1. NAME OF THE MEDICINAL PRODUCT

Healol Voriconazole 200 mg powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg voriconazole.

After reconstitution with 19 mL water for injection or 19 mL of 9 mg/mL (0.9%) sodium chloride for infusion, each mL contains 10 mg of voriconazole.

Excipient(s) with known effects: Each vial contains 215.6 mg ~ 228.0 mg of sodium.

Each vial contains 1621.5 mg ~ 1707.4 mg of cyclodextrin.

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

3. PHARMACEUTICAL FORM

Powder for solution for infusion

Product Description Before Reconstitution: white or almost white lyophilized cake or powder
Product Description After Reconstitution: a clear solution
Product Description further dilution: a clear solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Voriconazole is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

Treatment of invasive aspergillosis;

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

Treatment of serious *Candida* infections including esophageal candidiasis;

Treatment of candidemia in non-neutropenic patients and the following *Candida* infections: disseminated infection in skin and infections in abdomen, kidney, bladder wall and wounds;

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

Prevention of breakthrough of fungal infections in febrile high-risk neutropenic patients.

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 haematopoietic stem cell transplantation.

Voriconazole should be administered primarily to immunocompromised patients with progressive, possibly life-threatening infections.

4.2 Posology and method of administration

Voriconazole requires reconstitution and dilution (see Section 6.6) prior to administration as an intravenous infusion. Voriconazole powder for solution for infusion is not recommended for bolus injection.

It is recommended that voriconazole be administered at a maximum rate of 3 mg/kg per hour over 1 to 3 hours.

Blood products and concentrated electrolytes
Voriconazole must not be infused concomitantly with any blood product or any short-term infusion of concentrated electrolytes, even if the two infusions are running in separate intravenous lines (or cannulas). Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of voriconazole therapy (see Section 4.4).

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 (see Section 6.2).

Use in adults
Therapy must be initiated with the specified intravenous loading dose regimen of voriconazole to achieve adequate plasma concentrations on Day 1. Intravenous treatment should be continued for at least 7 days before switching to oral treatment (see Section 5.1). Once the patient is clinically improved and can tolerate medication given by mouth, the oral tablet form or oral suspension form of voriconazole may be utilized. On the basis of the high oral bioavailability (96%), switching between intravenous and oral administration is appropriate when clinically indicated (see Section 5.2).

Detailed information on dosage recommendations is provided in the following table

	Intravenous
Loading Dose Regimen for All Indications (first 24 hours)	6 mg/kg every 12 hours
Maintenance Dose (after first 24 hours) Prevention of breakthrough infections	3 mg/kg every 12 hours
Fluconazole-resistant serious invasive *Candida*/Invasive aspergillosis/Scedosporium and Fusarium infections[a]/Prophylaxis of invasive fungal infections	4 mg/kg every 12 hours
Candidemia in non-neutropenic patients and other deep tissue Candida infections	3-4 mg/kg every 12 hours[b]
Esophageal candidiasis	Not evaluated

a. In the pivotal clinical study of invasive aspergillosis, the median duration of IV voriconazole therapy was 10 days (range 2-85 days). The median duration of oral voriconazole therapy was 76 days (2-232 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.

Dosage adjustment

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 maintenance dose to a minimum of 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 intravenously every 12 hours (see Sections 4.4 and 4.5).

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
In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, sulphobutylether β-cyclodextrin sodium (SBECD), 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.

Voriconazole is hemodialyzed with a clearance of 121 mL/min. A four-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

The intravenous vehicle, SBECD, is hemodialyzed with a clearance of 55 mL/min.

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). 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.

Use in pediatrics
Use in children (2 to <12 years) and young adolescents (12 to 14 years and <50 kg)
The recommended dosing regimen is as follows:

	Intravenous
Loading Dose Regimen (first 24 hours)	9 mg/kg every 12 hours
Maintenance Dose (after first 24 hours)	8 mg/kg twice daily

Note: Based on a population pharmacokinetic analysis in 112 immunocompromised pediatric patients aged 2 to <12 years and 26 immunocompromised adolescents aged 12 to <17 years.

It is recommended to initiate the therapy with intravenous regimen, and oral regimen should be considered only after there is a significant clinical improvement. It should be noted that an 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.

Safety and effectiveness in pediatric patients below the age of 2 years has not been established (see Section 5.1). Therefore, voriconazole is not recommended for children less than 2 years of age. Use in pediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied (see Sections 4.8 and 5.2).

Use in all other adolescents (12 to 14 years and ≥50 kg; 15 to 16 years regardless of body weight)
Voriconazole should be dosed as adults.

Dosage adjustment
If patient response is inadequate, the dose may be increased by 1 mg/kg steps. If patients are unable to tolerate treatment, reduce the dose by 1 mg/kg steps.

Prophylaxis in adults and children
Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. It may only be continued up to 180 days after transplantation in case of continuing immunosuppression or graft versus host disease (GvHD) (see Section 5.1).

Dosage
The recommended dosing regimen for prophylaxis is the same as for treatment in the respective age groups. Please refer to the treatment tables above.

Duration of prophylaxis
The safety and efficacy of voriconazole use for longer than 180 days has not been adequately studied in clinical trials.

4.3 Contraindications

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

Coadministration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide, quinidine or ivabradine with voriconazole is contraindicated since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsade de pointes* (see Section 4.5).

Coadministration of voriconazole and sirolimus is contraindicated, since voriconazole has been shown to significantly increase plasma concentrations of sirolimus in healthy subjects (see Section 4.5).

Coadministration of voriconazole with rifabutin, rifampicin, carbamazepine, long-acting barbiturates (e.g., phenobarbital) and St John's Wort is contraindicated since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see Section 4.5).

Coadministration of standard doses of voriconazole with efavirenz doses of 400 mg QD 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, for lower doses see Section 4.4).

Coadministration of voriconazole with high-dose ritonavir (400 mg and above twice daily) is contraindicated because ritonavir significantly decreased plasma voriconazole concentrations in healthy subjects at this dose (see Section 4.5, for lower doses, see Section 4.4).

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).

Coadministration 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).

Coadministration of voriconazole with tolvaptan is contraindicated because voriconazole may significantly increase plasma concentrations of tolvaptan (see Section 4.5).

Coadministration 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).

Coadministration 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).

4.4 Special warnings and precautions for use

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

Infusion-related reactions: Infusion-related reactions, predominantly flushing and nausea have been observed during administration of the intravenous formulation of voriconazole. Depending on the severity of symptoms, consideration should be given to stopping treatment (see Section 4.8).

Cardiac adverse events: Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During clinical development and post- marketing surveillance, there have been rare cases of *torsade de pointes* in patients taking voriconazole. These cases involved seriously ill patients with multiple confounding 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)

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be monitored and corrected, if necessary, prior to initiation of and during voriconazole therapy (see Section 4.2).

A study has been conducted in healthy volunteers which examined the effect on QT interval of single doses of voriconazole up to 4 times the usual daily dose. 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 (see Section 5.1).

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 hematological 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.

Monitoring of hepatic function: 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).

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

Renal adverse events: 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.

Monitoring of renal function: Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine (see Section 4.2).

Monitoring of pancreatic function: Adults and children with risk factors for acute pancreatitis (e.g., recent chemotherapy, hematopoietic stem cell transplantation [HSCT]), should be monitored for development of pancreatitis during voriconazole treatment.

Dermatological adverse events: During treatment with voriconazole, patients have developed severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal (see Section 4.8). If a patient develops severe cutaneous adverse reaction voriconazole should be discontinued.

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).

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). 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). 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 of the skin (SCC): In patients with photosensitivity skin reactions and additional risk factors, squamous cell carcinoma of the skin (including cutaneous SCC in situ, or Bowen's disease) 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.

Pediatric use: Safety and effectiveness in pediatric subjects below the age of two years has not been established (see Section 5.1). Voriconazole is indicated for pediatric patients aged two years or older. A higher frequency of liver enzyme elevations was observed in the pediatric population (see Section 4.8). Hepatic function should be monitored in both children and adults. Oral bioavailability may be limited in pediatric patients 2 to 12 years with malabsorption and very low body weight for age. In that case, intravenous voriconazole administration is recommended.

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

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).

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Co-administration of oral voriconazole and oral fluconazole resulted in a significant increase in Cmax and AUCτ of voriconazole in healthy subjects. 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 (see Section 4.5).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate): When voriconazole is coadministered with efavirenz the dose of 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 4.2, 4.3 and 4.5).

Glasdegib (CYP3A4 substrate): Coadministration of voriconazole is expected to increase glasdegib plasma concentrations and increase the risk of QTc prolongation (see Section 4.5). If concomitant use cannot be avoided, frequent ECG monitoring is recommended.

Tyrosine kinase inhibitors (CYP3A4 substrate): Coadministration 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).

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).

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, for higher doses see Section 4.3).

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).

Short acting opiates (CYP3A4 substrate): Reduction in the dose of alfentanil, fentanyl and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered when co-administered with voriconazole (see Section 4.5). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is co-administered with voriconazole and in an independent published study, concomitant use of voriconazole with fentanyl resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl by 1.4-fold, frequent monitoring for opiate-associated adverse events (including a longer respiratory monitoring period) may be necessary.

Long acting opiates (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).

4.5 Interaction with other medicinal products and other forms of interaction

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 metabolized by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide and ivabradine) coadministration 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, AUCτ 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 coadministration
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, coadministered with voriconazole 200 mg BID	Efavirenz C_{max} ↑ 38% Efavirenz AUC_τ ↑ 44% Voriconazole C_{max} ↓ 61% Voriconazole AUC_τ ↓ 77%	Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is **contraindicated** (see Section 4.3).
Efavirenz 300 mg QD, coadministered with voriconazole 400 mg BID*	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%	Voriconazole may be coadministered 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).
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]*		**Contraindicated** (see Section 4.3)
300 mg QD	Voriconazole C_{max} ↓ 69% Voriconazole AUC_τ ↓ 78%	
300 mg QD (coadministered with voriconazole 400 mgBID)*	Rifabutin C_{max} ↑ 195% Rifabutin AUC_τ ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104% Voriconazole AUC_τ ↑ 87%	
Rifampicin (600 mg QD) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓ 93% Voriconazole AUC_τ ↓ 96%	**Contraindicated** (see Section 4.3)
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]*		
High dose (400 mg BID)	Ritonavir C_{max} and AUC_τ ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUC_τ ↓ 82%	Co-administration of voriconazole and high doses of ritonavir (400 mg and higher BID) is **contraindicated** (see Section 4.3).
Low dose (100 mg BID)*	Ritonavir C_{max} ↓ 25% Ritonavir AUC_τ ↓13% Voriconazole C_{max} ↓ 24% Voriconazole AUC_τ ↓ 39%	Coadministration 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 (coadministered 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.
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 forvoriconazole-associated adverse events is recommended if voriconazole is used sequentially after fluconazole.
Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]*		Concomitant use ofvoriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended.
300 mg QD	Voriconazole C_{max} ↓ 49% Voriconazole AUC_τ ↓ 69%	
300 mg QD (co-administered with voriconazole 400 mg BID)*	Phenytoin C_{max} ↑ 67% Phenytoin AUC_τ ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 34% Voriconazole AUC_τ ↑ 39%	Phenytoin may be coadministered 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.
Flucloxacillin *[CYP450 inducer]*	Although not studied, flucloxacillin has been reported to significantly decrease plasma voriconazole concentrations	If concomitant administration of voriconazole with flucloxacillin cannot be avoided, monitor for potential 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.
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]*	Maximum increase in prothrombin time was approximately 2-fold	Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.
Other oral coumarins (including but not limitedto: phenprocoumon, acenocoumarol) *[CYP2C9 and CYP3A4 substrates]*	Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.	
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.
Benzodiazepines *[CYP3A4 substrates]*		Dose reduction of benzodiazepines should be considered.
Midazolam (0.05 mg/kg IV single dose)	In an independent published study, Midazolam $AUC_{0-\infty}$ ↑ 3.7-fold	
Midazolam (7.5 mg oral single dose)	In an independent published study, Midazolam C_{max} ↑ 3.8-fold Midazolam $AUC_{0-\infty}$ ↑10.3-fold	
Other benzodiazepines (including but not limited to: triazolam, alprazolam)	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.	
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	Coadministration 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.	Coadministration 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. When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.
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. When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.
Long Acting Opiates *[CYP3A4 substrates]*		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.
Oxycodone (10 mg single dose)	In an independent published study, Oxycodone C_{max} ↑ 1.7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3.6-fold	
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)	S-Ibuprofen C_{max} ↑ 20% S-Ibuprofen $AUC_{0-\infty}$ ↑ 100%	Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.
Diclofenac (50 mg single dose)	Diclofenac C_{max} ↑ 114% Diclofenac $AUC0_{0-\infty}$ ↑ 78%	
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%	No dose adjustment of voriconazole is recommended.
	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.	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.
Short Acting Opiates *[CYP3A4 substrates]*		Dose reduction of alfentanil, fentanyl and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be
Alfentanil (20 µg/kg single dose, with concomitant naloxone)	In an independent published study, Alfentanil $AUC_{0-\infty}$ ↑ 6-fold	
Fentanyl (5 µg/kg single dose)	In an independent published study, Fentanyl $AUC_{0-\infty}$ ↑1.34-fold	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.
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]*	Voriconazole C_{max} and AUCτ ↔	No dose adjustment
Azithromycin (500 mg QD)	Voriconazole C_{max} and AUCτ ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	
Mycophenolic acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_τ ↔	No dose adjustment
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

4.6 Fertility, Pregnancy and lactation

Pregnancy
No adequate information on the use of voriconazole in pregnant women is available.

Studies in animals have shown reproductive toxicity at high doses (see Section 5.3). The potential risk to humans is unknown.

Voriconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus.

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

Lactation
The excretion of voriconazole into breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with voriconazole.

Fertility
In an animal study, no impairment of fertility was demonstrated in male and female rats (see Section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety profile of voriconazole in adults is based on an integrated safety database of more than 2,000 subjects (1,603 adult patients in therapeutic studies). This represents a heterogeneous population, containing patients with hematological malignancy, HIV infected patients with esophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidemia 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 2,000 subjects in voriconazole clinical trials.

The table below includes all causality adverse reactions in 1,873 adults from pooled therapeutic (1,603) and prophylaxis (270) studies. The most commonly reported adverse events were visual impairment, liver function test abnormal, pyrexia, rash, vomiting, nausea, diarrhea, headache, peripheral edema 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 analyzed by age, race, or gender.

(Adults in combined therapeutic and prophylaxis studies): ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC.

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Frequency Not Known (cannot be estimated from the available data)
Infections and infestations		sinusitis	Pseudomembranous colitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)					squamous cell carcinoma (including cutaneous SCC in situ, or Bowen's disease) *[,g]
Blood and lymphatic system disorders		agranulocytosis[a], pancytopenia, thrombocytopenia[b], leukopenia, anaemia	bone marrow failure, lymphadenopathy, eosinophilia	disseminated intravascular coagulation	
Immune system disorders			hypersensitivity	anaphylactoid reaction	
Endocrine disorders			adrenal insufficiency, hypothyroidism	hyperthyroidism	
Metabolism and nutrition disorders	oedema peripheral	hypoglycaemia, hypokalaemia, hyponatraemia*			
Psychiatric disorders		depression, hallucination, anxiety, insomnia, agitation, confusional state			
Nervous system disorders	headache	syncope, tremor, hypertonia[e], paraesthesia, somnolence, dizziness	brain oedema, encephalopathy[c], extrapyramidal disorder[d], neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia	hepatic encephalopathy, Guillain-Barré syndrome, nystagmus	
Eye disorders	visual impairment[h]	retinal haemorrhage	optic nerve disorder[f], papilloedema[g], oculogyric crisis, diplopia, scleritis, blepharitis	optic atrophy, corneal opacity	
Ear and labyrinth disorders			hypoacusis, vertigo, tinnitus		

Cardiac disorders		arrhythmia supraventricular, tachycardia, bradycardia	ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia	*torsade de pointes*, atrioventricular block complete, bundle branch block, nodal rhythm	
Vascular disorders		hypotension, phlebitis	thrombophlebitis, lymphangitis		
Respiratory, thoracic and mediastinal disorders		acute respiratory distress syndrome, pulmonary oedema			
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea	cheilitis, dyspepsia, constipation, gingivitis	peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis		
Hepatobiliary disorders	liver function test abnormal	jaundice, jaundice cholestatic, hepatitis[i]	hepatic failure, hepatomegaly, cholecystitis, cholelithiasis		
Skin and subcutaneous tissue disorders	rash	dermatitis exfoliative, alopecia, rash maculo-papular, pruritus	Stevens-Johnson syndrome[g], photosensitivity reaction, purpura, urticaria, eczema	toxic epidermal necrolysis[g], angioedema, pseudoporphy-ria, erythema multiforme, psoriasis, drug eruption	cutaneous lupus erythematosus*, drug reaction with eosinophilia and systemic symptoms[*,g]
Musculoskeletal and connective tissue disorders		back pain	arthritis		
Renal and urinary disorders		renal failure acute, haematuria	renal tubular necrosis, proteinuria, nephritis		
General disorders and	pyrexia	chest pain, face oedema[j], asthenia, chills	infusion site reaction,		
administration site conditions			influenza like illness		
Investigations		blood creatinine increased	blood urea increased, blood cholesterol increased		

*ADR identified post-marketing.
[a] Includes febrile neutropenia and neutropenia.
[b] Includes immune thrombocytopenic purpura.
[c] Includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy.
[d] Includes akathisia and parkinsonism.
[e] Includes nuchal rigidity and tetany.
[f] Prolonged optic neuritis has been reported post-marketing. See Section 4.4.
[g] See Section 4.4.
[h] See "Visual impairments" paragraph in Section 4.8.
[i] Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.
[j] Includes periorbital oedema, lip oedema, and oedema mouth.

Visual Impairments
In clinical trials, visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, color 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 levels and/or doses.

There have been post-marketing reports of prolonged visual adverse events (see Section 4.4).

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 administration 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 paracoccidioidomycosis. Voriconazole had no clinically relevant effect on visual function as assessed by testing of visual acuity, visual fields, color 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 during the first week of therapy and resolved during continued voriconazole therapy.

Dermatological 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 adverse reactions (SCARs), including Stevens-Johnson syndrome (uncommon), toxic epidermal necrolysis (rare), drug reaction with eosinophilia and systemic symptoms (DRESS) which was reported post-marketing (not known), and erythema multiforme (rare) during treatment with voriconazole (see Section 4.4).

If patients develop a rash they should be monitored closely and voriconazole discontinued if lesions progress. Patients receiving long-term voriconazole therapy have developed photosensitive skin reactions (see Section 4.4).

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).

Liver Function Tests
The overall incidence of transaminase increases >3 x ULN (not necessarily comprising an adverse event) in the voriconazole clinical program was 18.0% (319/1,768) in adults and 25.8% (73/283) in pediatric subjects who received voriconazole for pooled therapeutic and prophylaxis use. Liver function test abnormalities may be associated with higher plasma levels 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.

Pediatric Use
The safety of voriconazole was investigated in 288 pediatric 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 in these 288 pediatric patients was similar to that in adults. A higher frequency of liver enzyme elevations reported as adverse events (14.2% transaminases increased in pediatrics compared to 5.3% in adults) was observed in pediatric patients as compared to adults. The safety of voriconazole was investigated in additional pediatric patients aged 2 to <12 years who were observed in compassionate use programs (158 pediatric patients). The adverse event profile in these pediatric patients was similar to that observed in adults.

Post-marketing data suggest there might be a higher occurrence of skin reactions in the pediatric population compared to adults.

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

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

4.9 Overdose

In clinical trials there were three cases of accidental overdose. All occurred in pediatric 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 be symptomatic and supportive.

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. In an overdose, hemodialysis may assist in the removal of voriconazole and SBECD from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mode of action
Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450 mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Pharmacokinetic/Pharmacodynamic relationship
In 10 therapeutic studies, the median for the average and maximum plasma concentrations in individual subjects across the studies was 2,425 ng/mL (inter-quartile range 1,193 to 4,380 ng/mL) and 3,742 ng/mL (inter-quartile range 2,027 to 6,302 ng/mL), respectively. A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy in therapeutic studies was not found.

Pharmacokinetic-pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances.

Microbiology
In vitro, voriconazole displays broad-spectrum antifungal activity with 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* fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium* which have limited susceptibility to existing antifungal agents.

Clinical efficacy (with partial or complete response, see below under Clinical Experience) has been demonstrated for *Aspergillus* spp. including *A. flavus, A. fumigatus, A. terreus, A. niger, A. nidulans, Candida* spp., including *C. albicans, C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis* and limited numbers of *C. dubliniensis, C. inconspicua* and *C. guilliermondii, Scedosporium* spp., including *S. apiospermum, S. prolificans* and *Fusarium* spp.

Other treated fungal infections (with often partial or complete response) 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 mcg/mL.

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

Breakpoints
Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. 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.

The species most frequently involved in causing human infections include *C. albicans, C. parapsilosis, C. tropicalis, C. glabrata,* and *C. krusei*, all of which usually exhibit minimum inhibitory concentrations (MICs) of less than 1 mg/L for voriconazole.

However, the *in vitro* activity of voriconazole against *Candida* species is not uniform. Specifically, for *C. glabrata*, the MICs of voriconazole for fluconazole-resistant isolates are proportionally higher than are those of fluconazole-sus-ceptible isolates. Therefore, every attempt should be made to identify *Candida* to species level. If antifungal susceptibility testing available, the MIC results may be interpreted using breakpoint criteria.

<u>European Committee on Antimicrobial Susceptibility Testing (EUCAST) Breakpoints</u>

Candida species: The interpretive standards for voriconazole against *Candida* species are applicable only to tests performed using EUCAST microbroth dilution reference method for minimum inhibitory concentrations (MICs) read at 24 hours.

<u>Breakpoint criteria established by EUCAST</u>

Candida and Aspergillus Species	Minimal Inhibitory Concentration (MIC) breakpoint (mg/L)	
	≤S (Susceptible)	>R (Resistant)
Candida albicans[1]	0.06	0.25
Candida dubliniensis[1]	0.06	0.25
Candida glabrata	Insufficient evidence (IE)	IE
Candida krusei	IE	IE
Candida parapsilosis[1]	0.125	0.25
Candida tropicalis[1]	0.125	0.25
Candida guilliermondii[2]	IE	IE
Non-species related breakpoints for Candida[3]	IE	IE
Aspergillus fumigatus[4]	1	1
Aspergillus nidulans[4]	1	1
Aspergillus flavus	IE[5]	IE[5]
Aspergillus niger	IE[5]	IE[5]
Aspergillus terreus	IE[5]	IE[5]
Non-species related breakpoints[6]	IE	IE

[1] Strains with MIC values above the Susceptible/Intermediate (S/I) breakpoint are rare or not yet reported. The identification and antifungal susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant. A clinical response of 76% was achieved in infections caused by the species listed below when MICs were lower than or equal to the epidemiological cut-offs. Therefore, wild type populations of *C. albicans, C. dubliniensis, C. parapsilosis* and *C. tropicalis* are considered susceptible.
[2] The epidemiological cut-off values (ECOFFs) for these species are in general higher than for *C. albicans*.
[3] Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific *Candida* species. They are for use only for organisms that do not have specific breakpoints.
[4] Area of technical uncertainty (ATU) is 2. Report as R with the following comment: "In some clinical situations (non-invasive infections forms) voriconazole can be used provided sufficient exposure is ensured".
[5] The ECOFFs for these species are in general one two-fold dilution higher than for *A. fumigatus*.
[6] Non-species related breakpoints have not been determined.

<u>Clinical and Laboratory Standards Institute (CLSI) Breakpoints</u>

<u>Breakpoint criteria established by CLSI</u>

<u>Susceptibility Testing Methods</u>
Aspergillus species and other filamentous fungi: No interpretive criteria have been established for *Aspergillus* species and other filamentous fungi.

<u>*Candida* species:</u> The interpretive standards for voriconazole against *Candida* species are applicable only to tests performed using Clinical and Laboratory Standards Institute (CLSI) microbroth dilution reference method M27 for MIC read at 48 hours or disk diffusion reference method M44 for zone diameter read at 24 hours.

<u>Broth Dilution Techniques:</u> Quantitative methods are used to determine antifungal MICs. These MICs provide estimates of the susceptibility of *Candida* species to antifungal agents. MICs should be determined using a standardized procedure at 48 hours. Standardized procedures are based on a microdilution method (broth) with standardized inoculums concentrations and standardized concentrations of voriconazole powder. The MIC values should be interpreted according to the criteria provided in the table below.

<u>Diffusion Techniques:</u> Qualitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of *Candida* species to an antifungal agent. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper discs impregnated with 1 microgram of voriconazole to test the susceptibility of yeasts to voriconazole. Disc diffusion interpretive criteria are also provided in the table below.

Susceptibility Interpretive Criteria for Voriconazole

	Broth Dilution at 48 hours (MIC in µg/mL)			Disk Diffusion at 24 hours (Zone diameters in mm)		
	Susceptible (S)	Susceptible -dose dependent (S-DD)	Resistant (R)	Susceptible (S)	Susceptible -dose dependent (S-DD)	Resistant (R)
Voriconazole	⩽1.0	2.0	⩾4.0	⩾17	14-16	⩽13

Note 1: Shown are the breakpoints (µg/mL) for voriconazole against *Candida* species. If MICs are measured using a scale that yields results falling between categories, the next higher category is implied. Thus, an isolate with a voriconazole MIC of 1.5 µg/mL would be placed in the S-DD category.

The susceptible category implies that isolates are inhibited by the usually achievable concentrations of antifungal agent tested when the recommended dosage is used for the site of infection. The susceptible-dose dependent category implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are physiologically concentrated or when a high dosage of drug is used. The resistant category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Quality Control
Standardized susceptibility test procedures require the use of quality control organisms to control the technical aspects of the test procedures. Standard voriconazole powder and 1 µg discs should provide the following range of values noted in the table below.

NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

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

	Broth Dilution (MIC in µg/mL)		Disk Diffusion (Zone diameter in mm) @ 24-hour
	@24-hour	@48-hour	
QC Strain			
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	*	*	31-42

* 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.

<u>*Aspergillus* Infections – efficacy in aspergillosis patients with poor prognosis</u>
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/bron-choscopic 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 favor 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, hematological malignancies, cancer and AIDS.

<u>Serious invasive *Candida* infections – efficacy in non-neutropenic patients</u>
The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidemia was demonstrated in an open, comparative study. Three hundred and seventy (370) non-neutropenic patients with documented candidemia (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), voriconazole and the regimen of amphotericin B followed by fluconazole had response rates of 65% and 71%, respectively.

<u>Serious refractory *Candida* infections</u>
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-resis-tant 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.

<u>Other serious rare fungal pathogens</u>
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.

<u>Primary Prophylaxis of Invasive Fungal Infections – Efficacy in hematopoietic stem cell transplant (HSCT) recipients without prior proven or probable invasive fungal infection (IFI)</u>

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 randomization

<u>Secondary Prophylaxis of IFI – Efficacy in HSCT recipients with prior proven or probable IFI</u>

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 pediatric 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 esophageal 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, randomized, 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

General Pharmacokinetic Characteristics
The pharmacokinetics of voriconazole have been characterized 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 hematopoietic 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 an approximately 2.5-fold increase in exposure (AUCτ). 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 (see table below).

Voriconazole Pharmacokinetic Parameters in Adults Receiving Different Dosing Regimens

Geometric mean (CV%)[a]	6 mg/kg IV (loading dose)	3 mg/kg IV Q12h	4 mg/kg IV Q12h	400 mg Oral (loading dose)	200 mg Oral Q12h	300 mg Oral Q12h
n	35	23	40	17	48	16
AUC_{12} (µg · h/mL)	13.9 (32)	13.7 (53)	33.9 (54)	9.31 (38)	12.4(78)	34.0 (53)
C_{max} (µg/mL)	3.13 (20)	3.03 (25)	4.77 (36)	2.30 (19)	2.31(48)	4.74 (35)
C_{min} (µg/mL)	--	0.46 (97)	1.73 (74)	--	0.46 (120)	1.63 (79)

[a] Parameters were estimated based on non-compartmental analysis from 5 pharmacokinetic studies. AUC_{12} = area under the curve over 12 hour dosing interval, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration.

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 (e.g., 6 mg/kg IV every 12 hours on day 1 followed by 3 mg/kg IV every 12 hours; 400 mg oral every 12 hours on day 1 followed by 200 mg oral every 12 hours). 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 is estimated to be 96%. Bioequivalence was established between the 200 mg tablet and the 40 mg/mL oral suspension when administered as a 400 mg every 12 hours loading dose followed by a 200 mg every 12 hours maintenance dose. When multiple doses of voriconazole are administered with high fat meals, C_{max} and AUC_τ are reduced by 34% and 24%, respectively, when administered as a tablet and by 58% and 37%, respectively, when administered as the oral suspension.

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 plays a key role 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 (AUCτ) 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 following 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), after tablet dosing. 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 a similar study, after dosing with the oral suspension, the mean AUC for healthy young females was 45% higher than in healthy young males, whereas the mean C_{max} was comparable between genders. The steady-state trough voriconazole concentra-tions (C_{min}) seen in females were 100% and 91% higher than in males receiving the tablet and the oral suspension, respectively.

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_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. However, the safety profile of voriconazole in young and elderly patients wassimilar and, therefore, no dosage adjustment is necessary for the elderly.

Pediatrics
The recommended doses in children and adolescent patients are based on a population pharmacokinetic analysis of data pooled from 112 immunocompromised pediatric patients aged 2 to <12 years and 26 immunocompromised adolescent patients aged 12 to ≤17 years. Multiple intravenous doses of 3, 4, 6, 7 and 8 mg/kg twice daily and multiple oral doses (using the powder for oral suspension) of 4 mg/kg, 6 mg/kg and 200 mg twice daily were evaluated in 3 pediatric pharmacokinetic studies. Intravenous loading doses of 6 mg/kg IV twice daily on day 1 followed by 4 mg/kg intravenous dose twice daily and 300 mg oral tablets twice daily were evaluated in one adolescent pharmacokinetic study. Larger inter-subject variability was observed in pediatric patients compared to adults.

A comparison of the pediatric and adult population pharmacokinetic data indicated that the predicted total exposure (AUCτ) 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 pediatric patients relative to adults reflects the higher elimination capacity in pediatric patients due to a greater liver mass to body mass ratio.

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

Voriconazole exposures in the majority of adolescent patients were comparable to those in adults receiving the same dosing regimens. However, lower voriconazole exposure was observed in some young adolescents with low body weight compared to adults. It is likely that these subjects may metabolise voriconazole more similarly to children than to adults. Based on the population pharmacokinetic analysis, 12- to 14-year-old adolescents weighing less than 50 kg should receive children's doses (see Section 4.2).

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. See dosing and monitoring recommendations under Sections 4.2 and 4.4.

In patients with moderate to severe renal dysfunction (serum creatinine levels ≥220 micromol/L (2.5 mg/dL), accumulation of the intravenous vehicle, SBECD, occurs. See dosing and monitoring recommendations under Sections 4.2 and 4.4.

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, AUCτ 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). For dosing information, refer to use in patients with hepatic impairment Section 4.2.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulphobutylether Beta Cyclodextrin Sodium (SBECD)
Water for Injections

6.2 Incompatibilities

<u>**Blood products and concentrated electrolytes**</u>
Voriconazole must not be infused concomitantly with any blood product or any short-term infusion of concentrated electrolytes, even if the two infusions are running in separate intravenous lines (or cannulas). Electrolyte disturbances, such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of voriconazole therapy (see Sections 4.2 and 4.4).

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

<u>**Total parenteral nutrition (TPN)**</u>
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 Infusion. Compatibility with other concentrations is unknown.

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf-life

Unopened vial: 24 months
Shelf life after reconstitution and further dilution: Store at 2 ℃ to 8 ℃ for 24 hours.

6.4 Special precautions for storage

Unopened vial: Store below 30℃
Storage condition after reconstitution and further dilution: Store at 2 ℃ to 8 ℃ for 24 hours.

6.5 Nature and contents of container

The container closure chosen for drug product is a 30 mL type I clear glass vial with a 20mm chlorobutyl rubber stopper and 20mm or 20.2mm aluminum-plastic overseal. One glass vial is packed in a carton along with package insert.

6.6 Special precautions for disposal and other handling

Voriconazole is supplied in single use vials. The vial contents are reconstituted with 19 mL of Water for Injections to obtain a clear solution containing 10 mg/mL of voriconazole and an extractable volume of 20 mL. Discard the vial if vacuum does not pull the diluent into the vial. For administration, the required volume of the reconstituted solution (table below) is added to a recommended compatible infusion solution (detailed below) to obtain, where appropriate, a final voriconazole solution containing 0.5-5 mg/mL.

Dilution

Voriconazole must be infused over 1 to 3 hours, at a concentration of 5 mg/mL or less. Therefore, the required volume of the 10 mg/mL voriconazole concentrate should be further diluted as follows (appropriate diluents listed below):

1. Calculate the volume of 10 mg/mL voriconazole concentrate required based on the patient's weight (see table below).

2. In order to allow the required volume of voriconazole concentrate to be added, withdraw and discard at least an equal volume of diluent from the infusion bag or bottle to be used. The volume of diluent remaining in the bag or bottle should be such that when the10 mg/mL voriconazole concentrate is added, the final concentration is not less than 0.5 mg/mL nor greater than 5 mg/mL.

3. Using a suitable size syringe and aseptic technique, withdraw the required volume of voriconazole concentrate from the appropriate number of vials and add to the infusion bag or bottle. DISCARD PARTIALLY USED VIALS.

The final voriconazole solution must be infused over 1 to 3 hours at a maximum rate of 3 mg/kg per hour.

Required Volumes of 10 mg/mL HEALOL VORICONAZOLE Concentrate

Body Weight (kg)	Volume of HEALOL VORICONAZOLE Concentrate (10 mg/mL) required for:				
	3 mg/kg dose (number of vials)	4 mg/kg dose (number of vials)	6 mg/kg dose (number of vials)	8 mg/kg dose (number of vials)	9 mg/kg dose (number of vials)
10	-	4.0 mL (1)	-	8.0 mL (1)	9.0 mL (1)
15	-	6.0 mL (1)	-	12.0 mL (1)	13.5 mL (1)
20	-	8.0 mL (1)	-	16.0 mL (1)	18.0 mL (1)
25	-	10.0 mL (1)	-	20.0 mL (1)	22.5 mL (2)
30	9.0 mL (1)	12 mL (1)	18 mL (1)	24.0 mL (2)	27.0 mL (2)
35	10.5 mL (1)	14 mL (1)	21 mL (2)	28.0 mL (2)	31.5 mL (2)
40	12.0 mL (1)	16 mL (1)	24 mL (2)	32.0 mL (2)	36.0 mL (2)
45	13.5 mL (1)	18 mL (1)	27 mL (2)	36.0 mL (2)	40.5 mL (3)
50	15.0 mL (1)	20 mL (1)	30 mL (2)	40.0 mL (2)	45.0 mL (3)
55	16.5 mL (1)	22 mL (2)	33 mL (2)	44.0 mL (3)	49.5 mL (3)
60	18.0 mL (1)	24 mL (2)	36 mL (2)	48.0 mL (3)	54.0 mL (3)
65	19.5 mL (1)	26 mL (2)	39 mL (2)	52.0 mL (3)	58.5 mL (3)
70	21.0 mL (2)	28 mL (2)	42 mL (3)	-	-
75	22.5 mL (2)	30 mL (2)	45 mL (3)	-	-
80	24.0 mL (2)	32 mL (2)	48 mL (3)	-	-
85	25.5 mL (2)	34 mL (2)	51 mL (3)	-	-
90	27.0 mL (2)	36 mL (2)	54 mL (3)	-	-
95	28.5 mL (2)	38 mL (2)	57 mL (3)	-	-
100	30.0 mL (2)	40 mL (2)	60 mL (3)	-	-

Voriconazole is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2℃ to 8℃, unless reconstitution has taken place in controlled and validated aseptic conditions.

The reconstituted solution can be diluted with:

0.9% Sodium Chloride Intravenous Infusion
Compound Sodium Lactate Intravenous Infusion
5% Glucose and Compound Sodium Lactate Intravenous Infusion
5% Glucose and 0.45% Sodium Chloride Intravenous Infusion
5% Glucose Intravenous Infusion
5% Glucose in 20 mEq Potassium Chloride Intravenous Infusion
0.45% Sodium Chloride Intravenous Infusion
5% Glucose and 0.9% Sodium Chloride Intravenous Infusion

The compatibility of voriconazole with diluents other than described above or in Section 6.2 is unknown.

6.7 Special Precautions for disposal

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

7. PRODUCT REGISTRATION HOLDER AND MANUFACTURER

Product Registration Holder:
Healol Pharmaceuticals Sdn. Bhd.,
74-3, Jalan Wangsa Delima 6, KLSC Wangsa Maju, 53300 Kuala Lumpur, Malaysia.

Manufacturer:
Hainan Poly Pharm. Co., Ltd.
Guilinyang Economic, Development Area Haikou, Hainan, 571127 China

8. DATE OF REVISION

07 April 2026