NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Posaconazole JUNO (posaconazole) modified release 100 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Posaconazole JUNO modified release tablets contain 100 mg of posaconazole per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Posaconazole JUNO modified release tablets are yellow, coated, capsule-shaped tablets, debossed with “100P” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Posaconazole JUNO is indicated for use in the treatment of the following invasive fungal infections in patients 18 years of age or older:

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

Posaconazole JUNO is also indicated for the prophylaxis of invasive fungal infections, including both yeasts and moulds, in patients 13 years of age and older, who are at high risk of developing these infections, such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients.

4.2 Dose and method of administration

Coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections (see section 4.5 Interactions with Other Medicines and Other Forms of Interaction).

Non-Interchangeability between Posaconazole JUNO Modified Release Tablets and Posaconazole Oral Suspension (available from other sponsors)
The prescriber should follow the specific dosing instructions for each formulation. The Posaconazole Juno modified release tablets and the oral suspension available from other sponsors are not to be used interchangeably, due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations.

Dose

The recommended dose for Posaconazole Juno modified release tablets are shown in Table 1 below.

Table 1: Recommended Dose for Posaconazole Juno Modified Release Tablets According to Indication

Indication	Dose and duration of therapy
Prophylaxis of Invasive Fungal Infections	Loading dose of 300 mg (three 100 mg modified release tablets) twice a day on the first day, then 300 mg (three 100 mg modified release tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukaemia or myelodysplastic syndromes, prophylaxis with NOXAFIL should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3.
Refractory Invasive Fungal Infections (IFI)/Patients with IFI intolerant to 1st line therapy	Loading dose of 300 mg (three 100 mg modified release tablets) twice a day on the first day, then 300 mg (three 100 mg modified release tablets) once a day thereafter. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Coccidioidomycosis	
Refractory Oesophageal Candidiasis	Loading dose of 300 mg (three 100 mg modified release tablets) twice a day on the first day, then 300 mg (three 100 mg modified release tablets) once a day thereafter. Each dose may be taken without regard to food intake. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

Special Populations

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

Method of administration

Posaconazole JUNO modified release tablets should be swallowed whole, and not be divided, crushed, or chewed. Posaconazole JUNO modified release tablets may be taken without regard to food intake.

4.3 Contraindications

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

Coadministration of posaconazole and ergot alkaloids (ergotamine, dihydroergotamine) is contraindicated as posaconazole may increase the plasma concentration of ergot alkaloids, which may lead to ergotism (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

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

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

4.4 Special warnings and precautions for use

Hypersensitivity
There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing posaconazole to patients with hypersensitivity to other azoles. Subjects with severe or serious reactions to azoles were excluded from key studies of posaconazole.

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

QT prolongation
Some azoles have been associated with prolongation of the QTc interval on the electrocardiogram (ECG). Results from a multiple time-matched ECG analysis in healthy volunteers did not show an increase in the mean QTc interval. Nevertheless, 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 detailed guidance.

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 18 years have not been established. Clinical experience of posaconazole oral suspension (available in other brands) 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.

4.5 Interaction with other medicines and other forms of interaction

Posaconazole oral suspension is unavailable in this brand, however, is available in other brands. The information listed in this section referencing Posaconazole oral suspension may also be of relevance to Posaconazole Juno modified release tablets, therefore this is included for prescriber 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
Rifabutin (300 mg once a day) decreased the C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration time curve) of posaconazole by 43% and 49%, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk.

Phenytoin
Phenytoin (200 mg once a day) decreased the C_{max} and AUC of posaconazole by 41% and 50%, respectively. Concomitant use of posaconazole and phenytoin should be avoided unless the benefit to the patient outweighs the risk.

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

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

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

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

Efavirenz
Efavirenz (400 mg once a day) decreased the C_{max} and AUC of posaconazole by 45% and 50%, respectively. Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.

Fosamprenavir
Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended. 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.

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).

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.

Ciclosporin

In heart transplant patients on stable doses of ciclosporin, posaconazole 200 mg once daily increased ciclosporin concentrations requiring dose reductions. Cases of elevated ciclosporin 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 ciclosporin, the dose of ciclosporin should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of ciclosporin should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of ciclosporin should be adjusted as necessary.

Tacrolimus

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

Sirolimus

Repeat dose administration of oral posaconazole (400 mg twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9 fold, respectively, in healthy subjects. When initiating therapy in patients already taking sirolimus, the dose of sirolimus should be reduced (e.g., to about 1/10 of the current dose) with frequent monitoring of sirolimus whole blood trough concentrations. Sirolimus concentrations should be performed upon initiation, during coadministration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly.

Rifabutin

Posaconazole increased the C_{max} and AUC of rifabutin by 31% and 72%, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. If the drugs are coadministered, careful monitoring of full blood counts and adverse effects related to increased rifabutin levels (e.g., uveitis) is recommended.

Midazolam and Posaconazole oral suspension (available from other sponsors)

Repeat dose administration of oral posaconazole (200 mg oral suspension twice daily for 7 days) increased the C_{max} and AUC of IV midazolam (0.4 mg single dose) an average of 1.3- and 4.6-fold, respectively. Posaconazole 400 mg oral suspension twice daily for 7 days increased the IV midazolam C_{max} and AUC by 1.6- and 6.2-fold, respectively. Both doses of posaconazole increased C_{max} and AUC of oral midazolam (2 mg single oral dose) by 2.2- and 4.5-fold, respectively. In addition, oral posaconazole (200 mg or 400 mg oral suspension) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-10 hours during co-administration. It is recommended that dose adjustments of benzodiazepines, metabolised by CYP3A4, be considered during co-administration with posaconazole.

Zidovudine (AZT), lamivudine (3TC), 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 and Posaconazole oral suspension (available from other sponsors)
Repeat dose administration of oral posaconazole (50, 100, and 200 mg oral suspension once daily for 13 days) increased the C_{max} and AUC of simvastatin (40 mg single dose) an average of 7.4- to 11.4-fold, and 5.7- to 10.6-fold, respectively. Increased HMG-CoA reductase inhibitor (statin) 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 and Posaconazole oral suspension (available from other sponsors)
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.

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

4.6 Fertility, pregnancy and lactation

Effects on fertility
Posaconazole 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 pregnancy was 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.

Posaconazole JUNO 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 Undesirable effects

Posaconazole Oral Suspension (available from other sponsors)

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

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

Uncommon and rare treatment related medically significant adverse events reported during clinical trials with posaconazole oral suspension have included adrenal insufficiency,

pancreatitis, allergic and/or hypersensitivity reactions.

Some azoles have been associated with prolongation of the QT interval on the electrocardiogram. A pooled analysis of 173 posaconazole oral suspension-dosed healthy volunteers utilizing time matched ECGs did not show a potential to prolong the QT interval. In addition, rare cases of torsade de pointes have been reported in patients taking posaconazole.

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

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

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

General disorders and administration site conditions	
Common	Asthenia, fatigue, pyrexia (fever)

Clinical Laboratory Values

In (uncontrolled) trials of patients with invasive fungal infections treated with posaconazole 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 posaconazole at doses up to 400 mg, the incidence of clinically significant liver function test abnormalities was as follows: ALT and AST (> 3 X ULN) 3% and 6%, respectively: total bilirubin (> 1.5 X ULN) 3 %; and alkaline phosphatase (> 3 X ULN) 3 %.

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

Endocrine disorders: pseudoaldosteronism

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

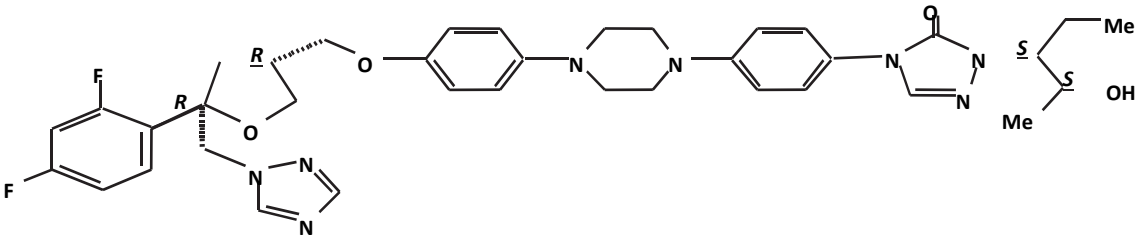
Antiinfective for systemic use, triazole derivative, ATC code: J02AC04

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.

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 INDEX NAME: D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydropropyl]-1,5-dihydro-5-oxo-4H1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl).

CAS Number
171228-49-2

IUPAC NAME: 4-4-[4-(4-{(3R,5R)-5-(2,4-difluorophenyl)-5-(1H-1,2,4-triazol-1ylmethyl)tetrahydro-3-furanyl]methoxyphenyl)piperazino]phenyl-1-[(1S,2S)-1-ethyl-2hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-5-one.

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

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.

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

- species of *Candida* (including *C. albicans* isolates resistant to fluconazole, voriconazole and itraconazole,

- *C. krusei* and *C. glabrata* which are inherently less susceptible to fluconazole,
- *C. lusitaniae* which is inherently less susceptible to amphotericin B),
- *Aspergillus* (including isolates resistant to fluconazole, voriconazole, itraconazole and amphotericin B)
- organisms not previously regarded as being susceptible to azoles such as the zygomycetes (e.g. species of *Absidia*, *Mucor*, *Rhizopus* and *Rhizomucor*).

In vitro posaconazole exhibited fungicidal activity against species of:

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

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

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

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

Antifungal drug combinations
When combinations of posaconazole with either amphotericin B or caspofungin were tested *in vitro* and *in vivo* there was little or no antagonism and in some instances there was an additive effect. 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 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

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:

In a single dose study (P112) investigating the effect of a high fat meal on the bioavailability of posaconazole following administration of posaconazole 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 5. The effect of food on the absorption of posaconazole 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 posaconazole modified release tablets without regard to food intake. Posaconazole JUNO modified release tablets can therefore be administered with or without food.

Table 5: 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, 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.

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

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

Excretion
Posaconazole modified release tablet is eliminated with a mean half-life (t½) 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 mean pharmacokinetic parameters in patients and healthy volunteers following administration of posaconazole modified release tablet 300 mg daily are displayed in Table 6. 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 6: 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 7.

Table 7: 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 8 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 8: 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

There is no paediatric experience with Posaconazole modified release tablets.

Gender

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

Weight

Pharmacokinetic modeling for posaconazole suggests that patients weighing greater than 120

kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg.

Renal impairment
A specific study has not been conducted with posaconazole modified release tablets. 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).

Posaconazole is not removed by haemodialysis.

Hepatic impairment
A specific study has not been conducted with the posaconazole modified release tablets. Due to the limited pharmacokinetic data in patients with hepatic impairment; posaconazole should be used with caution in patients with severe hepatic impairment since the prolonged half-life that may occur will lead to increased exposure.

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

5.3 Preclinical safety data

As observed with other azole antifungal agents, effects related to inhibition of steroid hormone synthesis were seen in repeated-dose toxicity studies with posaconazole. Adrenal suppressive effects were observed in toxicity studies in rats and dogs at exposures equal to or greater than those obtained at therapeutic doses in humans.

Reproduction, peri- and postnatal development studies were conducted in rats. At exposures lower than those obtained at therapeutic doses in humans, posaconazole caused skeletal variations and malformations, dystocia, increased length of gestation, reduced mean litter size and postnatal viability. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. As observed with other azole antifungal agents, these effects on reproduction were considered related to a treatment-related effect on steroidogenesis.

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 of adrenal steroidogenesis. The increase in phaeochromocytomas is considered to be a rat-specific phenomenon that follows changes in calcium homeostasis. Altered calcium homeostasis has not been observed in humans receiving posaconazole oral suspension. The results of animal studies indicate little carcinogenic risk for posaconazole in clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Posaconazole JUNO modified release tablet*:* Methacrylic acid-Ethyl acrylate copolymer(1:1) (Type-B), triethyl citrate, xylitol, microcrystalline cellulose, hyprolose, propyl gallate, colloidal anhydrous silica, croscarmellose sodium, sodium stearylfumarateand 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

36 months

6.4 Special precautions for storage

Store below 25^{o}C. Store in original container.

6.5 Nature and contents of container

Posaconazole JUNO modified release tablets are available in Aluminium/Aluminium, PVC/PCTFE (Aclar)/Aluminium or PVC/PE/PVDC/Aluminium blister packs of 24 and 96 tablets.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Juno Pharmaceuticals NZ Ltd
RSM New Zealand (Auckland)
RSM House, Level 2
62 Highbrook Drive
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Auckland, 2013, New Zealand

For Medical Information please call 0800 816 921

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
ALL	Editorial updates
8	Sponsor address updated.