SINGAPORE PRODUCT INFORMATION

VORICONAZOLE - AFT

Powder for injection

(Voriconazole)

1 PRODUCT NAME

Voriconazole-AFT powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg voriconazole.

The powder is reconstituted with either water for injections or (0.9%) Sodium Chloride for Infusion to obtain an extractable volume of 20 ml of clear concentrate containing 10 mg/ml of voriconazole.

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

3 PHARMCEUTICAL FORM

Voriconazole - AFT is a white to off white lyophilized powder which provides a clear solution upon reconstitution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Voriconazole is a broad spectrum, triazole antifungal agent and is indicated as follows:

Treatment of invasive aspergillosis;

Treatment of candidemia in non-neutropenic patients;

Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*);

Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.;

Prophylaxis in patients ≥12 years old who are at high risk of developing invasive fungal infections. The indication is based on a study which includes patients ≥12 years old undergoing allogeneic haematopoietic stem cell transplantation (see Section 5.1).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults

Therapy must be initiated with the specified loading dose regimen of either intravenous or oral voriconazole to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability, switching between intravenous and oral administration is appropriate when clinically indicated.

Dosage recommendations are provided in the table below.

	Intravenous dosing
Loading Dose Regimen (first 24 hours)	6 mg/kg every 12 hours (for first 24 hours)
Maintenance Dose (after first 24 hours)	
Prophylaxis of invasive fungal infections	3-4 mg/kg every 12 hours
Serious invasive *Candida*/Invasive aspergillosis/*Scedosporium* and *Fusarium* infections[a]	4 mg/kg every 12 hours
Candidemia in non-neutropenic patients	3-4 mg/kg every 12 hours[b]

[a] In the pivotal clinical study of invasive aspergillosis, the median duration of IV voriconazole therapy was 10 days (range 2-85 days) (see Section 5.1).

[b] In clinical trials, patients with candidemia received 3 mg/kg every 12 hours as primary therapy, while patients with other deep tissue *Candida* infections received 4 mg/kg as salvage therapy. Appropriate dose should be based on severity and nature of the infection.

Clinical data to establish the safety of intravenously administered hydroxypropylbetadex in long-term treatment are limited.

Paediatrics

Age of ≤ 2 years

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.

Age ≥ 2 to 12 years

The recommended maintenance dosing regimen in paediatric patients 2 to <12 years is as follows:

Loading Dose Regimen	No oral or intravenous loading dose is recommended
Maintenance Dose	Intravenous Dose*: 7 mg/kg twice daily

* Based on a population pharmacokinetic analysis in 82 immunocompromised patients aged 2 to <12 years.

If paediatric patients are unable to tolerate an intravenous dose of 7 mg/kg twice daily, a dose reduction from 7 mg/kg to 4 mg/kg twice daily may be considered based on the population pharmacokinetic analysis and previous clinical experience. This provides equivalent exposure to 3 mg/kg twice daily in adults.

Age 2 to < 12 years with hepatic or renal impairment

Use in the patients aged 2 to < 12 years with hepatic or renal impairment have not been studied (see Section 4.4 Special warnings and precautions for use).

Adolescents (12 - 16 years of age)

Adolescents (12 - 16 years of age) should be dosed as adults. See dosing recommendation under the section heading, Adults.

Clinical data to establish the safety of intravenously administered hydroxypropylbetadex in the paediatric population are limited.

Method of administration

Voriconazole – AFT powder for injection is not recommended for bolus injection.

Voriconazole – AFT powder for injection requires reconstitution and dilution prior to administration as an intravenous infusion (see Section 6.2 Incompatibilities).

It is recommended that Voriconazole – AFT powder for injection is administered at a maximum rate of 3 mg/kg per hour over 1 to 2 hours. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of voriconazole therapy (see Section 4.4 Special warnings and precautions for use, Cardiovascular).

Reconstitution instructions

Voriconazole-AFT 200mg powder for solution for infusion is stable in all of the following reconstitution solutions both at below 25 °C and at 5 °C for at least 72 hours:

Water for injections, Sodium Chloride 0.9% solution, Compound Sodium Lactate solution, 5% Glucose and Lactate Ringer's solution, 5% Glucose and 0.45% Sodium chloride solution, 5% Glucose solution, 5% Glucose in 20 mEq Potassium Chloride solution, 0.45% Sodium Chloride solution and 5% Glucose and 0.9% Sodium Chloride solution

Product is for single use in one patient only. Discard any residue. Only clear solutions without particles should be used.

Dosage adjustment

Adults

If patient response at 3 mg/kg every 12 hours is inadequate, the intravenous maintenance dose may be increased to 4 mg/kg every 12 hours.

If patients are unable to tolerate 4 mg/kg every 12 hours, reduce the intravenous dose to 3 mg/kg every 12 hours.

Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV every 12 hours. 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).

The dose recommendation for concomitant use of intravenous voriconazole and oral efavirenz has not been determined (see Section 4.5 Interactions with other medicines and other forms of interactions).

Treatment duration depends upon patients' clinical and mycological response.

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 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, Renal impairment).

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)).

Elderly

No dose adjustment is necessary for elderly patients.

4.3 CONTRAINDICATIONS

Voriconazole – AFT is contraindicated in patients with known hypersensitivity to voriconazole or to any of the excipients.

Coadministration of the CYP3A4 substrates, terfenadine, ivabradine, pimozide 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).

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 warnings 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 4.5 Section 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).

Co-administration of voriconazole with naloxegol is contraindicated because voriconazole may significantly increase plasma concentrations of naloxegol which may precipitate opioid withdrawal symptoms (see Section 4.5 Interactions with other medicines and other forms of interactions).

Co-administration of voriconazole with tolvaptan is contraindicated because voriconazole may significantly increase plasma concentrations of tolvaptan (see Section 4.5 Interactions with other medicines and other forms of interactions).

Co-administration of voriconazole with venetoclax is contraindicated at initiation and during the venetoclax dose titration phase since voriconazole is likely to significantly increase plasma concentrations of venetoclax and increase risk of tumour lysis syndrome (see Section 4.5 Interactions with other medicines and other forms of interactions).

Co-administration of voriconazole with lurasidone is contraindicated since it may result in significant increases in lurasidone exposure and the potential for serious adverse reactions (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, hypokalaemia 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 Dose and method of administration).

Infusion – related reactions

Anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnoea, faintness, nausea, pruritus and rash have occurred during the administration of the intravenous formulation of voriconazole. Depending on the severity of symptoms, consideration should be given to stopping treatment.

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 – AFT treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.

Dermatological adverse reactions

Severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported with the use of voriconazole. If a patient develops a suspected SCAR, voriconazole should be discontinued immediately and an alternative treatment should be considered.

In addition, voriconazole has been associated with photosensitivity skin reaction. An increased risk of skin toxicity with concomitant use of methotrexate, a drug associated with ultraviolet (UV) reactivation has been observed. There is a potential for this risk to be observed with other drugs associated with UV reactivation. 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 later in this section).

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.

Adrenal events

Reversible cases of adrenal insufficiency have been reported in patients receiving azoles, including voriconazole. Adrenal insufficiency has been reported in patients receiving azoles with or without concomitant corticosteroids. In patients receiving azoles without corticosteroids, adrenal insufficiency is related to direct inhibition of steroidogenesis by azoles. In patients taking corticosteroids, voriconazole associated CYP3A4 inhibition of their metabolism may lead to corticosteroid excess and adrenal suppression (see Section 4.5 Interactions with other medicines and other forms of interactions). Cushing's

syndrome with and without subsequent adrenal insufficiency has also been reported in patients receiving voriconazole concomitantly with corticosteroids.

Patients on long-term treatment with voriconazole and corticosteroids (including inhaled corticosteroids e.g. budesonide) should be carefully monitored for adrenal cortex dysfunction both during treatment and when voriconazole is discontinued (see Section 4.5 Interactions with other medicines and other forms of interactions). Patients should be instructed to seek immediate medical care if they develop signs and symptoms of Cushing's syndrome or adrenal insufficiency.

Long-term treatment

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 immunosupression), 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), Visual Impairment).

Visual impairment

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 (See Section 4.7 Effect on ability to drive and use machines). The effect of voriconazole on visual function is not known if treatment continues beyond 28 days. If treatment continues beyond 28 days, visual function including visual acuity, visual field and colour perception should be monitored.

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 with voriconazole since methadone levels increased following co-administration of voriconazole. 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_{τ} 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 co-administered 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)

Co-administration 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).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

When voriconazole is co-administered with efavirenz, the maintenance dose of oral voriconazole should be increased to 400 mg every 12 hours and that of efavirenz should be decreased to 300 mg every 24 hours (see Sections 4.3 Contraindications and 4.5 Interactions with other medicines and other forms of interactions). The dose recommendation for concomitant use of intravenous voriconazole and oral efavirenz has not been determined (see Section 4.2 Dose and method of administration).

Glasdegib (CYP3A4 substrate)

Co-administration of voriconazole is expected to increase glasdegib plasma concentrations and increase the risk of QTc prolongation (see Section 4.5 Interactions with other medicines and other forms of interactions). If concomitant use cannot be avoided, frequent ECG monitoring is recommended.

Tyrosine kinase inhibitors (CYP3A4 substrate)

Co-administration of voriconazole with tyrosine kinase inhibitors metabolised by CYP3A4 is expected to increase tyrosine kinase inhibitor plasma concentrations and the risk of adverse reactions. If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring is recommended (see Section 4.5 Interactions with other medicines and other forms of interactions).

Hepatic toxicity

In clinical trials, there have been 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 and bilirubin) 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 Dose 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.

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

Hydroxypropylbetadex

In patients with moderate to severe renal dysfunction accumulation of cyclodextrins may occur.

Use in the elderly

No data available.

Paediatric use

Safety and efficacy in paediatric subjects below the age of two years has not been established (see Section 5.1 Pharmacodynamic properties, Clinical trials). A higher frequency of liver enzyme elevations was observed in the paediatric population (see Section 4.8 Adverse effects (undesirable effects)). Hepatic function and pancreatic function should be monitored.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes, in particular for substances metabolised by CYP3A4 since voriconazole is a strong CYP3A4 inhibitor though the increase in AUC is substrate dependent (see Interaction table below).

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

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

Interaction table

Interactions between voriconazole and other medicinal products are listed in the table below (once daily as “QD”, twice daily as “BID”, three times daily as “TID” and not determined as “ND”). The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔),

below (↓) or above (↑) the 80%-125% range. The asterisk (*) indicates a two-way interaction. AUC_{τ}, AUC_{t} and $AUC_{0-\infty}$ represent area under the curve over a dosing interval, from time zero to the time with detectable measurement and from time zero to infinity, respectively.

The interactions in the table are presented in the following order: contraindications, those requiring dose adjustment and careful clinical and/or biological monitoring, and finally those that have no significant pharmacokinetic interaction but may be of clinical interest in this therapeutic field.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Astemizole, cisapride, pimozide, quinidine, terfenadine and ivabradine *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes*.	**Contraindicated** (see Section 4.3).
Carbamazepine and long-acting barbiturates (including but not limited to: phenobarbital, mephobarbital) *[potent CYP450 inducers]*	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	**Contraindicated** (see Section 4.3).
Efavirenz (a non-nucleoside reverse transcriptase inhibitor) *[CYP450 inducer; CYP3A4 inhibitor and substrate]* Efavirenz 400 mg QD, co-administered with voriconazole 200 mg BID Efavirenz 300 mg QD, co-administered with voriconazole 400 mg BID*	 Efavirenz C_{max} ↑ 38% Efavirenz AUC_{τ} ↑ 44% Voriconazole C_{max} ↓ 61% Voriconazole AUC_{τ} ↓ 77% Compared to efavirenz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUC_{τ} ↑ 17% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 23% Voriconazole AUC_{τ} ↓ 7%	Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is **contraindicated** (see Section 4.3). Voriconazole may be co-administered with efavirenz if the voriconazole maintenance dose is increased to 400 mg BID and the efavirenz dose is decreased to 300 mg QD. When voriconazole treatment is stopped, the initial dose of efavirenz should be restored (see Section 4.2).

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Ergot alkaloids (including but not limited to: ergotamine and dihydroergotamine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.	**Contraindicated** (see Section 4.3)
Lurasidone *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of lurasidone.	**Contraindicated** (see Section 4.3)
Naloxegol *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of naloxegol.	**Contraindicated** (see Section 4.3)
Rifabutin *[potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with voriconazole 350 mg BID)* 300 mg QD (co-administered with voriconazole 400 mg BID)*	 Voriconazole C_{max} ↓ 69% Voriconazole AUC_{τ} ↓ 78% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ 4% Voriconazole AUC_{τ} ↓ 32% Rifabutin C_{max} ↑ 195% Rifabutin AUC_{τ} ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104% Voriconazole AUC_{τ} ↑ 87%	**Contraindicated** (see Section 4.3)
Rifampicin (600 mg QD) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓ 93% Voriconazole AUC_{τ} ↓ 96%	**Contraindicated** (see Section 4.3)

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]* High dose (400 mg BID) Low dose (100 mg BID)*	 Ritonavir C_{max} and AUC_{τ} ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUC_{τ} ↓ 82% Ritonavir C_{max} ↓ 25% Ritonavir AUC_{τ} ↓ 13% Voriconazole C_{max} ↓ 24% Voriconazole AUC_{τ} ↓ 39%	 Co-administration of voriconazole and high doses of ritonavir (400 mg and higher BID) is **contraindicated** (see Section 4.3). Co-administration of voriconazole and low dose ritonavir (100 mg BID) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
St. John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg TID (co-administered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole $AUC_{0-\infty}$ ↓ 59%	**Contraindicated** (see Section 4.3)
Tolvaptan *[CYP3A substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of tolvaptan.	**Contraindicated** (see Section 4.3)
Venetoclax *[CYP3A substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of venetoclax.	Concomitant administration of voriconazole is **contraindicated** at initiation and during venetoclax dose titration phase (see Section 4.3). Dose reduction of venetoclax is required as instructed in venetoclax prescribing information during steady daily dosing; close monitoring for signs of toxicity is recommended.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Fluconazole (200 mg QD) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	Voriconazole C_{max} ↑ 57% Voriconazole AUC_{τ} ↑ 79% Fluconazole C_{max} ND Fluconazole AUC_{τ} ND	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse events is recommended if voriconazole is used sequentially after fluconazole.
Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with voriconazole 400 mg BID)*	Voriconazole C_{max} ↓ 49% Voriconazole AUC_{τ} ↓ 69% Phenytoin C_{max} ↑ 67% Phenytoin AUC_{τ} ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 34% Voriconazole AUC_{τ} ↑ 39%	Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended. Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID (100 mg to 200 mg oral BID in patients less than 40 kg) (see Section 4.2).
Letermovir *[CYP2C9 and CYP2C19 inducer]*	Voriconazole C_{max} ↓ 39% Voriconazole AUC_{0-12} ↓ 44% Voriconazole C_{12} ↓ 51%	If concomitant administration of voriconazole with letermovir cannot be avoided, monitor for loss of voriconazole effectiveness.
Lemborexant *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of lemborexant.	Concomitant use of voriconazole and lemborexant should be avoided.
Glasdegib *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of glasdegib and increase risk of QTc prolongation.	If concomitant use cannot be avoided, frequent ECG monitoring is recommended.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Tyrosine kinase inhibitors (including but not limited to: axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) *[CYP3A4 substrates]*	Although not studied, voriconazole may increase plasma concentrations of tyrosine kinase inhibitors metabolised by CYP3A4.	If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring is recommended.
Anticoagulants Warfarin (30 mg single dose, co-administered with 300 mg BID voriconazole) *[CYP2C9 substrate]* Other oral coumarins (including but not limited to: phenprocoumon, acenocoumarol) *[CYP2C9 and CYP3A4 substrates]*	Maximum increase in prothrombin time was approximately 2-fold. Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.	Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.
Ivacaftor *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of ivacaftor with risk of increased adverse reactions.	Dose reduction of ivacaftor is recommended.
Eszopiclone *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations and sedative effect of eszopiclone.	Dose reduction of eszopiclone is recommended.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Benzodiazepines *[CYP3A4 substrates]* Midazolam (0.05 mg/kg IV single dose)	In an independent published study, Midazolam $AUC_{0-\infty}$ ↑ 3.7-fold	Dose reduction of benzodiazepines should be considered.
Midazolam (7.5 mg oral single dose)	In an independent published study, Midazolam C_{max} ↑ 3.8-fold	
Other benzodiazepines (including but not limited to: triazolam, alprazolam)	Midazolam $AUC_{0-\infty}$ ↑ 10.3-fold Although not studied, voriconazole is likely to increase the plasma concentrations of other benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Immunosuppressants *[CYP3A4 substrates]* Sirolimus (2 mg single dose)	In an independent published study, Sirolimus C_{max} ↑ 6.6-fold Sirolimus $AUC_{0-\infty}$ ↑ 11-fold	Co-administration of voriconazole and sirolimus is **contraindicated** (see Section 4.3).
Everolimus *[also P-gp substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	Co-administration of voriconazole and everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see Section 4.4).
Ciclosporin (In stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin C_{max} ↑ 13% Ciclosporin AUC_{τ} ↑ 70%	When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary</u>.
Tacrolimus (0.1 mg/kg single dose)	Tacrolimus C_{max} ↑ 117% Tacrolimus AUC_{τ} ↑ 221%	When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary</u>.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Long-acting Opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose)	In an independent published study, Oxycodone C_{max} ↑ 1.7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3.6-fold	Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse events may be necessary.
Methadone (32-100 mg QD) *[CYP3A4 substrate]*	R-methadone (active) C_{max} ↑ 31% R-methadone (active) AUC_{τ} ↑ 47% S-methadone C_{max} ↑ 65% S-methadone AUC_{τ} ↑ 103%	Frequent monitoring for adverse events and toxicity related to methadone, including QT prolongation, is recommended. Dose reduction of methadone may be needed.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) *[CYP2C9 substrates]* Ibuprofen (400 mg single dose) Diclofenac (50 mg single dose)	S-Ibuprofen C_{max} ↑ 20% S-Ibuprofen $AUC_{0-\infty}$ ↑ 100% Diclofenac C_{max} ↑ 114% Diclofenac $AUC_{0-\infty}$ ↑ 78%	Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.
Omeprazole (40 mg QD)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	Omeprazole C_{max} ↑ 116% Omeprazole AUC_{τ} ↑ 280% Voriconazole C_{max} ↑ 15% Voriconazole AUC_{τ} ↑ 41% Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicinal products.	No dose adjustment of voriconazole is recommended. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose be halved.
Oral Contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ethinylestradiol (1 mg/0.035 mg QD)	Ethinylestradiol C_{max} ↑ 36% Ethinylestradiol AUC_{τ} ↑ 61% Norethisterone C_{max} ↑ 15% Norethisterone AUC_{τ} ↑ 53% Voriconazole C_{max} ↑ 14% Voriconazole AUC_{τ} ↑ 46%	Monitoring for adverse events related to oral contraceptives, in addition to those for voriconazole, is recommended.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Short-acting Opiates *[CYP3A4 substrates]* Alfentanil (20 µg/kg single dose, with concomitant naloxone) Fentanyl (5 µg/kg single dose)	In an independent published study, Alfentanil $AUC_{0-\infty}$ ↑ 6-fold In an independent published study, Fentanyl $AUC_{0-\infty}$ ↑ 1.34-fold	Dose reduction of alfentanil, fentanyl and other short-acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse events is recommended.
Statins (e.g., lovastatin) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis.	If concomitant administration of voriconazole with statins metabolised by CYP3A4 cannot be avoided, dose reduction of the statin should be considered.
Sulphonylureas (including but not limited to: tolbutamide, glipizide, glyburide) *[CYP2C9 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of sulphonylureas and cause hypoglycaemia.	Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.
Vinca Alkaloids (including but not limited to: vincristine and vinblastine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of vinca alkaloids and lead to neurotoxicity.	Dose reduction of vinca alkaloids should be considered.
Other HIV Protease Inhibitors (including but not limited to: saquinavir, amprenavir and nelfinavir)* *[CYP3A4 substrates and inhibitors]*	Not studied clinically. In vitro studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (including but not limited to: delavirdine, nevirapine)* *[CYP3A4 substrates, inhibitors or CYP450 inducers]*	Not studied clinically. *In vitro* studies show that the metabolism of voriconazole may be inhibited by NNRTIs and voriconazole may inhibit the metabolism of NNRTIs. The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by a NNRTI.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Tretinoin *[CYP3A4 substrate]*	Although not studied, voriconazole may increase tretinoin concentrations and increase risk of adverse reactions (pseudotumor cerebri, hypercalcaemia).	Dose adjustment of tretinoin is recommended during treatment with voriconazole and after its discontinuation.
Cimetidine (400 mg BID) *[non-specific CYP450 inhibitor and increases gastric pH]*	Voriconazole C_{max} ↑ 18% Voriconazole AUC_{τ} ↑ 23%	No dose adjustment
Digoxin (0.25 mg QD) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUC_{τ} ↔	No dose adjustment
Indinavir (800 mg TID) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUC_{τ} ↔ Voriconazole C_{max} ↔ Voriconazole AUC_{τ} ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) *[CYP3A4 inhibitor]* Azithromycin (500 mg QD)	 Voriconazole C_{max} and AUC_{τ} ↔ Voriconazole C_{max} and AUC_{τ} ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment
Mycophenolic acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_{t} ↔	No dose adjustment

Medicinal product *[Mechanism of Interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Corticosteroids Prednisolone (60 mg single dose) [CYP3A4 substrate]	 Prednisolone C_{max} ↑ 11% Prednisolone $AUC_{0-\infty}$ ↑ 34%	No dose adjustment. Patients on long-term treatment with voriconazole and corticosteroids (including inhaled corticosteroids e.g., budesonide) should be carefully monitored for adrenal cortex dysfunction both during treatment and when voriconazole is discontinued (see Section 4.4).
Ranitidine (150 mg BID) *[increases gastric pH]*	Voriconazole C_{max} and AUC_{τ} ↔	No dose adjustment

Calcium channel blockers (CYP3A4 substrates): Although not studied clinically, voriconazole has been shown to inhibit felodipine metabolism *in vitro*. Therefore, voriconazole is likely to increase the plasma concentrations of calcium channel blockers that are metabolised by CYP3A4. Frequent monitoring of adverse events and toxicity related to calcium channel blockers are recommended during co-administration. Dose adjustment of the calcium channel blocker may be needed.

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

There are no adequate studies in pregnant women. Studies in rats have shown reproductive toxicity, including teratogenicity (cleft palates) at oral doses of ≥ 10 mg/kg/day and disturbance of parturition (dystocia) at oral doses of ≥ 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 fetal 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 fetus.

Women of childbearing potential

Women of childbearing potential must always use effective contraception during treatment.

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 (UNDESIREABLE EFFECTS)

Clinical trial

The safety of voriconazole in adults is based on an integrated safety database of more than 2000 subjects (1603 adult 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.

In addition, the safety of voriconazole was investigated in 279 patients (including 270 adults) 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 all causality adverse reactions in 1873 adults from pooled therapeutic (1603) and prophylaxis (270) studies. The most commonly reported adverse events were visual impairment, liver function test abnormal, pyrexia, 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**
Infections and infestations	
Common	Sinusitis
Uncommon	Pseudomembranous colitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Frequency Not Known (Cannot be Estimated from the Available Data)	squamous cell carcinoma (including cutaneous SCC in situ, or Bowen's disease)*[h]
Blood and lymphatic system disorders	
Common	Agranulocytosis [a], pancytopenia, thrombocytopenia [b], leukopenia, anaemia
Uncommon	Bone marrow failure, lymphadenopathy, eosinophilia
Rare	Disseminated intravascular coagulation
Immune system disorders	

MedDRA System Organ Class Frequency †	**Adverse Drug Reactions**
Uncommon	Hypersensitivity
Rare	Anaphylactoid reaction
Endocrine disorders	
Uncommon	Adrenal insufficiency, hypothyroidism
Rare	Hyperthyroidism
Metabolism and nutrition disorders	
Very common	Oedema peripheral
Common	Hypoglycaemia, hypokalaemia, hyponatraemia
Psychiatric disorders	
Common	Depression, hallucination, anxiety, insomnia, agitation, confusional state
Nervous system disorders	
Very common	Headache
Common	Syncope, tremor, hypertonia [c], paraesthesia, somnolence, dizziness
Uncommon	Brain oedema, encephalopathy [d], extrapyramidal disorder [e], neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia
Rare	Hepatic encephalopathy, Guillain-Barré syndrome, seizure, nystagmus
Eye disorders	
Very common	Visual impairment [f]
Common	Retinal haemorrhage
Uncommon	Optic nerve disorder [g], papilloedema [h], oculogyric crisis, diplopia, scleritis, blepharitis
Rare	Optic atrophy, corneal opacity
Ear and labyrinth disorders	
Uncommon	Hypoacusis, vertigo, tinnitus
Cardiac disorders	
Common	Arrhythmia supraventricular, tachycardia, bradycardia
Uncommon	Ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia
Rare	Torsades de pointes, atrioventricular block complete, bundle branch block, nodal rhythm
Vascular disorders	
Common	Hypotension, phlebitis
Uncommon	Thrombophlebitis, lymphangitis
Respiratory, thoracic and mediastinal disorders	
Common	Acute respiratory distress syndrome, pulmonary oedema

MedDRA System Organ Class Frequency †	Adverse Drug Reactions
Gastrointestinal disorders	
Very common	Diarrhoea, vomiting, abdominal pain, nausea
Common	Cheilitis, dyspepsia, constipation, gingivitis
Uncommon	Peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis
Hepatobiliary disorders	
Very common	Liver function test abnormal
Common	Jaundice, jaundice cholestatic, hepatitis [i]
Uncommon	Hepatic failure, hepatomegaly, cholecystitis, cholelithiasis
Skin and subcutaneous tissue disorders	
Very common	Rash
Common	Dermatitis exfoliative, alopecia, rash maculopapular, pruritus
Uncommon	Stevens-Johnson syndrome [h], photosensitivity reaction, purpura, urticaria, eczema
Rare	Toxic epidermal necrolysis [h], drug reaction with eosinophilia and systemic symptoms (DRESS) [h], angioedema, pseudoporphyria, erythema multiforme, psoriasis, drug eruption
Frequency Not Known (Cannot be Estimated from the Available Data)	cutaneous lupus erythematosus*, drug reaction with eosinophilia and systemic symptoms*[,h]
Musculoskeletal, connective tissue and bone disorders	
Common	Back pain
Uncommon	Arthritis
Frequency Not Known (Cannot be Estimated from the Available Data)	periostitis
Renal and urinary disorders	
Common	Renal failure acute, haematuria
Uncommon	Renal tubular necrosis, proteinuria, nephritis
General disorders and administration site conditions	
Very common	Pyrexia
Common	Chest pain, face oedema [j], asthenia, chills
Uncommon	Infusion site reaction, influenza-like illness
Investigations	
Common	Blood creatinine increased
Uncommon	Blood urea increased, blood cholesterol increased

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

* ADR identified post-marketing

a: Includes febrile neutropenia and neutropenia b: Includes immune thrombocytopenic purpura. c: Includes nuchal rigidity and tetany. d: Includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy. e: Includes akathisia and parkinsonism. f: See Section 4.8 Adverse effects (undesirable effects), Visual Impairment. g: Prolonged optic neuritis has been reported post-marketing. See Section 4.4 Special warnings and precautions for use. h: See Section 4.4 Special warnings and precautions for use. i: Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity. j: Includes periorbital oedema, lip oedema and oedema mouth.

Description of selected adverse reactions

Visual impairment

In clinical trials, visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, colour blindness, cyanopsia, eye disorder, halo vision, night blindness, oscillopsia, photopsia, scintillating scotoma, visual acuity reduced, visual brightness, visual field defect, vitreous floaters and xanthopsia) with voriconazole were very common. These visual impairments 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 impairments were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairments 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 warnings 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 adverse reactions

Dermatological reactions were very common in patients treated with voriconazole in clinical trials, 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 severe cutaneous reactions (SCARs), including Stevens-Johnson syndrome (uncommon), toxic epidermal necrolysis (rare), drug reaction with eosinophilia and systemic symptoms (DRESS) which was reported post-marketing (rare)

and erythema multiforme (rare) during treatment with voriconazole (see Section 4.4 Special warnings and precautions for use).

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 warnings and precautions for use).

Dermatological adverse reactions potentially related to phototoxicity (pseudoporphyria, cheilitis, and cutaneous lupus erythematosus) are also reported with voriconazole. Sun avoidance and photoprotection are recommended for all patients. If phototoxicity occurs, voriconazole discontinuation and dermatological evaluation should be considered (see Section 4.4 Special warnings and precautions for use).

There have been post-marketing reports of cutaneous lupus erythematosus and squamous cell carcinoma (SCC) (see Section 4.4 Special warnings and precautions for use).

Liver function tests

The overall incidence of transaminase increases >3 x ULNin the voriconazole clinical program was 18.0% (319/1,768) in adults and 25.8% (73/283) in paediatric subjects who received voriconazole for pooled therapeutic and prophylaxis use. 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 associated with cases of serious hepatic toxicity, in patients with other serious underlying conditions. This includes cases of jaundice, hepatitis and hepatic failure leading to death (see Section 4.4 Special warnings and precautions for use).

Infusion-related reactions

During infusion of the intravenous formulation of voriconazole in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnoea, faintness, nausea, pruritus and rash have occurred. Symptoms appeared immediately upon initiating the infusion (see Section 4.4 Special warnings and precautions for use).

Paediatric use

The safety of voriconazole was investigated in 288 paediatric patients aged 2 to <12 years (169) and 12 to <18 years (119) who received voriconazole for prophylaxis (183) and therapeutic use (105). The adverse event profile of these 288 paediatrics was similar to adults. A higher frequency of liver enzyme elevations reported as adverse events was observed in paediatric patients as compared to adults.

Post-marketing experience

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.

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 ± 24 mL/min.In an overdose, haemodialysis may assist in the removal of voriconazole and hydroxypropylbetadex from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Voriconazole is a triazole antifungal agent. Voriconazole's primary mode of action is the inhibition of fungal cytochrome P450-mediated 14α-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 14α-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. marneffei*, *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 µg/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 [a] (microgram/mL)			**Disk Diffusion [b] (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

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 *in vitro* results with clinical response was based upon 249 baseline *Candida* species isolates from six clinical trials (Pfaller *et. al.*, 2006, J. Clin. Microbiol., 819-826).

[a] CLSI Microbroth dilution reference method M27; [b] Disc diffusion reference method M44.

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

QC strain	Minimum Inhibitory Concentration (MIC in µg/mL)		Disk Diffusion (Zone diameter in mm)
	at 24 hours	at 48 hours	
***Candida parapsilosis* ATCC 22019^**	0.016-0.12	0.03-0.25	28-37
***Candida krusei* ATCC 6258^**	0.06-0.5	0.12-1.0	16-25
***Candida albicans* ATCC 90028^**	ϕ	ϕ	31-42

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

^ ATCC is a registered trademark of the American Type Culture Collection.

Clinical experience

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

Aspergillus infections – efficacy in aspergillosis patients with poor prognosis

Voriconazole has *in vitro* fungicidal activity against *Aspergillus* spp. 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, multicenter study in 277 immunocompromised patients treated for 12 weeks. 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. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12 hours. Median duration of IV voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of PO voriconazole therapy was 76 days (range 2-232 days).

A satisfactory global response (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53% of voriconazole-treated patients compared to 31% of patients treated with comparator. The 84-day survival rate for voriconazole was statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of voriconazole for both time to death and time to discontinuation due to toxicity.

This study confirmed findings from an earlier, prospectively designed study where there was a positive outcome in subjects with risk factors for a poor prognosis, including graft versus host disease, and, in particular, cerebral infections (normally associated with almost 100% mortality).

The studies included cerebral, sinus, pulmonary and disseminated aspergillosis in patients with bone marrow and solid organ transplants, haematological malignancies, cancer and AIDS.

Serious invasive Candida infections – efficacy in non-neutropenic patients

The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidaemia was demonstrated in an open,

comparative study. Three hundred and seventy (370) non-neutropenic patients (above 12 years of age) with documented candidaemia 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. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medication was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of *Candida* from blood and infected deep tissue sites at 12 weeks after the end of therapy (EOT). In this analysis a successful response was seen in 41% of patients in both treatment arms 12 weeks after EOT.

Patients who did not have an assessment 12 weeks after EOT were counted as failures. In a secondary analysis, which utilised DRC assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT) voriconazole and the regimen of amphotericin B followed by fluconazole had successful response rates of 65% and 71%, respectively.

Serious refractory Candida infections

The study comprised 55 patients with serious refractory systemic *Candida* infections (including candidemia, disseminated and other invasive candidiasis) where prior antifungal treatment, particularly with fluconazole, had been ineffective. Successful response was seen in 24 patients (15 complete, 9 partial responses). In fluconazole-resistant non-*albicans* species, a successful outcome was seen in 3/3 *C. krusei* (complete responses) and 6/8 *C. glabrata* (5 complete, 1 partial response) infections. The clinical efficacy data were supported by limited susceptibility data.

Other serious rare fungal pathogens

Voriconazole was shown to be effective against the following rare fungal pathogens:

Scedosporium spp. - Successful response to voriconazole therapy was seen in 16 of 28 patients (55%) with *S. apiospermum* and in 2 of 7 patients (29%) 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 (41%) patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with fusariosis had an infection caused by several organisms; two of them had a successful outcome.

The majority of patients receiving voriconazole treatment of the above-mentioned rare infections were intolerant of, or refractory to, prior antifungal therapy.

Primary prophylaxis of invasive fungal infections – Efficacy in allogeneic hematopoietic 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. 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 was 96 days for voriconazole and 68 days for itraconazole in the MITT group.

Success rates and other secondary endpoints are presented in the table below:

Study Endpoints	**Voriconazole N=224**	**Itraconazole N=241**	**Difference in proportions and the 95% confidence interval (CI)**	**P-Value**
Success at day 180*	109 (48.7%)	80 (33.2%)	16.4% (7.7%, 25.1%)**	0.0002**
Success at day 100	121 (54.0%)	96 (39.8%)	15.4% (6.6%, 24.2%)**	0.0006**
Completed at least 100 days of study drug prophylaxis	120 (53.6%)	94 (39.0%)	14.6% (5.6%, 23.5%)	0.0015
Survived to day 180	184 (82.1%)	197 (81.7%)	0.4% (-6.6%, 7.4%)	0.9107
Developed proven or probable IFI to day 180	3 (1.3%)	5 (2.1%)	-0.7% (-3.1%, 1.6%)	0.5390
Developed proven or probable IFI to day 100	2 (0.9%)	4 (1.7%)	-0.8% (-2.8%, 1.3%)	0.4589
Developed proven or probable IFI while on study drug	0	3 (1.2%)	-1.2% (-2.6%, 0.2%)	0.0813

* Primary endpoint of the study.

** Difference in proportions, 95% CI and p-values obtained after adjustment for randomisation.

Pathogens responsible for breakthrough IFI in voriconazole & itraconazole groups	
Voriconazole*	*Aspergillus fumigatus*, *Candida krusei*, *Candida parapsilosis*
Itraconazole**	*Aspergillus fumigatus*, *Aspergillus* species

* Breakthrough IFIs occurred after study drug discontinuation.

** Three out of five cases occurred after study drug discontinuation.

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. 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 was 95.5 days in the MITT group.

Proven or probable IFIs developed in 7.5% (3/40) of patients during the first year after HSCT, including one candidemia, 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).

Duration of treatment

Intravenous and oral voriconazole allows flexibility in patient care and the possibility of prolonged treatment where indicated. In clinical trials, 714 patients received voriconazole therapy for greater than 12 weeks, with 155 subjects receiving voriconazole for over 6 months.

Clinical studies in children

Fifty-three paediatric patients aged 2 to <18 years were treated with voriconazole in two prospective, open-label, non-comparative, multi-center clinical trials. One study enrolled 31 patients with possible, proven or probable invasive aspergillosis (IA), of whom 14 patients had proven or probable IA and were included in the MITT efficacy analyses. The second study enrolled 22 patients with invasive candidiasis including candidaemia (ICC), and oesophageal candidiasis (EC) requiring either primary or salvage therapy, of whom 17 were included in the MITT efficacy analyses. Of the total of 31 patients included in the MITT analyses, 14 were 2 to <12 years old (5 patients with IA and 9 with ICC or EC) and 17 were 12 to <18 years old (9 patients with IA and 8 with ICC and EC). The overall rates of global response were 64.3% (9/14) at 6 weeks for patients with IA, 85.7% (6/7) at EOT for patients with ICC and 70% (7/10) at EOT for patients with EC. In subjects with IA, the success rate was 40% (2/5) for patients 2 to <12 years and 77.8% (7/9) for patients 12 to <18 years of age.

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 ≥60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec.

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_τ) (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. The oral maintenance dose of 200 mg (or 100 mg for patients less than 40 kg) achieves a voriconazole exposure similar to 3 mg/kg IV. A 300 mg (or 150 mg for patients less than 40 kg) oral maintenance dose achieves an exposure similar to 4 mg/kg IV. 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.

Long-term safety of hydroxypropylbetadex in humans is limited to 21 days (250 mg/kg/day).

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_{τ} of the tablets are reduced by 34% and 24% respectively, and C_{max} and AUC_{τ} of the suspension are reduced by 58% and 37%, 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_{τ}) 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.

Pharmacokinetics in special patient groups

Gender

In an oral multiple dose study, C_{max} and AUC_{τ} 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_{τ} were observed between healthy elderly males and healthy elderly females (≥ 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.

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.

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 Dose 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.

In patients with normal renal function, the pharmacokinetic profile of hydroxypropylbetadex, an ingredient of voriconazole intravenous formulation, has a

short half-life of 1 to 2 hours and demonstrates no accumulation following successive daily doses. In healthy subjects and in patients with mild to severe renal insufficiency, the majority (>85%) of an 8 g dose of hydroxypropylbetadex is eliminated in the urine. In subjects with mild, moderate and severe renal impairment, half-life values were increased over normal values by approximately two-, four- and six-fold, respectively. In these patients, successive infusions may result in accumulation of hydroxypropylbetadex until steady state is reached. Hydroxypropylbetadex is removed by hemodialysis, with a clearance of 37.5 ± 24 mL/min.

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_{τ} 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 Dose and method of administration).

Elderly

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

The recommended intravenous dose in paediatric patients is based on a population pharmacokinetic analysis of data pooled from 82 immunocompromised paediatric patients aged 2 to <12 years old who were evaluated in three pharmacokinetic studies (examining single intravenous doses of 3 and 4 mg/kg twice daily, multiple intravenous doses of 3, 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. A comparison of the paediatric and adult population pharmacokinetic data indicated that in order to obtain comparable exposures to those obtained in adults following intravenous maintenance doses of 4 mg/kg twice daily, intravenous maintenance doses of 7 mg/kg twice daily are required in paediatric patients. The higher intravenous maintenance dose in paediatric patients relative to adults reflects the higher elimination capacity in paediatric patients due to a greater liver mass to body mass ratio.

In order to obtain comparable exposures to those obtained in adults following intravenous maintenance doses of 3 mg/kg twice daily, intravenous maintenance doses

of 4 mg/kg twice daily are required in paediatric patients. Based on the population pharmacokinetic analysis, no loading dose or dosage adjustment according to age is warranted in patients aged 2 to <12 years old.

The recommended oral dose in paediatrics is based on a population pharmacokinetic analysis data obtained from 47 immunocompromised paediatric patients aged 2 to <12 years old who were evaluated in a pharmacokinetic study examining multiple oral suspension doses of 4 to 6 mg/kg twice daily. A comparison of the paediatric and adult population pharmacokinetic data indicated that in order to obtain comparable exposures to those obtained in adults following a maintenance dose of 200 mg twice daily, the same dose of 200 mg of oral solution twice daily is required in paediatric patients, independent of body weight. In paediatric patients there is a general trend towards low bioavailability at lower body weights and high bioavailability at higher body weights (towards the extent demonstrated in adults). The estimated bioavailability in paediatric patients following oral administration (POS) was 44.6%. Based on the population pharmacokinetic analysis, no dosage adjustment according to age or weight is warranted in patients aged 2 to <12 years old at the 200 mg bid oral solution dosing regimen. A loading dose is not indicated in paediatric patients.

A comparison of the paediatric and adult population pharmacokinetic data indicated that the predicted total exposure (AUC_{τ}) in children following administration of a 9 mg/kg IV loading dose was comparable to that in adults following a 6 mg/kg IV loading dose. The predicted total exposures in children following IV maintenance doses of 4 and 8 mg/kg twice daily were comparable to those in adults following 3 and 4 mg/kg IV twice daily, respectively. The predicted total exposure in children following an oral maintenance dose of 9 mg/kg (maximum of 350 mg) twice daily was comparable to that in adults following 200 mg oral twice daily. An 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.

The higher intravenous maintenance dose in paediatric patients relative to adults reflects the higher elimination capacity in paediatric patients due to a greater liver mass to body mass ratio.

Oral bioavailability may however be limited in paediatric patients with malabsorption and very low body weight for their age. In that case, intravenous voriconazole administration is recommended.

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.

5.3 PRECLINICAL SAFETY DATA

Repeated-dose toxicity studies with voriconazole indicated the liver to be the target organ. Hepatotoxicity occurred at plasma exposures similar to those obtained at therapeutic doses in humans, in common with other antifungal agents. In rats, mice and dogs, voriconazole also induced minimal adrenal changes. Conventional studies of safety pharmacology, genotoxicity or carcinogenic potential did not reveal a special hazard for humans.

In reproduction studies, voriconazole was shown to be teratogenic in rats and embryotoxic in rabbits at systemic exposures equal to those obtained in humans with therapeutic doses. In the pre- and post-natal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labor and produced dystocia with consequent maternal mortality and reduced peri-natal survival of pups. The effects on parturition are probably mediated by species-specific mechanisms, involving reduction of estradiol levels, and are consistent with those observed with other azole antifungal agents. Voriconazole administration induced no impairment of male or female fertility in rats at exposures similar to those obtained in humans at therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Voriconazole – AFT powder for injection contains hydroxypropylbetadex, sodium chloride and hydrochloric acid.

6.2 INCOMPATIBILITIES

Blood products and concentrated electrolytes

Voriconazole must not be infused concomitantly with any blood product or any short-term infusion of concentrated solution of electrolytes, even if the two infusions are running in separate lines. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of voriconazole therapy (see Section 4.4 Special warnings and precautions for use, Cardiovascular).

Intravenous solutions containing (non-concentrated) electrolytes

Voriconazole can be infused at the same time as other intravenous solutions containing (non-concentrated) electrolytes, but must be infused through a separate line.

Total parenteral nutrition (TPN)

Voriconazole can be infused at the same time as total parenteral nutrition, but must be infused in a separate line. If infused through a multiple-lumen catheter, TPN needs to be administered using a different port from the one used for voriconazole.

Voriconazole must not be diluted with 4.2% Sodium bicarbonate. Compatibility with other concentrations is unknown.

Voriconazole – AFT powder for injection must not be mixed with other medicinal products except those mentioned in Section 4.2 Method of administration, powder for injection.

Also see Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

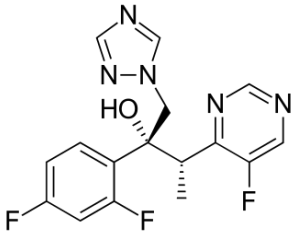
Voriconazole – AFT powder for injection is supplied in a single use glass vial. One glass vial is packed in a carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOSHEMICAL PROPERTIES

Chemical structure



Voriconazole is designated chemically as (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H -1,2,4-triazol-1-yl)-2-butanol with an empirical formula of $C_{16}H_{14}F_3N_5O$ and a molecular weight of 349.3.

CAS number

137234-62-9

7 MEDICINE CLASSIFICATION

S4 – Prescription only medicine

8 PRODUCT OWNER

AFT Pharmaceuticals Ltd.

129 Hurstmere Road

Takapuna, Auckland, New Zealand