin Alkaline Phosphatase	11/266 (4) 47/271 (17) 24/271 (9) 9/271 (3)	13/266 (5) 39/272 (14) 20/275 (7) 8/271 (3)
Oral suspension 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

Skin and Subcutaneous Tissue Disorders: photosensitivity reaction (frequency not known)

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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} < 20 mL/min), posaconazole was not removed by haemodialysis. Thus, haemodialysis is unlikely to be effective in removing posaconazole from the systemic circulation.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Anti-infective 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 **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

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, 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 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 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 oral suspension 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-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 11 for results from both studies.

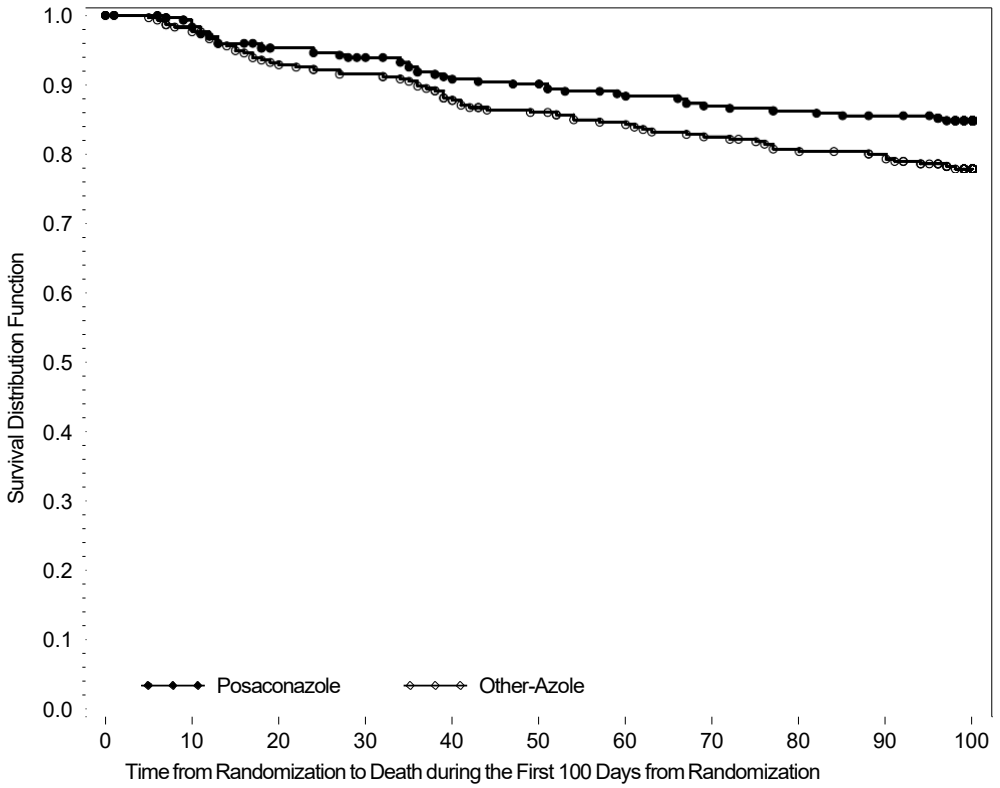
Table 11
Results from Clinical Studies in Prophylaxis of Invasive Fungal Infections

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-randomisation			
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 randomisation, 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 to be 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 leukemia (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 BD on Day 1, followed by 200 mg QD thereafter (Part 1A) and 300 mg BD 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 BD 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 C_{avg} between 500-2500 ng/mL. [C_{avg} 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_{avg} 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). Intersubject variability in mean AUC and C_{max} was high in healthy volunteers and patients despite the controlled conditions in pharmacokinetic studies. Steady-state is attained following 7 to 10 days of multiple-dose administration.

The pharmacokinetics of posaconazole are linear following single and multiple dose administration of up to 800 mg. No further increases in exposure are observed above a total daily dose of 800 mg in patients and healthy volunteers. There is no effect of altered pH on the absorption of posaconazole (See **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

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. Exposure further increased when posaconazole was given as 200 mg four times daily.

When given orally in healthy volunteers, posaconazole modified release tablets are 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 BD 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 modified release 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 Dose and Method of Administration**).

In a single dose study (P112) investigating the effect of a high fat meal on the bioavailability of posaconazole following administration of NOXAFIL Tablets 300 mg (3 x 100 mg) in healthy volunteers, the C_{max} was 16% higher and the $AUC_{0\text{-}72\ hours}$ was 51% higher with food relative to fasting. The results of the study are summarised below in Table 12. The effect of food on the absorption of NOXAFIL Modified Release Tablets is not considered clinically meaningful. Food effect was taken into consideration at the time of final dose selection of the 300 mg modified release tablet based on data from the pivotal clinical Phase 1b/Phase 3 pharmacokinetic/safety study P5615 in which patients took NOXAFIL Modified Release Tablets without regard to food intake. NOXAFIL Modified Release Tablets can therefore be administered with or without food.

Table 12
Statistical comparison of plasma pharmacokinetics of Posaconazole following single oral dose administration of 300 mg Posaconazole (as 3 tablets of 100 mg) to healthy subjects under fasting and fed conditions

	Fasting Conditions		**Fed Conditions** (High Fat Meal)*		**Fed/Fasting**
Pharmacokinetic Parameter	**N**	**GM (95% CI)**	**N**	**GM (95% CI)**	**GMR (90% CI)**
C_{max}† (ng/mL)	14	893 (731, 1090)	16	1,040 (915, 1180)	1.16 (0.96, 1.41)
$AUC_{0\text{-}last}$‡ hr•ng/mL	14	25600 (21500, 30400)	16	38700 (35000, 42700)	1.51 (1.33, 1.72)
T_{max}§ (hr)	14	5.00 (3.00, 8.00)	16	6.0 (5.00, 24.00)	N/A

GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio;
CI = Confidence interval
* 48.5 g fat
†C_{max} = maximum observed concentration
‡$AUC_{0\text{-}last}$ = $AUC_{0\text{-}72hr}$
§Median (Min, Max) reported for T_{max}

Distribution

Posaconazole oral suspension has a large apparent volume of distribution (1774 L) suggesting extensive penetration into the peripheral tissues. Posaconazole is highly protein bound (> 98.0 %), predominantly to serum albumin.

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

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 apparent total body clearance (Cl/F) of 32 L/hr.

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). Steady-state is attained following 7 to 10 days of multiple-dose administration.

Summary of the mean pharmacokinetic parameters in patients:

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 13.

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 13).

Table 13
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 mean pharmacokinetic parameters in patients and healthy volunteers following administration of posaconazole modified release tablet 300 mg daily are displayed in Table 14. Patients have approximately 25% lower exposure as compared to healthy volunteers after multiple dosing of posaconazole modified release tablet. The differences in exposure between healthy volunteers and patients are much less than the exposure differences reported for posaconazole oral suspension (Table 13).

Table 14
Pharmacokinetics of posaconazole modified release tablets in patients and healthy volunteers

Population	Dose	Mean (%CV)		
		C_{max} (ng/mL)	T_{max}[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)

Simulation based on the population pharmacokinetic model was performed in patients receiving posaconazole modified release tablet 300 mg daily (following 300 mg BD on Day 1). Simulated pharmacokinetics in patients and subpopulations of AML/MDS and HSCT patients are displayed in Table 15.

Table 15

Simulated multiple dose pharmacokinetics of posaconazole modified release tablets by patient sub population

Patient sub population	Dose	Mean (%CV)	
		AUC(τ) (ng·hr/mL)	C_{avg} (ng/mL)
AML/MDS	300 mg/day (n=1000)	40031 (53)	1668 (53)
HSCT*	300 mg/day (n=1000)	47307 (53)	1971 (53)
Total	300 mg/day (n=2000)	43669 (54)	1820 (54)

n= number of simulated patients; AUC(τ): Area under the concentration versus time curve during a dosing interval τ at steady state: C_{avg}: AUC(τ)τ
*In the population PK model developed for POS modified release tablet, HSCT patients were considered not different from the healthy volunteer population.

Coadministration of food, or medications known to alter gastric pH (antacid, ranitidine, esomeprazole) or motility (metoclopramide) shows no clinically meaningful effect on the pharmacokinetics of posaconazole when administered as a modified release tablet.

In Table 16 a comparison is shown of exposure (C_{avg}) in patients after administration of posaconazole modified release tablet and posaconazole oral suspension at therapeutic doses.

Table 16
Mean C_{avg} exposure at steady state from pivotal patient studies with Posaconazole modified release tablet and Posaconazole oral suspension

	Posaconazole modified release tablet	**Posaconazole oral suspension**		
	Prophylaxis in AML and HSCT	Prophylaxis in GVHD	Prophylaxis in Neutropenia	Treatment - Invasive Aspergillosis
Study	P05615	C98-316	P01899	P00041
Dose	300 mg QD	200 mg TDS	200 mg TDS	POS 200 mg QID (hospitalized) then 400 mg BD
Mean C_{avg} (ng/mL) (%CV)	=1970 (56%)*	1122 (67%)	583 (65%)	841 (83%)
Quartile	pC_{avg} range (ng/mL)	C_{avg} range (ng/mL)	C_{avg} range (ng/mL)	C_{avg} range (ng/mL)
Q1 Response	442-1223 N/A	22-557 55.6%	90-332 45.3%	55-277 24%
Q2 Response	1240-1710 N/A	557-915 79.4%	322-490 63.0%	290-544 53%
Q3 Response	1719-2291 N/A	915-1563 82.5%	490-734 53.7%	550-861 53%
Q4 Response	2304-9523 N/A	550-861 53%	734-2200 72.2%	877-2010 71%

mean C_{avg} = the average concentration when measured at steady state
*pC_{avg} = predicted C_{avg}

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).

Mean average steady-state plasma concentration was calculated for neutropenic paediatric patients aged between 11 months and 17 years treated with 12 mg/kg/day or 18 mg/kg/day of posaconazole oral suspension in two or three divided doses. Approximately 50% met the pre-specified target (Day 7 C_{avg} of 1200 ng/mL with acceptable range 500 ng/mL to 2500 ng/mL); 43% (30/70) of subjects fell below 500 ng/mL. In general, exposures tended to be closer to the target Day 7 C_{avg} in the older patients (7 to <18 years n = 36) than in younger patients (2 to <7 years; n = 33 and 3 to 23 months n = 1). (See **Section 4.1 Therapeutic Indications. Section 4.2 Dose and Method of Administration** and **Section 4.4 Special Warnings and Precautions for Use, Paediatric use**)

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 basedon a small proportion of elderly subjects ≥65 years of age (N=25 vs. 194 patients 18 – 64 yearsof age). However, in a population pharmacokinetic analysis (Study 1899), age did not influencethe 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.

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.

Renal impairment

Following single-dose administration of 400 mg of the oral suspension, there was no significant effect of mild (eGFR: 50-80 mL/min/1.73 m^2, n=6) or moderate (eGFR: 20-49 mL/min/1.73 m^2, n=6) renal impairment on posaconazole pharmacokinetics; therefore, no dose adjustment is required in patients with mild to moderate renal impairment. In subjects with severe renal impairment (eGFR: < 20 mL/min/1.73 m^2), the mean plasma exposure (AUC) was similar to that in patients with normal renal function (eGFR: >80 mL/min/1.73 m^2); however, the range of the AUC estimates was highly variable (CV=96%) in these subjects with severe renal impairment as compared to that in other renal groups (CV<40%). Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections (see **Section 4.2 Dose and Method of Administration**).

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

Hepatic impairment

In a small number of subjects (n=12) studied with hepatic impairment (Child-Pugh class A, B or C) receiving 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 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 BD 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

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 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 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 ofadrenal 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 oral suspension. Theresults of animal studies indicate little carcinogenic risk for posaconazole in clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

NOXAFIL Oral Suspension
List of excipients: polysorbate 80, simethicone, sodium benzoate, sodium citrate dihydrate, citric acid monohydrate, glycerol, xanthan gum, liquid glucose, titanium dioxide, artificial cherry flavouring, and purified water.

NOXAFIL Modified Release Tablet
List of excipients: hypromellose acetate succinate, microcrystalline cellulose, hydroxypropylcellulose, silicon dioxide, croscarmellose sodium, magnesium stearate, and Opadry® II Yellow (consists of the following ingredients: polyvinyl alcohol, Macrogol 3350, titanium dioxide, purified talc, and iron oxide yellow).

6.2 INCOMPATIBILITIES

Not applicable.

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

NOXAFIL Oral Suspension: Shake well before use. Store below 25°C. Do not freeze.

NOXAFIL Modified Release Tablets: Store below 30°C. Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

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 Tablets are available in blister packs of 24 and 96 tablets.

NOXAFIL Oral Suspension: AUST R 115556

NOXAFIL Modified Release Tablets: AUST R 216283

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

6.7 ANY UNUSED MEDICINAL PRODUCT OR WASTE MATERIAL SHOULD BE DISPOSED OF IN ACCORDANCE WITH LOCAL REQUIREMENTS.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.

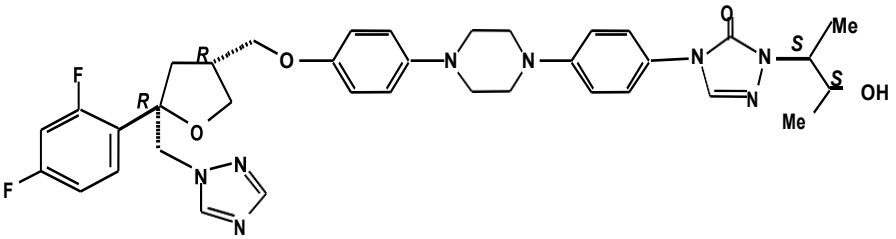
CAS INDEX NAME: D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydropropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)

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.

Chemical structure

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

SCH 56592 (Posaconazole)



CAS number

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

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9 DATE OF FIRST APPROVAL

15 March 2006

10 DATE OF REVISION

25 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.5	Addition of information regarding interaction with flucloxacillin

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