

# AUSTRALIAN PRODUCT INFORMATION

## VORICONAZOLE APO, Voriconazole

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### 1. NAME OF THE MEDICINE

Voriconazole

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VORICONAZOLE APO tablets contain the active ingredient Voriconazole.

50 mg tablets: each contains 50 mg of voriconazole.

200 mg tablets: each contains 200 mg of voriconazole.

Excipients with known effect: lactose monohydrate.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

### 3. PHARMACEUTICAL FORM

VORICONAZOLE APO 50 mg tablets are white to off-white round biconvex film-coated tablets with code V50 on one side.

VORICONAZOLE APO 200 mg tablets are white to off-white oval biconvex film-coated tablets with code V200 on one side.

### 4. CLINICAL PARTICULARS

#### 4.1. THERAPEUTIC INDICATIONS

Voriconazole is indicated for treatment of the following fungal infections:

Invasive aspergillosis.

Serious *Candida* infections (including *C. krusei*), including oesophageal and systemic *Candida* infections (hepatosplenic candidiasis, disseminated candidiasis, candidaemia).

Serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp.

Other serious fungal infections, in patients intolerant of, or refractory to, other therapy.

Prophylaxis in patients who are at high risk of developing invasive fungal infections. The indication is based on studies including patients undergoing haematopoietic stem cell transplantation.

#### 4.2. DOSE AND METHOD OF ADMINISTRATION

*Voriconazole powder for oral suspension and powder for injection are unavailable in the VORICONAZOLE APO brand. Information obtained using voriconazole powder for oral suspension and powder for injection formulations have been retained throughout the PI, where appropriate, for continuity and prescriber information.*

VORICONAZOLE APO tablets are to be taken at least one hour before, or one hour following, a meal.

**Use in Adults**

Therapy must be initiated with the specified loading dose regimen of voriconazole to achieve plasma concentrations on Day 1 that are close to steady state.

**Dosage recommendations for oesophageal candidiasis:**

	Oral Tablets	
	≥ 40 kg	< 40 kg
<b>Loading Dose Regimen (first 24 hours)</b>	400 mg every 12 hours (for the first 24 hours)	200 mg every 12 hours (for the first 24 hours)
<b>Maintenance Dose (after first 24 hours)</b>	200 mg twice daily	100 mg twice daily

Dosage recommendations for other indications are provided in the following table.

**Dosage recommendations for indications other than oesophageal candidiasis:**

	Oral Tablets	
	≥ 40 kg	< 40 kg
<b>Loading Dose Regimen (first 24 hours)</b>	400 mg every 12 hours (for the first 24 hours)	200 mg every 12 hours (for the first 24 hours)
<b>Maintenance Dose (after first 24 hours)</b>		
Serious <i>Candida</i> infections	200 mg twice daily	100 mg twice daily
Invasive aspergillosis; <i>Scedosporium</i> and <i>Fusarium</i> infections; other serious mould infections	200 mg twice daily	100 mg twice daily

**Dosage recommendations for prophylaxis of invasive fungal infections:**

	Oral Tablets	
	≥ 40 kg	< 40 kg
<b>Loading Dose Regimen (first 24 hrs)</b>		
<b>Maintenance Dose (after first 24 hrs)</b>	200 mg every 12 hrs	100 mg every 12 hrs

**Dosage Adjustment***Oral administration*

If patient response is inadequate, the maintenance dose may be increased to 300 mg twice daily for oral administration. For patients less than 40 kg, the oral dose may be increased to 150 mg twice daily. If patients are unable to tolerate treatment at these higher doses reduce the oral dose by 50 mg steps to a minimum 200 mg twice daily (or 100 mg twice daily for patients less than 40 kg) maintenance dose.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 200 mg to 400 mg orally twice daily (100 mg to 200 mg orally twice daily in patients less than 40 kg). The loading dose regimen remains unchanged see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

When voriconazole is coadministered with efavirenz, the voriconazole maintenance dose should be increased to 400 mg every 12 hours and the efavirenz dose should be decreased to 300 mg every 24 hours see section 4.3 CONTRAINDICATIONS and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Treatment duration depends upon patients' clinical and mycological response.

#### **Use in the Elderly**

No dose adjustment is necessary for elderly patients.

#### **Use in Patients with Renal Impairment**

The pharmacokinetics of orally administered voriconazole are not affected by renal impairment. Therefore, no adjustment is necessary for oral dosing for patients with mild to severe renal impairment.

In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), including dialysis patients, accumulation of the intravenous vehicle, hydroxypropylbetadex, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the risk benefit to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients and, if increases occur, consideration should be given to changing to oral voriconazole therapy see section 5.2 PHARMACOKINETIC PROPERTIES.

#### **Use in Patients with Hepatic Impairment**

No dose adjustment is necessary in patients with acute hepatic injury, manifested by elevated liver function tests (ALT, AST) (but continued monitoring of liver function tests for further elevations is recommended).

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole.

Voriconazole has not been studied in patients with severe chronic hepatic cirrhosis (Child- Pugh C). Voriconazole has been associated with elevations in liver function tests and clinical signs of liver damage such as jaundice, and must only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk. Patients with severe hepatic impairment must be carefully monitored for drug toxicity see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

#### **Use in Children**

Safety and efficacy in paediatric subjects below the age of 2 years has not been established. Therefore voriconazole is not recommended for children less than 2 years of age. Use in paediatric patients aged 2 to < 12 years with hepatic or renal insufficiency has not been studied see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Limited data are currently available to determine the optimal dosing regimen. Multiple intravenous doses (3, 4, 6 and 8 mg/kg twice daily) and oral doses (4 and 6 mg/kg twice daily) have been used in pharmacokinetic studies conducted in children 2 to 12 years. However, oral dose form tablet is not suitable for paediatric dosing.

The study results showed that 4 mg/kg IV twice daily in children achieved exposure comparable to that in adults receiving 3 mg/kg IV twice daily. The average voriconazole exposure in children receiving 6 mg/kg IV doses twice daily was slightly lower than in adults receiving 4 mg/kg IV doses twice daily. Based on the data, physicians may initiate therapy in children with 6 mg/kg IV twice daily. The dose may be increased to 7 mg/kg IV twice daily if clinically indicated.

Further study is required to determine the optimal oral dose for children 2 to <12 years.

**Adolescents** (12-16 years of age) should be dosed as adults.

### 4.3. CONTRAINDICATIONS

VORICONAZOLE APO (voriconazole) is contraindicated in patients with known hypersensitivity to voriconazole or to any of the excipients.

Coadministration of the CYP3A4 substrates, \*terfenadine, pimozone or quinidine with voriconazole is contraindicated since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes* see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Coadministration of voriconazole with rifabutin, rifampicin, carbamazepine and long-acting barbiturates (e.g. phenobarbitone) is contraindicated since these medicinal products are likely to decrease plasma voriconazole concentrations significantly see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

\*Coadministration of standard doses of voriconazole with patients receiving efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS. For information pertaining to lower doses of efavirenz see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Coadministration of voriconazole with patients receiving high doses of ritonavir (400 mg and higher twice daily) is contraindicated, because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at these doses see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS. For information pertaining to lower doses of ritonavir see section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE.

Coadministration of ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, is contraindicated since increased plasma concentrations of these medicinal products can lead to ergotism see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Coadministration of voriconazole and sirolimus is contraindicated, since voriconazole is likely to increase plasma concentrations of sirolimus significantly see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Coadministration of voriconazole with St John's Wort is contraindicated see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

### 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Hypersensitivity:** Caution should be used in prescribing voriconazole to patients with hypersensitivity to other azoles.

**\*Cardiovascular:** Some azoles, including voriconazole have been associated with QT interval prolongation. There have been rare cases of *torsades de pointes* in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory. Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as:

- Congenital or acquired QT-prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant medicinal product that is known to prolong QT interval see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation of and during voriconazole therapy see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION).

#### **Use in hepatic impairment**

In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with voriconazole (including clinical hepatitis, cholestasis and fulminant hepatic failure including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy.

\*Patients receiving voriconazole must be carefully monitored for hepatic toxicity. Clinical management should include laboratory evaluation of hepatic function (specifically AST and ALT) at the initiation of treatment with voriconazole and at least weekly for the first month of treatment. If treatment is continued, monitoring frequency can be reduced to monthly if there are no changes in the liver function tests.

If the liver function tests become markedly elevated, voriconazole should be discontinued, unless the medical judgment of the risk-benefit of the treatment for the patient justifies continued use see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION.

#### **Use in renal impairment**

The pharmacokinetic parameters of orally administered voriconazole are not affected by renal impairment. However, acute renal failure has been observed in severely ill patients undergoing treatment with voriconazole. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function.

In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), including dialysis patients, accumulation of the intravenous vehicle hydroxypropylbetadex occurs. Oral voriconazole should be administered to these patients unless an assessment of the risk to the patient justifies the use of intravenous voriconazole.

Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.

**Monitoring of Pancreatic Function:** Adults and children, with risk factors for acute pancreatitis (e.g. recent chemotherapy, haematopoietic stem cell transplantation (HSCT)), should be monitored closely during voriconazole treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.

**Dermatological Adverse Events:** Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with voriconazole. If a patient develops an exfoliative cutaneous reaction, voriconazole should be discontinued.

\*In addition voriconazole has been associated with photosensitivity skin reaction. It is recommended that patients, including children, avoid exposure to direct sunlight during voriconazole treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF) (see **Squamous Cell Carcinoma**).

The frequency of phototoxicity reactions is higher in the paediatric population. As an evolution towards squamous cell carcinoma has been reported, stringent measures for the photo-protection are warranted in this population of patients. In children experiencing photo-aging injuries such as lentigines or ephelides, sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation.

**Long-term Treatment Severe Adverse Events:** The following severe adverse events have been reported in relation with long-term voriconazole treatment:

**\*Squamous Cell Carcinoma (SCC):** In patients with photosensitivity skin reactions and additional risk factors (including immunosuppression), squamous cell carcinoma of the skin and melanoma have been reported during long-term therapy. If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Voriconazole discontinuation should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. If a patient develops a skin lesion consistent with premalignant skin lesions, squamous cell carcinoma or melanoma, voriconazole discontinuation should be considered.

**Non-infectious Periostitis:** Periostitis has been reported in transplant patients during long-term voriconazole therapy. If a patient develops skeletal pain and radiologic findings compatible with periostitis, voriconazole should be discontinued.

**Visual Adverse Events:** There have been post-marketing reports of prolonged visual adverse events, including optic neuritis and papilloedema. These events occurred primarily in ill patients who had underlying conditions and/or concomitant medications which may have caused or contributed to these events (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

**Methadone (CYP3A4 substrate):** Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

**Short Acting Opiates (CYP3A4 substrate):** Reduction in the dose of alfentanil and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g. sufentanil, fentanyl, remifentanil) should be considered when coadministered with voriconazole see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS. As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is coadministered with voriconazole, frequent monitoring for opiate associated adverse events (including a longer respiratory monitoring period) may be necessary.

**Oxycodone (CYP3A4 substrate):** Reduction in the dose of oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g. hydrocodone) should be considered when coadministered with voriconazole. Frequent monitoring for opiate associated adverse events may be necessary see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

**Everolimus (CYP3A4 substrate, P-gp substrate):** Coadministration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations. Currently there are insufficient data to allow dosing recommendations in this situation see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

**Fluconazole** (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Coadministration of oral voriconazole and oral fluconazole resulted in significant increase in  $C_{max}$  and AUC<sub>t</sub> of voriconazole in healthy subjects. The clinical significance of this drug interaction has not been established and the coadministration of voriconazole and oral fluconazole is not recommended.

**Phenytoin** (CYP2C9 substrate and potent CYP450 inducer): Careful monitoring of phenytoin levels is recommended when phenytoin is coadministered with voriconazole. Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

**Ritonavir** (potent CYP450 inducer; CYP3A4 inhibitor and substrate): Coadministration of voriconazole and low dose ritonavir (100 mg twice daily) should be avoided unless an assessment of the benefit/risk justifies the use of voriconazole see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS. Coadministration of voriconazole and ritonavir 400 mg and higher twice daily is contraindicated see section 4.3 CONTRAINDICATIONS.

**Advice about Lactose and Sucrose:** VORICONAZOLE APO Tablets contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

#### **Use in the elderly**

No dose adjustment is necessary for elderly.

#### **Paediatric use**

Safety and efficacy in paediatric subjects below the age of two years has not been established see section 5 PHARMACOLOGICAL PROPERTIES, CLINICAL TRIALS. Hepatic function and pancreatic function should be monitored.

#### **Effects on Laboratory Tests**

Interactions with laboratory tests have not been established.

## **4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

Unless otherwise specified, drug interaction studies have been performed in healthy male subjects, using multiple dosing to steady state with oral voriconazole at 200 mg twice daily. These results are relevant to other populations and routes of administration.

This section addresses the effects of other medicinal products on voriconazole, the effects of voriconazole on other medicinal products and two-way interactions. The interactions for the first two sections are presented in the following order: contraindications, those requiring dosage adjustment, those requiring careful clinical and/or biochemical monitoring, and finally those that have no significant pharmacokinetic interaction but may be of clinical interest in this therapeutic field.

#### **Effects of Other Medicinal Products on Voriconazole**

Voriconazole is metabolised by cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively.

The exposure to voriconazole is significantly reduced by the concomitant administration of the following agents:

**Rifampicin** (CYP450 inducer): Rifampicin (600 mg once daily) decreased the  $C_{max}$  (maximum plasma concentration) and  $AUC_t$  (area under the plasma concentration time curve within a dose interval) of voriconazole by 93% and 96%, respectively. Coadministration of voriconazole and rifampicin is contraindicated see section 4.3 CONTRAINDICATIONS.

**Rifabutin** (potent CYP450 inducer): Rifabutin (300 mg once daily) decreased the  $C_{max}$  and  $AUC_t$  of voriconazole at 200 mg twice daily by 69% and 78%, respectively. During coadministration with rifabutin, the  $C_{max}$  and  $AUC_t$  of voriconazole at 350 mg twice daily were 96% and 68% of the levels when administered alone at 200 mg twice daily. At a voriconazole dose of 400 mg twice daily  $C_{max}$  and  $AUC_t$  were 104% and 87% higher, respectively, compared with voriconazole alone at 200 mg twice daily. Voriconazole at 400 mg twice daily increased  $C_{max}$  and  $AUC_t$  of rifabutin by 195% and 331%, respectively. Coadministration of voriconazole with rifabutin is contraindicated see section 4.3 CONTRAINDICATIONS.

**Ritonavir** (potent CYP450 inducer; CYP3A4 inhibitor and substrate): The effect of the coadministration of oral voriconazole (200 mg twice daily) and high dose (400 mg) and low dose (100 mg) oral ritonavir was investigated in two separate studies in healthy volunteers. High doses of ritonavir (400 mg twice daily) decreased the steady state  $C_{max}$  and  $AUC_t$  of oral voriconazole by an average of 66% and 82% respectively, whereas low doses of ritonavir (100 mg twice daily) decreased the  $C_{max}$  and  $AUC_t$  of oral voriconazole by an average of 24% and 39% respectively. Administration of voriconazole did not have a significant effect on mean  $C_{max}$  and  $AUC_t$  of ritonavir in the high dose study, although a minor decrease in steady state  $C_{max}$  and  $AUC_t$  of ritonavir with an average of 25% and 13% respectively was observed in the low dose ritonavir interaction study. One outlier subject with raised voriconazole levels was identified in each of the ritonavir interaction studies. Coadministration of voriconazole and high doses of ritonavir (400 mg and higher twice daily) is contraindicated see section 4.3 CONTRAINDICATIONS. Coadministration of voriconazole and low dose ritonavir (100 mg twice daily) should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole see section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE.

**Carbamazepine and phenobarbitone** (CYP450 inducers): Although not studied, carbamazepine or phenobarbitone are likely to significantly decrease plasma voriconazole levels. Coadministration of voriconazole with carbamazepine and long acting barbiturates are contraindicated see section 4.3 CONTRAINDICATIONS.

Significant drug interactions that may require voriconazole dosage adjustment, or frequent monitoring of voriconazole related adverse events/toxicity:

**Fluconazole** (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Coadministration of oral voriconazole and oral fluconazole resulted in significant increase in  $C_{max}$  and  $AUC_t$  of voriconazole in healthy subjects. The clinical significance of this drug interaction has not been established and the coadministration of voriconazole and oral fluconazole is not recommended. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Minor or no significant pharmacokinetic interactions that require no dosage adjustment:

**Cimetidine** (non-specific CYP450 inhibitor and increases gastric pH): Cimetidine (400 mg twice daily) increased voriconazole  $C_{max}$  and  $AUC_t$  by 18% and 23%, respectively. No dosage adjustment of voriconazole is recommended.

**Ranitidin:** (increases gastric pH): Ranitidine (150 mg twice daily) had no significant effect on voriconazole  $C_{max}$  and  $AUC_t$ .

**Macrolide antibiotics:** Erythromycin (CYP3A4 inhibitor; 1 g twice daily) and azithromycin (500 mg once daily) had no significant effect on voriconazole  $C_{max}$  and  $AUC_t$ .

### Effects of Voriconazole on Other Medicinal Products

Voriconazole inhibits the activity of cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Therefore, there is potential for voriconazole to increase the plasma levels of drugs metabolised by these CYP450 isoenzymes.

Voriconazole should be administered with caution in patients receiving concomitant medication that is known to prolong QT interval. When there is also a potential for voriconazole to increase the plasma levels of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, pimozide) co-administration is contraindicated see below and section 4.3 CONTRAINDICATIONS.

#### *Concomitant use of the following agents with voriconazole is contraindicated:*

**Terfenadine, pimozide and quinidine** (CYP3A4 substrates): Although not studied, coadministration of voriconazole with \*terfenadine, pimozide or quinidine is contraindicated, since increased plasma concentrations of these drugs can lead to QTc prolongation and rare occurrences of torsades de pointes see section 4.3 CONTRAINDICATIONS).

**Sirolimus** (CYP3A4 substrate): Voriconazole increased sirolimus (2 mg single dose)  $C_{max}$  and  $AUC_{\tau}$  by 556% and 1014%, respectively. Coadministration of voriconazole and sirolimus is contraindicated (see section 4.3 CONTRAINDICATIONS).

**Ergot alkaloids** (CYP3A4 substrates): Although not studied, voriconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. Coadministration of voriconazole with ergot alkaloids is contraindicated see section 4.3 CONTRAINDICATIONS.

**St John's Wort** (CYP450 inducer; P-gp inducer): In an independent published study in healthy volunteers, St John's Wort exhibited a short initial inhibitory effect followed by induction of voriconazole metabolism. After 15 days of treatment with St John's Wort (300 mg three times daily), plasma exposure following a single 400 mg dose of voriconazole decreased by 40-60%. Therefore, concomitant use of voriconazole with St John's Wort is contraindicated see section 4.3 CONTRAINDICATIONS.

#### *Interaction of voriconazole with the following agents may result in increased exposure to these drugs. Careful monitoring and/or dosage adjustment should be considered.*

**Cyclosporin** (CYP3A4 substrate): In stable, renal transplant recipients, voriconazole increased cyclosporin  $C_{max}$  and  $AUC_{\tau}$  by at least 13% and 70% respectively. When initiating voriconazole in patients already receiving cyclosporin it is recommended that the cyclosporin dose be halved and cyclosporin level carefully monitored. Increased cyclosporin levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporin levels must be carefully monitored and the dose increased as necessary.

**Tacrolimus** (CYP3A4 substrate): Voriconazole increased tacrolimus (0.1 mg/kg single dose)  $C_{max}$  and  $AUC_{\tau}$  by 117% and 221%, respectively. When initiating voriconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus levels carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.

**Methadone** (CYP3A4 substrate): Repeat dose administration of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 4 days) increased the  $C_{max}$  and  $AUC_{\tau}$  of pharmacologically active R-methadone by 31% (90% CI: 22%, 40%) and 47% (90% CI: 38%, 57%) respectively in subjects receiving a methadone maintenance dose (30-100 mg daily) see section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE.

**Short Acting Opiates** (CYP3A4 substrates):

**Alfentanil:** In an independent publication, steady-state administration of oral voriconazole increased the mean AUC<sub>0-∞</sub> of a single dose of alfentanil by 6-fold. Reduction in the dose of alfentanil and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g. fentanyl, sufentanil, remifentanil), should be considered when coadministered with voriconazole.

**Fentanyl:** In an independent published study, concomitant use of voriconazole (400 mg q12h on Day 1, then 200 mg q12h on Day 2) with a single intravenous dose of fentanyl (5 µg/kg) resulted in an increase in the mean AUC<sub>0-∞</sub> of fentanyl by 1.4-fold (range 1.12- to 1.60-fold). When voriconazole is coadministered with fentanyl, extended and frequent monitoring of patients for respiratory depression and other fentanyl-associated adverse events is recommended, and the fentanyl dose should be reduced if warranted.

**Long Acting Opiates** (CYP3A4 substrates):

**Oxycodone:** In an independent published study, coadministration of multiple doses of oral voriconazole (400 mg q12h on Day 1, followed by five doses of 200 mg q12h on Days 2 to 4) with a single 10 mg oral dose of oxycodone on Day 3 resulted in an increase in the mean C<sub>max</sub> and AUC<sub>0-∞</sub> of oxycodone by 1.7-fold (range 1.4- to 2.2-fold) and 3.6-fold (range 2.7- to 5.6- fold), respectively. The mean elimination half-life of oxycodone was also increased by 2.0- fold (range 1.4- to 2.5-fold). A reduction in oxycodone dosage may be needed during voriconazole treatment to avoid opioid related adverse effects. Extended and frequent monitoring for adverse effects associated with oxycodone and other long-acting opiates metabolised by CYP3A4 is recommended.

**Everolimus** (CYP3A4 substrate, P-gP substrate): Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus. Coadministration of voriconazole and everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations.

**Warfarin** (CYP2C9 substrate): Coadministration of voriconazole (300 mg twice daily) with warfarin (30 mg single dose) increased maximum prothrombin time by 93%. Close monitoring of prothrombin time is recommended if warfarin and voriconazole are coadministered.

**Other Oral Anticoagulants** (CYP2C9, CYP3A4 substrates): Although not studied, voriconazole may increase the plasma concentrations of coumarins and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly.

**Sulphonylureas** (CYP2C9 substrates): Although not studied, voriconazole may increase the plasma levels of sulphonylureas, (e.g. tolbutamide, glipizide, and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during coadministration.

**Stains** (CYP3A4 substrates): Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase plasma levels of statins that are metabolised by CYP3A4. It is recommended that dose adjustment of the statin be considered during coadministration. Increased statin levels have been associated with rhabdomyolysis.

**Benzodiazepines** (CYP3A4 substrates): Although not studied clinically, voriconazole has been shown to inhibit midazolam metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma levels of benzodiazepines that are metabolised by CYP3A4 (e.g. midazolam, triazolam and alprazolam) and lead to a prolonged sedative effect. It is recommended that dose adjustment of the benzodiazepine be considered during coadministration.

**Vinca Alkaloids** (CYP3A4 substrates): Although not studied, voriconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity. It is therefore recommended that dose adjustment of the vinca alkaloid be considered.

**Non-Steroidal Anti-Inflammatory Drugs** (CYP2C9 substrates): Voriconazole increased  $C_{max}$  and AUC of ibuprofen (400 mg single dose) by 20% and 100%, respectively. Voriconazole increased  $C_{max}$  and AUC of diclofenac (50 mg single dose) by 114% and 78%, respectively. Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

No significant pharmacokinetic interactions were observed when voriconazole was coadministered with the following agents. No dosage adjustment for these agents is recommended.

**Prednisolone** (CYP3A4 substrate): Voriconazole increased  $C_{max}$  and  $AUC_{\tau}$  of prednisolone (60 mg single dose) by 11% and 34%, respectively. No dosage adjustment is recommended.

**Digoxin** (P-glycoprotein mediated transport): Voriconazole had no significant effect on  $C_{max}$  and  $AUC_{\tau}$  of digoxin (0.25 mg once daily).

**Mycophenolic acid** (UDP-glucuronyl transferase substrate): Voriconazole had no effect on the  $C_{max}$  and  $AUC_{\tau}$  of mycophenolic acid (1 g single dose).

### **Two-way Interactions**

**Phenytoin** (CYP2C9 substrates and potent CYP450 inducer): Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk.

Phenytoin (300 mg once daily) decreased the  $C_{max}$  and  $AUC_{\tau}$  of voriconazole by 49% and 69%, respectively. Voriconazole (400 mg twice daily) increased  $C_{max}$  and  $AUC_{\tau}$  of phenytoin (300 mg once daily) by 67% and 81%, respectively.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg /kg intravenously twice daily or from 200 mg to 400 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg). Careful monitoring of phenytoin plasma levels is recommended when phenytoin is coadministered with voriconazole.

**Omeprazole** (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate): Omeprazole (40 mg once daily) increased voriconazole  $C_{max}$  and  $AUC_{\tau}$  by 15% and 41%, respectively. No dosage adjustment of voriconazole is recommended. Voriconazole increased omeprazole  $C_{max}$  and  $AUC_{\tau}$  by 116% and 280%, respectively. When initiating voriconazole in patients already receiving omeprazole, it is recommended that the omeprazole dose be halved. The metabolism of other proton pump inhibitors which are CYP2C19 substrates may also be inhibited by voriconazole.

**Oral Contraceptives** (CYP3A4 substrate): Coadministration of voriconazole and an oral contraceptive (norethisterone 1 mg and ethinylestradiol 0.035 mg once daily) in healthy female subjects resulted in increases in the  $C_{max}$  and  $AUC_{\tau}$  of ethinylestradiol (36% and 61% respectively) and norethisterone (15% and 53% respectively). Voriconazole  $C_{max}$  and  $AUC_{\tau}$  increased by 14% and 46% respectively. Oral contraceptives containing doses other than norethisterone 1 mg and ethinylestradiol 0.035 mg have not been studied. As the ratio between norethisterone and ethinylestradiol remained similar during interaction with voriconazole, their contraceptive activity would probably not be affected. Monitoring for adverse events related to oral contraceptives is recommended during coadministration.

**Indinavir** (CYP3A4 inhibitor and substrate): Indinavir (800 mg three times daily) had no significant effect on voriconazole  $C_{max}$  and  $AUC_{\tau}$ . Voriconazole did not have a significant effect on  $C_{max}$ ,  $C_{min}$  and  $AUC_{\tau}$  of indinavir.

**Other HIV protease inhibitors** (CYP3A4 substrates and inhibitors): In vitro studies suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir). In vitro studies also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors. Patients should be carefully monitored for drug toxicity during the coadministration of voriconazole and HIV protease inhibitors.

**Efavirenz** (a non-nucleoside reverse transcriptase inhibitor [CYP450 inducer; CYP3A4 inhibitor and substrate]): Use of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated see section 4.3 CONTRAINDICATIONS).

In healthy subjects, steady state efavirenz (400 mg oral once daily) decreased the steady state  $C_{max}$  and  $AUC_{\tau}$  of voriconazole by an average of 61% and 77%, respectively. In the same study, voriconazole at steady state (400 mg orally every 12 hours for 1 day, then 200 mg orally every 12 hours for 8 days) increased the steady state  $C_{max}$  and  $AUC_{\tau}$  of efavirenz by an average of 38% and 44%, respectively, in the same subjects.

In a separate study in healthy subjects, voriconazole dose of 300 mg twice daily in combination with low dose efavirenz (300 mg once daily) did not lead to sufficient voriconazole exposure.

Following coadministration of voriconazole 400 mg twice daily with efavirenz 300 mg orally once daily in healthy subjects, the  $AUC_{\tau}$  of voriconazole was decreased by 7% and  $C_{max}$  was increased by 23% compared to voriconazole 200 mg twice daily alone. The  $AUC_{\tau}$  of efavirenz was increased by 17% and  $C_{max}$  was equivalent compared to efavirenz 600 mg once daily alone. These differences were not considered to be clinically significant.

Voriconazole may be coadministered with efavirenz if the voriconazole maintenance dose is increased to 400 mg twice daily and the efavirenz dose is reduced by 50%, i.e. to 300 mg once daily see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION. When treatment with voriconazole is stopped, the initial dose of efavirenz should be restored.

The concomitant use of intravenous voriconazole and oral efavirenz has not been studied.

**Other non-nucleoside reverse transcriptase inhibitors (NNRTIs)** (CYP3A4 substrates, inhibitors or CYP450 inducers): In vitro studies show that the metabolism of voriconazole may be inhibited by delavirdine. Although not studied, the metabolism of voriconazole may be induced by nevirapine. Voriconazole may also inhibit the metabolism of NNRTIs. Patients should be carefully monitored for drug toxicity during the coadministration of voriconazole and NNRTIs.

#### Guidance on the Clinical Management of Drug Interactions

Contraindications	Dose adjustment of voriconazole	Dose adjustment and/or monitoring of other drugs	No dose adjustment of voriconazole or other drugs
Rifampicin Sirolimus Barbiturates (long acting) Carbamazepine Rifabutin Pimozide Quinidine Ergot alkaloids St John's Wort	Phenytoin <sup>(1,3)</sup>	Cyclosporin <sup>(2,3)</sup> Tacrolimus <sup>(2,3)</sup> Omeprazole <sup>(2)</sup> Warfarin <sup>(4)</sup> Phenytoin <sup>(3)</sup> Sulphonylureas <sup>(5)</sup> Statins <sup>(7)</sup> Benzodiazepines <sup>(7)</sup> Vinca Alkaloids <sup>(7)</sup> Nevirapine <sup>(7)</sup>	Indinavir Mycophenolate Mofetil Cimetidine Ranitidine Macrolide antibiotics Prednisolone Digoxin
Ritonavir (400 mg q12h)	Ritonavir (100 mg q12h)		<b>No established dosing recommendation</b>

Efavirenz (400 mg q24h)	Efavirenz <sup>(1)</sup>	Efavirenz <sup>(1)</sup> HIV protease inhibitors <sup>(7)</sup> (excluding indinavir & ritonavir) Methadone <sup>(7)</sup> Oral Contraceptive <sup>(7)</sup> Short acting opiates including fentanyl <sup>(7)</sup> Oxycodone and other long-acting opiates <sup>(7)</sup>	Everolimus <sup>(8)</sup> Fluconazole <sup>(8)</sup>
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<sup>1</sup> See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Dosage Adjustment.

<sup>2</sup> Reduce dose (halve dose of cyclosporin and omeprazole, reduce dose to one third for tacrolimus) <sup>3</sup> Carefully monitor blood levels

<sup>4</sup> Monitor prothrombin time <sup>5</sup> Monitor blood glucose <sup>6</sup> Monitor complete blood counts

<sup>7</sup> Monitor for potential drug toxicity and consider dose reduction <sup>8</sup> Coadministration with voriconazole is not recommended

## 4.6. FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

Fertility of male and female rats was not affected at oral doses of up to 50 mg/kg/day, corresponding to exposures 4-6 times the expected human exposure (based on AUC) at the maintenance dose.

### Use in pregnancy B3

There are no adequate studies in pregnant women. Studies in rats have shown reproductive toxicity, including teratogenicity (cleft palates) at oral doses of  $\geq 10$  mg/kg/day and disturbance of parturition (dystocia) at oral doses of  $\geq 3$  mg/kg/day, with exposures similar to or below those expected in humans at maintenance dosing. Voriconazole was not teratogenic in rabbits at oral doses of up to 100 mg/kg/day, but produced an increase in post-implantation loss and a decrease in foetal body weight, with exposures approximately 4 times the expected human exposure. Voriconazole must not be used during pregnancy except in patients with severe or potentially life-threatening fungal infections in whom voriconazole may be used if the benefit to the mother clearly outweighs the potential risk to the foetus.

### Women of Childbearing Potential

Women of childbearing potential must always use effective contraception during treatment see section 4.6 FERTILITY, PREGNANCY AND LACTATION.

### Use in lactation

It is not known whether voriconazole is excreted in the milk of laboratory animals or in human breast milk.

\*Breast-feeding must be stopped on initiation of treatment with voriconazole.

## 4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Voriconazole may cause changes to vision, including blurring, altered/enhanced visual perception and/or photophobia. Patients must avoid potentially hazardous tasks, such as driving or operating machinery whilst experiencing these symptoms. Patients should be advised not to drive at night while taking voriconazole.

## 4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

### Clinical Trial Data

The safety of voriconazole is based on an integrated safety database of more than 2000 subjects (1655 patients in therapeutic studies). This represents a heterogeneous population, containing patients with haematological malignancy, HIV infected patients with oesophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidaemia or aspergillosis and healthy volunteers. Five hundred and sixty one patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months.

In addition, the safety of voriconazole was investigated in 279 patients who were treated with voriconazole in prophylaxis studies. The adverse event profile in these prophylaxis studies was similar to the established safety profile from 2000 subjects in voriconazole clinical trials.

The table below includes adverse reactions from therapeutic and/or compassionate/ extension studies, if possibly causally related. The most commonly reported adverse events were visual disturbances, fever, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema and abdominal pain. The severity of the adverse events was generally mild to moderate. No clinically significant differences were seen when the safety data were analysed by age, race, or gender.

MedDRA System Organ Class Frequency	Adverse Drug Reactions
<b>Infections and infestations</b>	
Common	Sinusitis
<b>Blood and lymphatic system disorders</b>	
Common	Thrombocytopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic), leukopenia, pancytopenia
Uncommon	Lymphadenopathy, agranulocytosis, eosinophilia, disseminated intravascular coagulation, marrow depression
<b>Immune system disorders</b>	
Uncommon	Allergic reaction, anaphylactoid reaction
<b>Endocrine disorders</b>	
Uncommon	Adrenal cortex insufficiency
Rare	Hyperthyroidism, hypothyroidism
<b>Metabolism and nutrition disorders</b>	
Common	Hypokalaemia, hypoglycaemia
Uncommon	Hypercholesterolaemia, hyponatraemia
<b>Psychiatric disorders</b>	
Common	Hallucinations, confusion, depression, anxiety, agitation
<b>Nervous system disorders</b>	
Very common	Headache
Common	Dizziness, tremor, paraesthesia
Uncommon	Ataxia, brain oedema, hypertonia, hypoaesthesia, nystagmus, syncope, altered taste perception
Rare	Guillain-Barré syndrome, oculogyric crisis, extrapyramidal syndrome, hepatic coma, insomnia, encephalopathy, somnolence during infusion, convulsion, peripheral neuropathy

<b>Eye disorders</b>	
Very Common	Visual disturbances (including altered/enhanced visual perception, blurred vision, colour vision change, photophobia)
Uncommon	Blepharitis, optic neuritis, papilloedema, scleritis, diplopia
Rare	Retinal haemorrhage, corneal opacity, optic atrophy
<b>Ear and labyrinth disorders</b>	
Uncommon	Vertigo
Rare	Hypoacusis, tinnitus
<b>Cardiac disorders</b>	
Common	Lung oedema
Uncommon	Atrial arrhythmia, bradycardia, tachycardia, ventricular arrhythmia, ventricular fibrillation, supraventricular tachycardia, QT prolongation
Rare	Atrioventricular (AV) complete block, bundle branch block, nodal arrhythmia, torsades de pointes, ventricular tachycardia
<b>Vascular disorders</b>	
Common	Hypotension, thrombophlebitis, phlebitis
Rare	Lymphangitis
<b>Respiratory, thoracic and mediastinal</b>	
Common	Respiratory distress syndrome
<b>Gastrointestinal disorders</b>	
Very common	Nausea, vomiting, diarrhoea, abdominal pain
Common	Cheilitis, gastroenteritis
Uncommon	Constipation, duodenitis, dyspepsia, gingivitis, glossitis, pancreatitis, tongue oedema, peritonitis
Rare	Pseudomembranous colitis
<b>Hepatobiliary disorders</b>	
Common	Elevated liver function tests (including AST (SGOT), ALT (SGPT), alkaline phosphatase, GGT, LDH, bilirubin), jaundice, cholestatic jaundice
Uncommon	Cholecystitis, cholelithiasis, enlarged liver, hepatitis, hepatic failure
<b>Skin and subcutaneous tissue disorders</b>	
Very common	Rash
Common	Face oedema, pruritus, maculopapular rash, photosensitivity skin reaction, alopecia, exfoliative dermatitis, purpura
Uncommon	Fixed drug eruption, eczema, psoriasis, Stevens-Johnson syndrome, urticaria
Rare	Angioedema, discoid lupus erythematosus, erythema multiforme, toxic epidermal necrolysis, pseudoporphyria
<b>Musculoskeletal, connective tissue and bone</b>	
Common	Back pain
Uncommon	Arthritis

<b>Renal and urinary disorders</b>	
Common	Creatinine increased, acute kidney failure, haematuria
Uncommon	BUN increased, albuminuria, nephritis
Rare	Kidney tubular necrosis
<b>General disorders and administration site</b>	
Very common	Fever, peripheral oedema
Common	Chills, asthenia, chest pain, injection site reaction/inflammation, flu syndrome

†Frequencies are categorised as follows: very common  $\geq 10\%$ ; common from  $\geq 1\%$  to  $<10\%$ ; uncommon from  $\geq 0.1\%$  to  $<1\%$ ; rare from  $0.01\%$  to  $<0.1\%$

### Adverse Events Reported in Comparative Therapeutic Studies 305 and 307/602 at a rate of $\geq 1\%$ Possibly Related to Therapy or Causality Unknown

	Protocol 305 Voriconazole vs Fluconazole (oral therapy)		Protocol 307/602 Voriconazole vs Conventional Amphotericin B (IV/oral therapy)	
	Voriconazole N = 200 N (%)	Fluconazole N = 191 N (%)	Voriconazole N = 196 N (%)	Amphotericin B <sup>†</sup> N = 185 N (%)
<b>Body as a whole</b>				
Fever	-	-	7 (3.6)	25 (13.5)
Chills	-	-	-	36 (19.5)
Headache	-	-	7 (3.6)	8 (4.3)
Abdominal pain	-	-	5 (2.6)	6 (3.2)
Chest pain	-	-	4 (2.0)	2 (1.1)
<b>Cardiovascular system</b>				
Tachycardia	-	-	5 (2.6)	5 (2.7)
Hypertension	-	-	-	2 (1.1)
Hypotension	-	-	-	3 (1.6)
Vasodilatation	-	-	2 (1.0)	2 (1.1)
<b>Digestive system</b>				
Nausea	2 (1.0)	3 (1.6)	14 (7.1)	29 (15.7)
Vomiting	2 (1.0)	-	11 (5.6)	18 (9.7)
Liver function tests abnormal	6 (3.0)	2 (1.0)	9 (4.6)	4 (2.2)
Diarrhoea	-	-	3 (1.5)	6 (3.2)
Cholestatic jaundice	3 (1.5)	-	4 (2.0)	-
Dry mouth	-	-	3 (1.5)	-
<b>Haemic and lymphatic system</b>				
Thrombocytopenia	-	-	2 (1.0)	2 (1.1)
Anaemia	-	-	-	5 (2.7)
<b>Metabolic and nutritional systems</b>				
Alkaline phosphatase increased	10 (5.0)	3 (1.6)	6 (3.1)	4 (2.2)
Hepatic enzymes increased	3 (1.5)	-	7 (3.6)	5 (2.7)
AST (SGOT) increased	8 (4.0)	2 (1.0)	-	-
ALT (SGPT) increased	6 (3.0)	2 (1.0)	3 (1.5)	-
Hypokalaemia	-	-	-	36 (19.5)
Peripheral oedema	-	-	7 (3.6)	9 (4.9)
Hypomagnesaemia	-	-	2 (1.0)	10 (5.4)
Bilirubinaemia	-	-	-	3 (1.6)

Creatinine increased	-	-	-	59 (31.9)
<b>Nervous system</b>				
Hallucinations	-	-	10 (5.1)	-
Dizziness	-	2 (1.0)	5 (2.6)	-
<b>Skin and appendages</b>				
Rash	3 (1.5)	1 (0.5)	13 (6.6)	7 (3.8)
Pruritus	-	-	2 (1.0)	2 (1.1)
Maculopapular rash	3 (1.5)	-	-	-
<b>Special senses</b>				
Abnormal vision	31 (15.5)	8 (4.2)	55 (28.1)	1 (0.5)
Photophobia	5 (2.5)	2 (1.0)	7 (3.6)	-
Chromatopsia	2 (1.0)	-	2 (1.0)	-
<b>Urogenital</b>				
Kidney function abnormal	-	-	4 (2.0)	40 (21.6)
Acute kidney failure	-	-	-	11 (5.9)

† Amphotericin B followed by other licensed antifungal therapy

### Visual Disturbances

In clinical trials, voriconazole treatment-related visual disturbances were very common. In these studies, approximately 21% of subjects experienced altered/enhanced visual perception, blurred vision, colour vision change or photophobia. These visual disturbances were transient and fully reversible, with the majority spontaneously resolving within 60 minutes. There was evidence of attenuation with repeated doses of voriconazole. The visual disturbances were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual disturbances may be associated with higher plasma concentrations and/or doses.

There have been post-marketing reports of prolonged visual adverse events see section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE.

The mechanism of action is unknown, although the site of action is most likely to be within the retina.

In a study in healthy volunteers investigating the impact of voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude. The ERG measures electrical currents in the retina. The ERG changes did not progress over 29 days of treatment and were fully reversible on withdrawal of voriconazole.

The long-term effect of voriconazole (median 169 days; range 5-353 days) on visual function was evaluated in subjects with paracoccidioidomycoses. Voriconazole had no clinically relevant effect on visual function as assessed by testing of visual acuity, visual fields, colour vision and contrast sensitivity. There were no signs of retinal toxicity. 17/35 voriconazole subjects experienced visual adverse events. These events did not lead to discontinuation, were generally mild, occurred in the first week of therapy and resolved during continued voriconazole therapy.

### Dermatological Reactions

Dermatological reactions were common in patients treated with voriconazole. In clinical trials, rashes were reported by 19% (278/1493) of voriconazole treated patients, but these patients had serious underlying diseases and were receiving multiple concomitant medications. The majority of rashes were of mild to moderate severity. Patients have developed serious cutaneous reactions, including Stevens-Johnson syndrome (uncommon), toxic epidermal necrolysis (rare) and erythema multiforme (rare) during treatment with voriconazole.

If patients develop a rash they should be monitored closely and voriconazole discontinued if lesions progress. Photosensitivity reactions have been reported, especially during long-term therapy see section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE.

**Liver Function Tests**

The overall incidence of clinically significant transaminase abnormalities in the voriconazole clinical program was 13.4% (200/1493) of subjects treated with voriconazole. Liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

Voriconazole has been infrequently associated with cases of serious hepatic toxicity, in patients with other serious underlying conditions. This includes cases of jaundice, and cases of hepatitis and hepatic failure leading to death see section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE PRECAUTION.

**Paediatric Use**

The safety of voriconazole was investigated in 245 paediatric patients aged 2 to <12 years who were treated with voriconazole in pharmacokinetic studies (87 paediatric patients) and in compassionate use programs (158 paediatric patients). The adverse event profile of these 245 paediatrics was similar to adults although post-marketing data suggest there might be a higher occurrence of skin reactions in the paediatric population compared to adults.

There have been post-marketing reports of pancreatitis in paediatric patients.

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medical 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**

Clinical data on overdose with this agent is scant.

In clinical trials there were three cases of accidental overdose. All occurred in paediatric patients, who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole. It is recommended that treatment of overdose is symptomatic and supportive.

Monitor potassium, full blood count and liver function following an overdose.

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within one hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Voriconazole is haemodialysed with a clearance of 121 mL/min. The intravenous vehicle, hydroxypropylbetadex, is haemodialysed with a clearance of  $37.5 \pm 24$  ml/min. In an overdose, haemodialysis may assist in the removal of voriconazole and hydroxypropylbetadex from the body.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. PHARMACODYNAMIC PROPERTIES

Voriconazole, a broad-spectrum, triazole antifungal agent, is available as film-coated tablets for oral administration.

#### Mechanism of action

Voriconazole is a triazole antifungal agent. Voriconazole's primary mode of action is the inhibition of fungal cytochrome P450-mediated 14 $\alpha$ -sterol demethylation, an essential step in ergosterol biosynthesis. Voriconazole is more selective than some other azole drugs for fungal as opposed to various mammalian cytochrome P450 enzyme systems. The subsequent loss of normal sterols correlates with the accumulation of 14 $\alpha$ -methyl sterols in fungi and may be responsible for its fungistatic/fungicidal activity.

*In vitro*, voriconazole displays broad-spectrum antifungal activity with high antifungal potency against *Candida* species (including fluconazole resistant *C. krusei* and resistant strains of *C. glabrata* and *C. albicans*) and fungicidal activity against all *Aspergillus* species tested. In addition, voriconazole shows *in vitro* activity against emerging fungal pathogens, such as *Scedosporium* or *Fusarium*, some isolates of which have limited susceptibility to existing antifungal agents. In addition, voriconazole exhibits *in vitro* fungicidal activity against some strains within these species.

In animal studies there is a correlation between minimum inhibitory concentration values and efficacy against experimental mycoses. Furthermore, there appears to be a correlation between minimum inhibitory concentration values and clinical outcome for *Candida* species.

#### Microbiology

Clinical efficacy has been demonstrated for *Aspergillus* spp. including *A. flavus*, *A. fumigatus*, *A. terreus*, *A. niger*, *A. nidulans*, *Candida* spp., including *C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. inconspicua*, *C. krusei*, *C. parapsilosis*, *C. tropicalis* and *C. guilliermondii*, *Scedosporium* spp., including *S. apiospermum*, *S. prolificans* and *Fusarium* spp.

Other successfully treated fungal infections included isolated cases of *Alternaria* spp., *Blastomyces dermatitidis*, *Blastoschizomyces capitatus*, *Cladosporium* spp., *Coccidioides immitis*, *Conidiobolus coronatus*, *Cryptococcus neoformans*, *Exserohilum rostratum*, *Exophiala spinifera*, *Fonsecaea pedrosoi*, *Madurella mycetomatis*, *Paecilomyces lilacinus*, *Penicillium* spp including *P. marneffeii*, *Phialophora richardsiae*, *Scopulariopsis brevicaulis* and *Trichosporon* spp including *T. beigelii* infections.

*In vitro* activity against clinical isolates has been observed for *Acremonium* spp., *Alternaria* spp., *Bipolaris* spp., *Cladophialophora* spp, *Histoplasma capsulatum*, with most strains being inhibited by concentrations of voriconazole in the range 0.05 to 2  $\mu\text{g/mL}$ .

*In vitro* activity against the following pathogens has been shown, but the clinical significance is unknown: *Curvularia* spp. and *Sporothrix* spp.

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained to isolate and identify causative organisms prior to therapy. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

*Susceptibility Testing***Voriconazole Interpretive Criteria (breakpoints) for susceptibility testing against *Candida* Species**

	Minimum Inhibitory Concentrations <sup>a</sup> (microgram/mL)			Disk Diffusion <sup>b</sup> (Zone diameters in mm)		
	Susceptible	Susceptible-dose dependent	Resistant	Susceptible	Susceptible-dose dependent	Resistant
Voriconazole	≤1.0	2.0	≥4.0	≥17	14-16	≤13
<p>In 10 therapeutic studies (4 mg/kg IV twice daily or 200 mg orally twice daily), the median for the average voriconazole plasma concentrations was 2.4 µg/mL (inter-quartile range 1.2 to 4.4 µg/mL). Correlation of <i>in vitro</i> results with clinical response was based upon 249 baseline <i>Candida</i> species isolates from six clinical trials (Pfaller <i>et. al.</i>, 2006, J. Clin. Microbiol., 819-826).</p> <p><sup>a</sup> CLSI Microbroth dilution reference method M27    <sup>b</sup> Disc diffusion reference method M44.</p>						

**Acceptable Quality Control Ranges for Voriconazole to be used in Validation of Susceptibility Test Results**

	Minimum Inhibitory Concentration (MIC in µg/mL)		Disk Diffusion (Zone diameter in mm)
	@24-hour	@48-hour	
QC Strain			
<i>Candida parapsilosis</i> ATCC 22019 <sup>^</sup>	0.016-0.12	0.03-0.25	28-37
<i>Candida krusei</i> ATCC 6258 <sup>^</sup>	0.06-0.5	0.12-1.0	16-25
<i>Candida albicans</i> ATCC 90028 <sup>^</sup>	†	†	31-42

†Quality control ranges have not been established for this strain/antifungal agent combination due to their extensive inter-laboratory variation during initial quality control studies.

<sup>^</sup> ATCC is a registered trademark of the American Type Culture Collection.

**Clinical trials****Duration of Treatment**

In clinical trials, 705 patients received voriconazole therapy for greater than 12 weeks, with 164 subjects receiving voriconazole for over 6 months.

**Clinical Experience**

Successful outcome in this section is defined as complete or partial response.

**Invasive Aspergillosis**

The efficacy and survival benefit of voriconazole compared to conventional amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in an open, randomised, multicentre study. The total duration of treatment was 12 weeks. Patients could be switched to Other Licensed Antifungal Therapy (OLAT) during the 12 week study period, either due to lack of efficacy of the initial randomised treatment (IRT) or for safety/tolerability reasons. Efficacy was assessed at 12 weeks (primary endpoint) and at the end of IRT by a Data Review Committee.

Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of seven days, after which the oral formulation at a dose of 200 mg twice daily could be used. Patients in the comparator group received conventional amphotericin B as a slow infusion at a daily dose of 1.0-1.5 mg/kg/day.

In this study, 277 immunocompromised patients with invasive aspergillosis (modified intent to treat population) were evaluated. At week 12, a satisfactory global response (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53% of patients in the voriconazole group compared to 31% of patients in the comparator group. At the end of IRT, a satisfactory global response was seen in 53.5% of voriconazole treated patients compared to 21.8% of conventional amphotericin B treated patients. Subjects in the voriconazole group were treated longer than subjects in the amphotericin B group before switching to OLAT (median duration of IRT was 73 vs. 12 days respectively). OLAT included liposomal amphotericin B formulations, itraconazole and flucytosine. Survival in the voriconazole group (71%) was greater than in the comparator group (58%) at week 12.

### Efficacy of Voriconazole in the Primary Treatment of Acute Invasive Aspergillosis

	Satisfactory Global Response	Survival at Week 12 <sup>b</sup>	Discontinuations due to AEs <sup>c</sup>
<b>Voriconazole</b>	Study 307/602 <sup>a</sup> 76/144 (53%) <sup>e</sup>	Study 307/602 102/144 (71%)	Study 307/602 40/196 (20%)
<b>Comparator</b>	42/133 (31%) <sup>d, e</sup>	77/133 (58%)	103/185 (56%)
	p < 0.0001	p = 0.02	--

<sup>a</sup> MITT (modified intent to treat) population assessed by independent Data Review Committee

<sup>b</sup> MITT population proportion of subjects alive

<sup>c</sup> Safety population discontinuations from initial randomised treatment due to adverse events/laboratory abnormalities (all causality)

<sup>d</sup> Amphotericin B

<sup>e</sup> Response rate stratified by protocol

The results of this comparative trial confirmed the results of an earlier trial in the primary treatment of patients with acute invasive aspergillosis (Study 304). In this study, an overall success rate of 54% was seen in patients treated with voriconazole.

Voriconazole successfully treated cerebral, sinus, pulmonary and disseminated aspergillosis in patients with bone marrow and solid organ transplants, haematological malignancies, cancer and AIDS.

### Serious Candida Infections

#### Systemic Candida Infections

The efficacy of voriconazole compared to the regimen of (conventional) amphotericin B followed by fluconazole in the primary treatment of candidaemia was demonstrated in an open comparative study (Study 150-608). Three hundred and seventy (370) non-neutropenic patients with documented candidaemia (positive blood culture and clinical signs of infection) were included in the study, of which 248 were treated with voriconazole. The patient population was seriously ill, with approximately 50% of subjects in the intensive care unit and 40% mechanically ventilated at baseline. The median treatment duration was 15 days in both treatment arms. A successful response (resolution/improvement in all clinical signs and symptoms of infection, blood cultures negative for Candida, infected deep tissue sites negative for Candida) was seen in 41% of patients in both treatment arms 12 weeks after the End of Therapy (EOT). In this analysis, patients who did not have an assessment 12 weeks after EOT were set to failure. According to a secondary analysis, which compared response rates at the latest time point most relevant to the evaluation of the patient (EOT, or 2, 6, or 12 weeks after EOT, which is more appropriate for this type of study), voriconazole

and the regimen of amphotericin B followed by fluconazole had response rates of 65% and 71%, respectively. Forty-seven percent of isolated pathogens in the voriconazole treatment group were from non-albicans species, including *C glabrata* and *C krusei*, although *C albicans* was the most commonly isolated species in the small subgroup of patients (n = 14) with confirmed deep tissue infections. When considering response at 12 weeks after EOT by pathogen, the success rates were comparable between voriconazole (43%) and amphotericin B followed by fluconazole (46%) for baseline *Candida albicans* infections. Success rates were more favourable with voriconazole (38.6%) than with amphotericin followed by fluconazole (32.3%) for baseline non- albicans infections.

### Refractory *Candida* Infections

Study 309/604 (the combined results of 2 open-label, non-comparative trials) assessed voriconazole in the treatment of fungal infections in patients refractory to, or intolerant of, other antifungal medications. Of the 301 patients assessed for efficacy, 87 patients had serious candidiasis: 38 had oesophageal candidiasis and 47 had invasive candidiasis, of which 26 patients had deep tissue *Candida* infections.

The median duration of IV therapy was 11 days (range 1-138 days) and of oral therapy was 81 days (range 1-326 days). Overall, 25/47 (53.2%) of invasive candidiasis subjects had a successful response, with 16/47 (34.0%) having a complete response and 9/47 (19.1%) having a partial response; 6/47 (12.8%) were assessed as stable. Of the subjects with deep tissue *Candida* infection, 14/26 (53.8%) had a successful response, with 8/26 (30.8%) having a complete response, 6/26 (23.1%) having a partial response and 5/26 (19.2%) assessed as stable.

### Oesophageal Candidiasis

Study 150-305 was a randomised, double-blind, comparative study versus oral fluconazole in immunocompromised patients with endoscopically-proven oesophageal candidiasis. 200 patients were randomised to receive voriconazole (200 mg twice daily) and 191 to receive fluconazole (400 mg once daily on day 1 followed by 200 mg once daily from day 2 onwards).

Over half of the patients in each group had advanced AIDS with CD4 cell counts <50 cells/ $\mu$ L. Outcome was assessed by repeat endoscopy at day 43 or the end of therapy. Voriconazole and fluconazole showed equivalent efficacy against oesophageal candidiasis in the per protocol and intention to treat analysis.

### Efficacy of Voriconazole in the Treatment of Oesophageal Candidiasis

Treatment	Success/total (%)	
	PP	ITT
Voriconazole	113/115 (98%)	175/200 (88%)
Fluconazole	134/141 (95%)	171/191 (90%)

### Other Serious Fungal Pathogens

The efficacy, safety and tolerability of voriconazole in the treatment of systemic and invasive fungal infections in patients failing, or intolerant to other therapy, or for invasive fungal infections due to pathogens for which there is no licensed therapy was assessed in two, open, non-comparative studies (Studies 309/604). A total of 301 patients were evaluated for efficacy, of whom 72 cases had invasive infections due to fungal pathogens other than *Aspergillus* spp. or *Candida* spp.

Patients received an initial intravenous loading dose of 6 mg/kg q12h or an oral loading dose of 400 mg for the first 24 hours, followed by maintenance dosing with 4 mg/kg q12h or 200 mg twice daily, respectively, for up to 12 weeks. The primary endpoint was satisfactory global response at End of Therapy, defined as 'complete' or 'partial' global response.

Overall 39/72 (54.2%) subjects with other (non-*Aspergillus*, non-*Candida*) serious fungal infections had a satisfactory global outcome at end of voriconazole therapy. In pooled analyses of patients enrolled across

the development program, including those from the combined 309/604 studies, voriconazole was shown to be effective against the following additional fungal pathogens:

*Scedosporium* spp. Successful response to voriconazole therapy was seen in 16 of 28 patients with *S. apiospermum* and in 2 of 7 patients with *S. prolificans* infection. In addition, a successful response was seen in 1 of 3 patients with mixed organism infections.

*Fusarium* spp. Seven of 17 patients were successfully treated with voriconazole. Of these seven patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with *fungus* had an infection caused by several organisms; two of them had a successful outcome.

The majority of patients receiving voriconazole treatment for rare fungal infections were intolerant of, or refractory to, prior antifungal therapy.

Other successfully treated fungal infections included isolated cases of: *Alternaria* spp., *Blastomyces dermatitidis*, *Blastoschizomyces capitatus*, *Cladosporium* spp., *Coccidioides immitis*, *Conidiobolus coronatus*, *Cryptococcus neoformans*, *Exserohilum rostratum*, *Exophiala spinifera*, *Fonsecaea pedrosoi*, *Madurella mycetomatis*, *Paecilomyces lilacinus*, *Penicillium* spp including *P. marneffeii*, *Phialophora richardsiae*, *Scopulariopsis brevicaulis*, and *Trichosporon* spp. including *T. beigelii* infections.

#### **Primary Prophylaxis of Invasive Fungal Infections – Efficacy in haematopoietic stem cell transplant (HSCT) recipients without prior proven or probable invasive fungal infection (IFI)**

Voriconazole was compared to itraconazole as primary prophylaxis in an open-label, comparative, multicenter study of adult and adolescent allogeneic HSCT recipients without prior proven or probable IFI (Study A1501073). Patients were aged  $\geq 12$  years and receiving allogeneic HSCT for acute leukaemia (AML, ALL, or myelodysplastic syndrome), failure of therapy for lymphoma or transformation of chronic myeloid leukaemia. Patients with possible, probable or proven IFI during the 6 months prior to study entry, a history of zygomycosis, impaired hepatic function, use of systemic antifungals within 7 days before study entry, or patients who received concomitant medications with major interactions with azoles were excluded from the study. Success was defined as the ability to continue study drug prophylaxis for 100 days after HSCT (without stopping for  $>14$  days) and survival with no proven or probable IFI for 180 days after HSCT. The modified intent-to-treat (MITT) group included 465 allogeneic HSCT recipients, with myeloablative (58%) or reduced-intensity (42%) conditioning regimens. Prophylaxis with study drug was started immediately after HSCT: 224 received voriconazole and 241 received itraconazole. The median duration of study drug prophylaxis in the MITT group was 96 days for voriconazole and 68 days for itraconazole.

The primary endpoint was the success of antifungal prophylaxis at 180 days post-transplant. To be a success at this time point, the patient had to meet all of the following conditions:

- survive until Day 180 post-transplant with no breakthrough IFI
- not discontinue study drug for  $> 14$  days during the first 100 days of prophylaxis
- for patients randomised to itraconazole, not receive  $> 14$  days of itraconazole capsules during the first 100 days of prophylaxis.

Success rates were 48.7% (109/224) for voriconazole, and 33.2% (80/241) for itraconazole ( $p=0.0002$ ). The number and proportion of patients with insufficient prophylaxis i.e. those who missed  $> 14$  days of prophylaxis during the first 100 days after transplant (or if randomised to itraconazole, took  $> 14$  days of itraconazole capsules during this period) was 104/224 (46.4%) in the voriconazole group and 147/241 (61.0%) in the itraconazole group, resulting in a treatment difference of -14.6% (95% CI: -23.5%, -5.6%;  $p=0.0015$ ). Proven or probable IFI developed in 1.3% (3/224) of voriconazole patients and 2.1% (5/241) itraconazole patients during the 180 days after HSCT. The survival rate at Day 180 was 82.1% (184/224) vs 81.7% (197/241) and at 1 year was 73.7% (165/224) vs 68.5% (165/241) for voriconazole and itraconazole, respectively.

### Secondary Prophylaxis of IFI – Efficacy in HSCT recipients with prior proven or probable IFI

Voriconazole was investigated as secondary prophylaxis in an open-label, non-comparative, multicenter study of adult allogeneic HSCT recipients with prior proven or probable IFI (Study A1501038). The primary endpoint was the rate of occurrence of proven and probable IFI during the first year after HSCT. The MITT group included 40 patients with prior IFI, including 31 with aspergillosis, 5 with candidiasis, and 4 with other IFI. The median duration of study drug prophylaxis in the MITT group was 95.5 days. Nine patients (22.5%) received empiric antifungal therapy for between 9 and 365 days.

Recurrent proven or probable IFIs in the MITT population was reported in 3/28 (10.7%) [95% CI (2, 28)] of evaluable patients during the first year after HSCT, including one candidaemia, one scedosporiosis (both relapses of prior IFI), and one zygomycosis. The survival rate at Day 180 was 80.0% (32/40) and at 1 year was 70.0% (28/40).

### Paediatric Use

Sixty four (64) paediatric patients aged 9 months up to 15 years who had definite or probable invasive fungal infections were treated with voriconazole. This population included 34 patients 2 to <12 years old and 23 patients 12–15 years of age. The majority (59/64) had failed previous antifungal therapies. Therapeutic trials included eight patients aged 12-15 years, the remaining patients received voriconazole in the compassionate use programs. Underlying diseases in these patients included haematologic malignancies and aplastic anaemia (27 patients) and chronic granulomatous disease (14 patients). The most commonly treated fungal infection was aspergillosis (46/64; 71%). In addition, a successful response was seen in one patient with infection caused by *Aspergillus fumigatus* and *Phialophora richardsiae*. Other fungal infections were caused by *Scedosporium*, *Candida*, *Fusarium*, *Conidiobolus*, *Alternaria* and *Trichosporon* spp.

### Clinical Outcome in Paediatric Patients by Age and Fungal Infection

Age (years)	Infection	Success/Treated
2 – <12 years	Aspergillosis	11/23
	Other	4/11
	Total	15/34
12-15 years	Aspergillosis	5/17
	Other	4/6
	Total	9/23

### Clinical Studies Examining QT Interval

A placebo-controlled, randomised, single-dose, crossover study to evaluate the effect on the QT interval of healthy volunteers was conducted with three oral doses of voriconazole and ketoconazole. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600 mg of voriconazole were 5.1, 4.8, and 8.2 msec, respectively and 7.0 msec for ketoconazole 800 mg. No subject in any group had an increase in QTc of  $\geq 60$  msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec. Subjects who were CYP2C19 genotype poor metabolisers were excluded from this study; however, the dose of 1600 mg voriconazole achieved plasma concentrations of approximately 5,400 to 16,900 ng/mL which covered the exposure seen in 95% of patients in Phase 2/3 trials where poor metabolisers were not excluded.

## 5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 200 mg or 300 mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or haematopoietic tissue), the observed pharmacokinetic characteristics of rapid and consistent absorption, accumulation and non-linear pharmacokinetics were in agreement with those observed in healthy subjects.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose from 200 mg twice daily to 300 mg twice daily leads to a 2.5-fold increase in exposure (AUC<sub>t</sub>) (area under the plasma concentration time curve over the 12-hour dosing interval) while increasing the intravenous dose from 3 mg/kg twice daily to 4 mg/kg twice daily produces a 2.3-fold increase in exposure. When the recommended intravenous or oral loading dose regimens are administered, plasma concentrations close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by day 6 in the majority of subjects.

### **Absorption**

Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations ( $C_{max}$ ) achieved 1 to 2 hours after dosing. The oral bioavailability of voriconazole in adults is estimated to be 96%.

When multiple doses of voriconazole are administered with high fat meals,  $C_{max}$  and AUC<sub>t</sub> of the tablets are reduced by 34% and 24% respectively.

The absorption of voriconazole is not affected by changes in gastric pH.

### **Distribution**

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58%.

Cerebrospinal fluid samples from eight patients in a compassionate programme showed detectable voriconazole concentrations in all patients.

### **Metabolism**

*In vitro* studies showed that voriconazole is metabolised by the hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.

The inter-individual variability of voriconazole pharmacokinetics is high.

*In vivo* studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolisers. For Caucasians and Blacks the prevalence of poor metabolisers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on average, 4-fold higher voriconazole exposure (AUC<sub>t</sub>) than their homozygous extensive metaboliser counterparts. Subjects who are heterozygous extensive metabolisers have on average 2-fold higher voriconazole exposure than their homozygous extensive metaboliser counterparts.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma. This metabolite has minimal antifungal activity and does not contribute to the overall efficacy of voriconazole.

### **Excretion**

Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine.

After administration of a radiolabelled dose of voriconazole, approximately 80% of the radioactivity is recovered in the urine after multiple intravenous dosing and 83% in the urine after multiple oral dosing. The majority (>94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

The terminal half-life of voriconazole depends on dose and is approximately 6 hours at 3 mg/kg (intravenously) or 200 mg (orally). Because of non-linear pharmacokinetics, the terminal half-life is not useful in the prediction of the accumulation or elimination of voriconazole.

### **Pharmacokinetic-Pharmacodynamic (PK/PD) Relationships**

In 10 therapeutic studies, the median for the average and maximum plasma concentrations in individual subjects across the studies was 2425 ng/mL (inter-quartile range 1193 to 4380 ng/mL) and 3742 ng/mL (inter-quartile range 2027 to 6302 ng/mL), respectively. A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy in therapeutic studies was not found.

PK/PD analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both LFT abnormalities and visual disturbances.

### **Pharmacokinetics in Special Patient Groups**

#### **Gender**

In an oral multiple dose study,  $C_{max}$  and  $AUC_t$  for healthy young females were 83% and 113% higher, respectively, than in healthy young males (18-45 years). In the same study, no significant differences in  $C_{max}$  and  $AUC_t$  were observed between healthy elderly males and healthy elderly females ( $\geq 65$  years).

In the clinical program, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female patients were similar. Therefore, no dosage adjustment based on gender is necessary.

#### **Elderly**

In an oral multiple dose study  $C_{max}$  and  $AUC_t$  in healthy elderly males ( $\geq 65$  years) were 61% and 86% higher, respectively, than in healthy young males (18-45 years). No significant differences in  $C_{max}$  and  $AUC_t$  were observed between healthy elderly females ( $\geq 65$  years) and healthy young females (18-45 years).

In the therapeutic studies no dosage adjustment was made on the basis of age. A relationship between plasma concentrations and age was observed. The safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly.

#### **Paediatrics**

A population pharmacokinetic analysis was conducted on data from 35 immunocompromised subjects aged 2 to <12 years old who were included in the intravenous single or multiple dose pharmacokinetic studies. Twenty-four of these subjects received multiple doses of voriconazole. Average steady state plasma concentrations in children receiving a maintenance dose of 4 mg/kg twice daily were similar to those in adults receiving 3 mg/kg twice daily, with medians of 1186 ng/mL in children and 1155 ng/mL in adults. Therefore, intravenous maintenance doses of 4 mg/kg twice daily in children aged between 2 to <12 years of age matched the exposure in adults receiving intravenous doses of 3 mg/kg twice daily.

Another pharmacokinetic study in 47 immunocompromised subjects aged 2 to <12 years old evaluated intravenous doses of 4, 6 and 8 mg/kg twice daily and multiple oral suspension doses of 4 and 6 mg/kg twice daily. The majority of patients received more than one dose level with a maximum duration of dosing of 30 days. The non-linearity of the pharmacokinetics of voriconazole in children is less pronounced than that in adults. On average, the exposure achieved in adults receiving maintenance doses of 4 mg/kg twice daily is approximately 30  $\mu\text{g}\cdot\text{h}/\text{mL}$ . The average voriconazole exposures ( $AUC_t$ ) in children following multiple intravenous doses of 6 and 8 mg/kg twice daily were approximately 20 and 29.8  $\mu\text{g}\cdot\text{h}/\text{mL}$ , respectively, with high inter-subject variability. A great percentage of children in the 8 mg/kg intravenous dose group had higher exposure than the typical range observed in adults receiving intravenous 4 mg/kg dose. Average absolute bioavailability of the oral suspension was 66% in children with high inter-subject variability. Bioavailability was lower in children aged 2 to <6 years old (43.6%-63.4%) than in children aged 6 to <12 years old (66.7%-90.9%).

### Renal Impairment

In a single oral dose (200 mg) study in subjects with normal renal function and mild (creatinine clearance 41-60 mL/min) to severe (creatinine clearance <20 mL/min) renal impairment, the pharmacokinetics of voriconazole were not significantly affected by renal impairment. The plasma protein binding of voriconazole was similar in subjects with different degrees of renal impairment.

In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, hydroxypropylbetadex, occurs. Oral voriconazole should be administered to patients with moderate to severe renal dysfunction including dialysis patients, unless an assessment of the benefit risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients, and if increases occur, consideration should be given to changing to oral voriconazole therapy see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION.

A pharmacokinetic study in subjects with renal failure undergoing haemodialysis showed that voriconazole is dialysed with clearance of 121 mL/min. A 4-hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Mean voriconazole plasma concentrations were measured at the end of infusion on study days 3, 4 and 5 for both dialysis and normal subjects. Exposure to voriconazole was lower in the dialysis subjects. Combining the Day 3, 4 and 5 data, the ratio of the post infusion means (dialysis/normal subjects) was 50% (95% CI: 32%, 80%) for voriconazole.

### Hepatic Impairment

After a single oral dose (200 mg), AUC was 233% higher in subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared with subjects with normal hepatic function. Protein binding of voriconazole was not affected by impaired hepatic function.

In a multiple oral dose study, AUC<sub>t</sub> was similar in subjects with moderate hepatic cirrhosis (Child-Pugh B) given maintenance doses of 100 mg twice daily and subjects with normal hepatic function given 200 mg twice daily. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C) see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION.

## 5.3. PRECLINICAL SAFETY DATA

### Genotoxicity

Voriconazole showed no mutagenic potential in gene-mutation assays in bacterial (*Salmonella typhimurium*) and mammalian (Chinese hamster ovary) cells. While *in vitro* exposure of human lymphocytes to voriconazole produced equivocal effects on chromosomes, *in vivo* treatment of male and female mice at doses up to and including the maximum tolerated dose produced no evidence of chromosome damage as determined by the micronucleus assay.

### Carcinogenicity

Carcinogenic potential was studied in mice and rats at oral doses of up to 100 mg/kg/day and 50 mg/kg/day for 24 months, respectively. Hepatocellular adenoma appeared in male and female mice at 100 mg/kg/day and in female rats at 50 mg/kg/day. There was also an increased incidence of hepatocellular carcinoma in mice at 100 mg/kg/day. Although mean plasma drug concentrations indicated there is no safety margin in humans in terms of exposure, adenoma and carcinoma (as well as non-neoplastic changes) are known to occur in rodents after chronic administration of compounds that are hepatic enzyme inducers.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. LIST OF EXCIPIENTS

VORICONAZOLE APO film coated tablets contain the following inactive ingredients: lactose monohydrate, pregelatinised maize starch, croscarmellose sodium, povidone, colloidal anhydrous silica, magnesium stearate and Opadry White OY-LS-28908.

### 6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3. SHELF LIFE

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

### 6.4. SPECIAL PRECAUTIONS FOR STORAGE

VORICONAZOLE APO tablets should be stored below 30°C.

### 6.5. NATURE AND CONTENTS OF CONTAINER

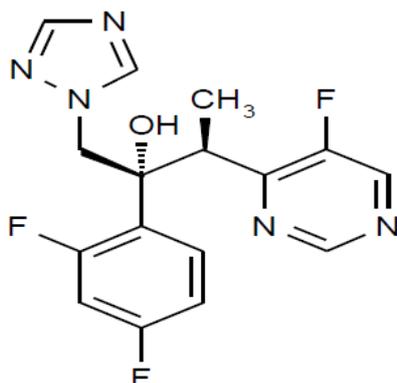
VORICONAZOLE APO 50 mg and 200 mg tablets are available in PVC / Aluminium blisters packs of 56 tablets.

### 6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

### 6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure:



Chemical name: (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4-triazol-1-yl)-2-butanol

Molecular formula: C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>N<sub>5</sub>O

Molecular weight: 349.3

CAS number: 137234-62-9

Voriconazole drug substance is a white to off white powder. Its aqueous solubility is very low at 0.7 mg/mL at 25°C.

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

## 8. SPONSOR

Southern Cross Pharma Pty Ltd

Suite 5/118 Church Street

Hawthorn VIC 3122, Australia

## 9. DATE OF FIRST APPROVAL

19<sup>th</sup> October 2018

## 10. DATE OF REVISION

### Summary table of changes

Section Changed	Summary of new Information