Professional Information

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

VORZOL® IV 200 mg (powder for solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VORZOL IV 200 mg vial contains 200 mg voriconazole. When reconstituted as directed, each ml contains 10 mg voriconazole.

Sugar free.

Excipient with known effect:

Each vial contains 3 380,8 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White to almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of invasive aspergillosis.
- Treatment of serious invasive infections caused by *Candida* spp. (including *C. krusei*).
- Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.
- Prevention of breakthrough of fungal infections in febrile high-risk patients (allogeneic bone marrow transplants, relapsed leukaemia patients) where liposomal amphotericin B cannot be used.

4.2 Posology and method of administration

Posology

It is recommended that VORZOL be administered at a maximum rate of 3 mg/kg per hour over 1 to 2 hours.

For reconstitution directions refer to section 6.6: Special precautions for disposal and other handling.

Treatment

Use in Adults:

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

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 (for the first 24 hours)
Maintenance dose Regimen after first 24 hours	3 mg/kg every 12 hours

Prevention of breakthrough infections	
Invasive aspergillosis, serious *Candida* infections, *Scedosporium/Fusarium* infections	4 mg/kg every 12 hours

Dosage adjustment

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

If patients are unable to tolerate treatment at these higher doses, reduce the intravenous dose to the original maintenance dose, 3 mg/kg every 12 hours.

Phenytoin may be co-administered with VORZOL if the maintenance dose of VORZOL is increased to 5 mg/kg intravenously every 12 hours (see Section 4.6).

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, SBECD, occurs. Oral VORZOL should be administered to these patients, unless an assessment of the risk benefit to the patient justifies the use of intravenous VORZOL. Serum creatinine levels should be closely monitored in these patients and, if increases occur, consideration should be given to changing to oral VORZOL therapy.

VORZOL is haemodialysed with a clearance of 121 ml/min. A four-hour haemodialysis session does not remove a sufficient amount of VORZOL to warrant dose adjustment.

The intravenous vehicle, SBECD, is haemodialysed 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), but continued monitoring of liver function tests for future elevations is recommended.

VORZOL has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

VORZOL has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice. Patients with hepatic impairment must be carefully monitored for medicine toxicity (see also section 4.8).

Use in children

Safety and effectiveness in paediatric subjects below the age of 2 years has not been established. Therefore, VORZOL is not recommended for children less than 2 years of age.

Limited data are currently available to determine the optimal posology. However, the following regimen has been used in paediatric studies.

Children aged 2 to < 12 years

The recommended dosing regime is as follows:

	Intravenous
Loading dose Regimen (first 24 hours)	6 mg/kg every 12 hours (for the first 24 hours)

Maintenance Dose (after first 24 hours)	4 mg/kg every 12 hours

The pharmacokinetics and tolerability of higher doses have not been characterised in paediatric populations.

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

Duration of Treatment

Treatment duration depends on the patient's clinical and mycological response. The duration of VORZOL treatment in the clinical studies ranged from 12 weeks to more than 6 months.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Co-administration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide, quinidine or ivabradine with VORZOL is contraindicated since increased plasma concentrations of these medicinal products can lead to QTc prolongation and occurrences of *Torsades de pointes* (see section 4.5).
- Co-administration of VORZOL with rifampicin, carbamazepine and phenobarbital is contraindicated, since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see section 4.5).
- Co-administration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects. Voriconazole also significantly increases efavirenz plasma concentrations (see section 4.5, for lower doses see section 4.4).

- Co-administration of VORZOL with high dose ritonavir (400 mg and above twice daily) is contraindicated because ritonavir significantly decreased plasma VORZOL concentrations in healthy subjects at this dose (see section 4.5).
- Co-administration 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).
- Co-administration of VORZOL and sirolimus is contraindicated, since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see section 4.5).
- Co-administration of VORZOL with naloxegol, a CYP3A4 substrate, since increased plasma concentration of naloxegol can precipitate opioid withdrawal symptom (see sectin 4.5) is contraindicated, since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see section 4.5).
- Coadministration of voriconazole with tolvaptan since strong CYP3A4 inhibitors such as voriconazole significantly increase plasma concentrations of tolvaptan (see section 4.5).
- Coadministration of voriconazole with lurasidone since significant increases in lurasidone exposure have the potential for serious adverse reactions.
- Co-administration of VORZOL and rifabutin is contraindicated since VORZOL is likely to increase plasma concentrations of rifabutin significantly (see section 4.5).
- Co-administration of VORZOL with St. John's Wort (see section 4.5).
- Co-administration with venetoclax at initiation and during 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).
- Patients with prolonged QT syndrome.
- Pregnancy and lactation.
- Severe impairment of hepatic function.

4.4 Special warnings and precautions for use

Women of child-bearing potential

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

Hypersensitivity

Caution should be used in prescribing VORZOL to patients with hypersensitivity to other azoles (see also section 4.8).

Cardiovascular

Voriconazole, as contained in VORZOL, has been associated with QTc interval prolongation. There have been cases of torsades de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic cardiomyopathy, hypokalaemia and concomitant medicinal products that may have been contributory. VORZOL is contraindicated in patients with prolonged QT syndrome. Voriconazole should be administered with caution to patients with other potentially prodysrhythmic conditions, such as:

• Congenital or acquired QTc prolongation.

• Cardiomyopathy, in particular when heart failure is present.

• Sinus bradycardia.

• Existing symptomatic dysrhythmias.

• Concomitant medicinal products that are known to prolong QTc interval.

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2).

Infusion-related reactions

During infusion of the intravenous formulation of VORZOL in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnoea, faintness, nausea, pruritus, and rash have occurred. Symptoms appeared immediately upon initiating the infusion. Depending on the severity of the symptoms, consideration should be given to stopping treatment (see section 4.8).

Liver function tests

The overall incidence of clinically significant transaminase abnormalities in the VORZOL clinical programme was 13,4 % of subjects treated with VORZOL. Liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests are either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

VORZOL has been infrequently associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, and rare cases of hepatitis and hepatic failure leading to death.

Hepatic toxicity

In clinical trials, there have been cases of serious hepatic reactions during treatment with voriconazole (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of

hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy (see section 4.8).

Monitoring of hepatic function

Patients receiving VORZOL 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 VORZOL and at least weekly for the first month of treatment. Treatment duration should be as short as possible; however, if based on the benefit-risk assessment the treatment is continued (see section 4.2), 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, VORZOL should be discontinued, unless the medical judgment of the risk-benefit of the treatment for the patient justifies continued use.

Monitoring of hepatic function should be carried out in both children and adults.

Visual adverse events

There have been post-marketing reports of irreversible visual adverse events, including optic neuritis and papilloedema.

These visual disturbances may be transient and fully reversible, with the majority spontaneously resolving within 60 minutes.

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).

In clinical trials, voriconazole, as contained in VORZOL, treatment-related visual disturbances were very common. In these studies, approximately 21 % of subjects experienced altered/enhanced visual

perception, blurred vision, colour vision change or photophobia. These visual disturbances were transient and fully reversible, with the majority spontaneously resolving within 60 minutes. There was evidence of attenuation with repeated doses of voriconazole, as contained in VORZOL. The visual disturbance were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual disturbances may be associated with higher plasma concentrations and/or doses.

There have been post-marketing reports of irreversible visual adverse events.

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

The long-term effect of voriconazole, as contained in VORZOL (median 169 days; range 5 - 353 days) on visual function was evaluated in subjects with paracoccidioidomycosis. Voriconazole, as contained in VORZOL, had no clinically relevant effect on visual function as assessed by testing of visual acuity, visual fields, colour vision and contrast sensitivity. There were no signs of retinal toxicity. 17/35 voriconazole, as contained in VORZOL, 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, as contained in VORZOL, therapy.

Patients with renal adverse reactions

Acute renal failure has been observed in severely ill patients undergoing treatment with voriconazole, as contained in VORZOL. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medicinal products and have concurrent conditions that may result in decreased renal function (see section 4.8).

Monitoring of renal function

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

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. Inpatients 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 and intranasal corticosteroids) 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

Long term exposure (treatment or prophylaxis) greater than 180 days (6 months) requires careful assessment of the benefit-risk balance and the doctor should therefore consider the need to limit the exposure to VORZOL (see section 4.2 and 5.1).

Monitoring of pancreatic function

Patients, especially children, with risk factors for acute pancreatitis (e.g., recent chemotherapy, haematopoietic stem cell transplantation [HSCT]), should be monitored closely during VORZOL treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.

Dermatological adverse events

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with voriconazole, as contained in VORZOL. If a patient develops an exfoliative cutaneous reaction, VORZOL should be discontinued.

In addition, voriconazole, as contained in VORZOL, has been associated with photosensitivity skin reaction. It is recommended that patients avoid intense or prolonged exposure to direct sunlight during VORZOL treatment. In patients with photosensitivity skin reactions and additional risk factors, squamous cell carcinoma of the skin and melanoma have been reported during long-term therapy. If a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma, VORZOL discontinuation should be considered.

Dermatological reactions were common in patients treated with voriconazole, as contained in VORZOL, 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 rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with voriconazole, as contained in

VORZOL. If patients develop a rash they should be monitored closely and VORZOL discontinued if lesions progress.

Photosensitivity reactions have been reported, especially during long-term therapy.

Periostitis

Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients. If a patient develops skeletal pain and radiologic findings compatible with periostitis, VORZOL discontinuation should be considered after multidisciplinary advice.

Paediatric use

Safety and effectiveness in paediatric subjects below the age of two years has not been established. The safety of voriconazole, as contained in VORZOL, was investigated in 245 paediatric patients aged 2 to < 12 years who were treated with voriconazole, as contained in VORZOL, in pharmacokinetic studies (87 paediatric patients) and in compassionate use programs (158 paediatric patients). The adverse event profile of these 245 paediatric patients was similar to adults. Post-marketing data show a higher occurrence of skin reactions in the paediatric population compared to adults.

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

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 co-administration. Dose reduction of methadone may be needed (see section 4.5).

Short-acting opiates (CYP3A4 substrate)

Reduction in the dose of alfentanil and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 should be considered when co-administered with VORZOL (see section 4.5). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is co-administered with VORZOL, frequent monitoring for opiate-associated adverse events (including a longer respiratory monitoring period) may be necessary.

Oxycodone (CYP3A4 substrate)

Reduction in the dose of oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g., hydrocodone) should be considered when co-administered with voriconazole. Frequent monitoring for opiate-associated adverse reactions may be necessary (see section 4.5).

Ciclosporin and tacrolimus (CYP3A4 substrates)

Clinically significant medicinal interactions with VORZOL may occur in patients who are receiving treatment with ciclosporin or tacrolimus (see section 4.5).

Naloxegol (CYP3A4 substrates)

Co-administration of voriconazole and naloxegol is not recommended because voriconazole is expected to significantly increase naloxegol concentrations. Currently there are insufficient data to all dosing recommendations of naloxegol in this situation (see section 4.5).

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

Careful monitoring of phenytoin levels is recommended when phenytoin is co-administered with VORZOL. Concomitant use of VORZOL and phenytoin should be avoided.

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Co-administration of VORZOL and low-dose ritonavir (100 mg twice daily) should be avoided (see sections 4.3 and 4.5).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

When VORZOL is co-administered with efavirenz, the dose of VORZOL should be increased to 400 mg every 12 hours, and the dose of efavirenz should be decreased to 300 mg every 24 hours (see sections 4.2, 4.3 and 4.5).

QT interval prolongation

Voriconazole may prolong the QT interval without a clear relationship to plasma concentration. VORZOL should not be used concomitantly with other medicines which prolong the QT interval.

Glasdegib (CYP3A4 substrate)

Coadministration of voriconazole is expected to increase glasdegib plasma concentrations and increase the risk of QTcprolongation (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 tyrosinekinase inhibitor plasma concentrations and the risk of adverse reactions. If concomitant use cannot be avoided, dosereduction of the tyrosine kinase inhibitor and close clinical monitoring is recommended (see section 4.5).

Rifabutin (Potent CYP450 inducer)

Concomitant use of voriconazole and rifabutin is contraindicated (see section 4.5).

Everolimus (CYP3A4 substrate, P-gp substrate)

Co-administration 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 C_{max} and AUC_{τ} 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 reactions is recommended if voriconazole is used sequentially after fluconazole (see section 4.5).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially “sodium free”.

4.5 Interaction with other medicines 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.

Unless otherwise specified, medicine 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 QTc interval. When there is also a potential for voriconazole to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide and ivabradine), co-administration is contraindicated (see below and section 4.3).

Interaction table

Interactions between voriconazole and other medicinal products are listed in the table below (once daily as “QD”, twice daily as “BID”, three times daily as “TID” and not determined as “ND”). The direction of the arrow for each pharmacokinetic parameter is based on the 90 % confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80-125 % range. The asterisk (*) indicates a two-way interaction. AUC_{τ}, AUC_t and $AUC_{0-\infty}$ represent area under the curve over a dosing interval, from time zero to the time with detectable measurement and from time zero to infinity, respectively.

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

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration of voriconazole and listed medicines**
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 (e.g., 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		When VORZOL is co-administered with efavirenz, the VORZOL

reverse transcriptase inhibitor) *[CYP450 inducer; CYP3A4 inhibitor and substrate]* Efavirenz 400 mg QD, co-administered with voriconazole 200 mg BID* Efavirenz 300 mg QD, co-administered with voriconazole 400 mg BID*	Efavirenz C_{max} ↑ Efavirenz AUC$_\tau$ ↑ Voriconazole C_{max} ↓ Voriconazole AUC$_\tau$ ↓ Compared to efavirenz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUC$_\tau$ ↑ Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ Voriconazole AUC$_\tau$ ↓	maintenance dose should be increased to 400 mg twice daily and the efavirenz dose should be reduced by 50 %, i.e. to 300 mg once daily. When voriconazole treatment is stopped, the initial dose of efavirenz should be restored (see section 4.2 and 4.4).
Ergot alkaloids (e.g., 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)

Rifabutin *[potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with voriconazole 350 mg BID)* 300 mg QD (co-administered with voriconazole 400 mg BID)*	 Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓ Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓ Rifabutin C_{max} ↑ Rifabutin AUC_{τ} ↑ Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ Voriconazole AUC_{τ} ↑	Concomitant use of voriconazole and Rifabutin is contraindicated.
Rifampicin (600 mg QD) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓	Contraindicated (see section 4.3)
Ritonavir (protease inhibitor) *[potent CYP450 inducer;* *CYP3A4 inhibitor and substrate]*	 Ritonavir C_{max} and AUC_{τ} ↔ Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓	 Co-administration of voriconazole and high doses of ritonavir (400 mg

High dose (400 mg BID) Low dose (100 mg BID)*	Ritonavir C_{max} ↓ Ritonavir AUC_{τ} ↓ Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓	and above BID) is contraindicated (see section 4.3). Co-administration of voriconazole and low-dose ritonavir (100 mg BID) should be avoided.
St. John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg TID (co-administered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole $AUC_{0-\infty}$↓	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.

Everolimus *[CYP3A4 substrate, P-gp substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	Co-administration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see section 4.4).
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.	Co-administration of voriconazole and naloxegol is not recommended, as there is insufficient data to allow dosing recommendations of naloxegol in this situation (see section 4.4).
Fluconazole (200 mg QD) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	Voriconazole C_{max} ↑ Voriconazole AUCτ ↑ Fluconazole C_{max} ND Fluconazole AUCτ ND	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.

Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]* 300 mg QD	Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓	Concomitant use of voriconazole and phenytoin should be avoided. Careful monitoring of phenytoin plasma levels is recommended.
300 mg QD (co-administered with voriconazole 400 mg BID)*	Phenytoin C_{max} ↑ Phenytoin AUC_{τ} ↑ Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ Voriconazole AUC_{τ} ↑	Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID (see section 4.2).
Letermovir *[CYP2C9 and CYP2C19 inducer]*	Voriconazole C_{max} ↓ Voriconazole AUC_{0-12} ↓ Voriconazole C_{12} ↓	If concomitant administration of voriconazole with letermovir cannot be avoided, monitor for loss of voriconazole effectiveness.
Glasdegib *[CYP3A4 substrate]*	Although not studied, voriconazole may increase the plasma concentrations of glasdegib and increase risk of QTc prolomgation.	If concomitant use cannot be avoided, frequent ECG monitoring is recommended (See section 4.4).
Tyrosine kinase inhibitors (e.g., axitinib, bosutinib,	Although not studied, voriconazole may increase	If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor is

cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) *[CYP3A4 substrates]*	plasma concentrations of tyrosine kinase inhibitors metabolised by CYP3A4.	recommended (see section 4.4).
Anticoagulants Warfarin (30 mg single dose, co-administered with 300 mg BID voriconazole) *[CYP2C9 substrate]* Other oral coumarins (e.g., phenprocoumon, acenocoumarol) *[CYP2C9 and CYP3A4 substrates]*	Maximum increase in prothrombin time was approximately 2-fold. Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.	Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.

Ivacaftor *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of ivacaftor with risk of increased adverse effects.	Dose reduction of ivacaftor is recommended.
Benzodiazepines *[CYP3A4 substrates]* Midazolam (0.05 mg/kg IV singledose) Midazolam (7.5 mg oral single dose) Other benzodiazepines (e.g.,triazolam, alprazolam)	In an independent published study, Midazolam $AUC_{0-\infty}$ ↑ 3.7-fold In an independent published study, Midazolam C_{max} ↑ 3.8-fold Midazolam $AUC_{0-\infty}$ ↑ 10.3-fold Although not studied clinically, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	Dose reduction of benzodiazepines should be considered.
Tolvaptan *[CYP3A4 substrate]*	Although not studied clinically, voriconazole is likely to significantly increase the plasma concentrations of tolvaptan.	If concomitant administration of voriconazole with tolvaptan cannot be avoided, dose reduction of tolvaptan is recommended.

Immunosuppressants *[CYP3A4 substrates]* Sirolimus (2 mg single dose)	In an independent published study, Sirolimus C_{max} ↑ Sirolimus $AUC_{0-\infty}$ ↑	Co-administration of voriconazole and sirolimus is contraindicated (see section 4.3).
Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin C_{max} ↑ Ciclosporin AUC_{τ} ↑	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 C_{max} ↑ Tacrolimus AUC_t ↑	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

Tacrolimus (0,1 mg/kg single dose)		associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.
Long-Acting Opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose)	In an independent published study, Oxycodone C_{max} ↑ Oxycodone $AUC_{0-\infty}$↑	Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse reactions may be necessary.
Methadone (32-100 mg QD) *[CYP3A4 substrate]*	R-methadone (active) C_{max} ↑ R-methadone (active) AUC_{τ} ↑ S-methadone C_{max} ↑ S-methadone AUC_{τ} ↑	Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc 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} ↑ S-Ibuprofen $AUC_{0-\infty}$ ↑ Diclofenac C_{max} ↑ Diclofenac $AUC_{0-\infty}$ ↑	Frequent monitoring for adverse reactions and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.

Diclofenac (50 mg single dose)		
Omeprazole (40 mg QD)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	Omeprazole C_{max} ↑ Omeprazole AUC$_{\tau}$ ↑ Voriconazole C_{max} ↑ Voriconazole AUC$_{\tau}$ ↑ The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicinal products.	No dose adjustment of voriconazole is recommended. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose be halved.
Oral Contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ethinylestradiol (1 mg/0,035 mg QD)	Ethinylestradiol C_{max} ↑ Ethinylestradiol AUC$_{\tau}$ ↑ Norethisterone C_{max} ↑ Norethisterone AUC$_{\tau}$ ↑ Voriconazole C_{max} ↑ Voriconazole AUC$_{\tau}$ ↑	Monitoring for adverse reactions related to oral contraceptives, in addition to those for voriconazole, is recommended.
Short-acting Opiates		Dose reduction of alfentanil, fentanyl and other short-acting opiates similar in structure to

[CYP3A4 substrates] Alfentanil (20 µg/kg single dose, with concomitant naloxone) Fentanyl (5 µg/kg single dose)	In an independent published study, Alfentanil $AUC_{0-\infty}$↑ In an independent published study, Fentanyl $AUC_{0-\infty}$↑	alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse reactions is recommended.
Statins (e.g., lovastatin) *[CYP3A4 substrates]*	Although not studied clinically, voriconazole is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis.	Dose reduction of statins should be considered.
Sulfonylureas (e.g., tolbutamide, glipizide, glyburide) *[CYP2C9 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of sulfonylureas and cause hypoglycaemia.	Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.

Vinca Alkaloids (e.g., 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 (e.g., 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 medicine toxicity and/or lack of efficacy, and dose adjustment may be needed.
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (e.g., delavirdine, nevirapine)* *[CYP3A4 substrates, inhibitors or*	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 an NNRTI.	Careful monitoring for any occurrence of medicine toxicity and/or lack of efficacy, and dose adjustment may be needed.

CYP450 inducers]		
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} ↑ Voriconazole AUC_{τ} ↑	No dose adjustment
Digoxin (0,25 mg QD) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUC_{τ} ↔	No dose adjustment
Indinavir (800 mg TID) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUC_{τ} ↔ Voriconazole C_{max} ↔ Voriconazole AUC_{τ} ↔	No dose adjustment

Macrolide antibiotics Erythromycin (1 g BID) *[CYP3A4 inhibitor]* Azithromycin (500 mg QD)	Voriconazole C_{max} and AUC τ ↔ Voriconazole C_{max} and AUC τ ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment
Mycophenolic acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_t ↔	No dose adjustment
Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	Prednisolone C_{max} ↑ Prednisolone $AUC_{0-\infty}$ ↑	No dose adjustment
Ranitidine (150 mg BID) *[increases gastric pH]*	Voriconazole C_{max} and AUCτ ↔	No dose adjustment

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data available on the use of VORZOL in pregnant women.

Studies in animals have shown reproductive toxicity and teratogenicity.

VORZOL must not be used during pregnancy.

Women of childbearing potential

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

Breastfeeding

The excretion of voriconazole into breast milk has not been investigated. Breastfeeding must be stopped on initiation of treatment with VORZOL.

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

VORZOL has moderate influence on the ability to drive and use machines. It 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.

4.8 Undesirable effects

Summary of safety profile

The safety profile of voriconazole in adults is based on an integrated safety database of patients who participated in clinical trials. This represents a heterogeneous population, containing patients with haematological malignancy, HIV- infected patients with oesophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidaemia or aspergillosis and healthy volunteers.

The most commonly reported adverse reactions were visual impairment, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema, liver function test abnormal, respiratory distress and abdominal pain.

The severity of the adverse reactions was generally mild to moderate. No clinically significant differences were seen when the safety data were analysed by age, race, or gender.

Tabulated list of adverse reactions

In the table below, all causality adverse reactions and their frequency categories, by system organ class, are listed.

Undesirable effects reported in subjects receiving voriconazole:

System Organ Class	***Frequent***	***Less frequent***	***Frequency unknown***	***Frequency not known (cannot be estimated from 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)
Blood and lymphatic system disorders	Agranulocytosis[1], pancytopenia, thrombocytopenia[2], 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, convulsion, syncope,	Brain oedema, encephalopathy[4], extrapyramidal disorder[5],	Hepatic encephalopathy, Guillain-Barre	

	tremor, hypertonia[3], paraesthesia, somnolence, dizziness	neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia	syndrome, nystagmus	
Eye disorders	Visual impairment[6], retinal haemorrhage	Optic nerve disorder[7], papilloedema[8], 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	Torsades de pointes, atrioventricular block complete, bundle branch block, nodal rhythm	

		prolonged, supraventricular tachycardia		
Vascular disorders	Hypotension, phlebitis	Thrombophlebitis, lymphangitis		
Respiratory, thoracic and mediastinal disorders	Respiratory distress[9], acute respiratory distress syndrome, pulmonary oedema			
Gastrointestinal disorders	Diarrhoea, vomiting, abdominal pain, nausea, cheilitis, dyspepsia, constipati	Peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis		

	on, gingivitis			
Hepatobiliary disorders	Liver function test abnormal, jaundice, jaundice cholestatic, hepatitis[10]	Hepatic failure, hepatomegaly, cholecystitis, cholelithiasis		
Skin and subcutaneous tissue disorders	Rash, dermatitis exfoliative, alopecia, rash maculo-papular, pruritus, erythema	Stevens-Johnson syndrome[8], phototoxicity, purpura, urticaria, dermatitis allergic, rash papular, rash macular, eczema	Toxic epidermal necrolysis[8], medicine reaction with eosinophilia and systemic symptoms (DRESS)[8], angioedema, actinic keratosis*, pseudoporphyria, erythema multiforme,	Cutaneous lupus erythematosus*, ephelides*, lentigo*

			psoriasis, medicine eruption	
Musculoskeletal and connective tissue disorders	Back pain	Arthritis		Periostitis*
Renal and urinary disorders	Renal failure acute, haematuria	Renal tubular necrosis, proteinuria, nephritis		
General disorders and administration site conditions	Pyrexia, chest pain, face oedema[11], asthenia, chills	Infusion site reaction, influenza like illness		
Investigations	Blood creatinine increased	Blood urea increased, blood cholesterol increased		

*ADR identified post-marketing

[1] Includes febrile neutropenia and neutropenia.

[2] Includes immune thrombocytopenic purpura.

[3] Includes nuchal rigidity and tetany.

[4] Includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy.

[5] Includes akathisia and parkinsonism.

[6] See “Visual impairments” paragraph in section 4.8.

[7] Prolonged optic neuritis has been reported post-marketing. See section 4.4.

[8] See section 4.4.

[9] Includes dyspnoea and dyspnoea exertional.

[10] Includes medicine-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.

[11] Includes periorbital oedema, lip oedema, and oedema mouth.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “*6.04 Adverse Drug Reaction Reporting Form*”, found online under SAHPRA’s publications: https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf.

Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

There is no known antidote to voriconazole.

Voriconazole is haemodialysed with a clearance of 121 ml/min. The intravenous vehicle, SBECD, is haemodialysed with a clearance of 55 ml/min. In an overdose, haemodialysis may assist in the removal of voriconazole and SBECD from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives.

Mode of action

Voriconazole is a broad spectrum triazole antifungal medicine. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P450-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.

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 medicines.

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.

5.2 Pharmacokinetic properties

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

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose from 200 mg twice daily to 300 mg twice daily leads to a 2,5-fold increase in exposure (AUC_τ). The oral maintenance dose of 200 mg (or 100 mg for patients less than 40 kg) achieves a voriconazole exposure similar to 3 mg/kg IV. A 300 mg (or 150 mg for patients less than 40 kg) oral maintenance dose achieves an exposure similar to 4 mg/kg IV. When the recommended intravenous or oral loading dose regimens are administered, plasma concentrations close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by Day 6 in the majority of subjects.

Absorption

Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96 %. When multiple doses of voriconazole are administered with high fat meals, C_{max} and AUCτ are reduced. 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 patients in a compassionate programme showed detectable voriconazole concentrations.

Biotransformation

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

The inter-individual variability of voriconazole pharmacokinetics is high.

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

Elimination

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

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

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

Pharmacokinetic-Pharmacodynamic Relationships

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.

Pharmacokinetics in special patient groups

Gender

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

In the clinical programme, 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 higher than in healthy young males (18-45 years). No significant differences in C_{max} and AUC_{τ} were observed between healthy elderly females (≥ 65 years) and healthy young females (18-45 years).

In the therapeutic studies no dosage adjustment was made on the basis of age. A relationship between plasma concentrations and age was observed. The safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly (see section 4.2).

Paediatric population

The recommended doses in children and adolescent patients are based on a population pharmacokinetic analysis found that average steady state plasma concentrations in children receiving a maintenance dose of 4 mg/kg every 12 hours were similar to those in adults receiving 3 mg/kg every 12 hours. Therefore, a maintenance dose of 4 mg/kg every 12 hours is recommended for children aged between 2 to 12 years of age.

Renal impairment

In patients with moderate to severe renal dysfunction (serum creatinine levels >2,5 mg/dl), accumulation of the intravenous vehicle, SBECD, occurs (see sections 4.2 and 4.4).

Hepatic impairment

After an oral single-dose (200 mg), AUC was 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 an oral multiple-dose study, AUC_{τ} was similar in subjects with moderate hepatic cirrhosis (Child-Pugh B) given a maintenance dose of 100 mg twice daily and subjects with normal hepatic function given 200 mg twice daily. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C) (see sections 4.2 and 4.4).]

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulfobutyl ether beta-cyclodextrin sodium (SBECD)

Nitrogen

6.2 Incompatibilities

The compatibility of VORZOL with diluents other than those described above is unknown (see below).

VORZOL must not be infused into the same line or cannula concomitantly with other medicine infusions, including parenteral nutrition. 4,2 % Sodium Bicarbonate Intravenous Infusion is not compatible with VORZOL and must not be used as a diluent. Compatibility with other concentrations is unknown.

Blood products and concentrated electrolytes

VORZOL 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 hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of VORZOL therapy.

Intravenous solutions containing (non-concentrated) electrolytes

VORZOL 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)

VORZOL 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 VORZOL.

6.3 Shelf life

Powder for solution for infusion

24 months when stored at or below 30 °C.

Ready for use preparation

Based on the present knowledge on the stability behaviour of the reconstituted product of VORZOL powder for solution for infusion the following storage conditions and use periods of the preparations are proposed:

Stability statement for concentrate

Diluents	*Concentration [mg/ml]*	*Use periods / Storage condition*
Sterile Water for Injections 0,9 % Sodium Chloride for Infusion	10	No more than (NMT) 24 hours after preparation at 2 °C to 8 °C

Stability statement for intravenous injections/infusions

Diluents	*Concentration [mg/ml]*	*Use periods / Storage condition*
9 mg/ml (0,9 %) Sodium Chloride	0,5 5	NMT 3 hours after preparation at 20 °C to 30 °C
Lactated Ringers		
5 % Sucrose and Lactated Ringers		

5 % Sucrose and 0,45 % Sodium Chloride		
5 % Sucrose		
5 % Sucrose and 20 mEq Potassium Chloride		
0,45 % Sodium Chloride		
5 % Sucrose and 0,9 % Sodium Chloride		

6.4 Special precautions for storage

Powder for solution for infusion

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Voriconazole powder for solution for infusion will be packed in single 25 ml clear, glass vials, type I, closed with red chlorobutyl rubber stoppers and sealed with aluminium flip-off seals with plastic disc. The sealed vial is packed in an outer cardboard carton.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

VORZOL requires reconstitution and dilution prior to administration as an intravenous infusion.

Not for bolus injection.

The vial contents are reconstituted with 19 ml of Water for Injection to obtain a clear solution containing 10 mg/ml of VORZOL and an extractable volume of 20 ml. For administration, the required volume of the reconstituted solution is added to a recommended compatible infusion solution (tabulated below) to obtain, where appropriate, a final VORZOL solution containing 0,5 - 5 mg/ml.

Required volumes of 10 mg/ml VORZOL concentrate:

Body weight	***3 mg/kg dose (number of vials)***	***4 mg/kg dose (number of vials)***	***6 mg/kg (number of vials)***
10	-	4,0 ml (1)	-
15	-	6,0 ml (1)	-
20	-	8,0 ml (1)	-
25	-	10,0 ml (1)	-
30	9,0 ml (1)	12,0 ml (1)	18,0 ml (1)
35	10,5 ml (1)	14,0 ml (1)	21,0 ml (2)
40	12,0 ml (1)	16,0 ml (1)	24,0 ml (2)
45	13,5 ml (1)	18,0 ml (1)	27,0 ml (2)

50	15,0 ml (1)	20,0 ml (1)	30,0 ml (2)
55	16,5 ml (1)	22,0 ml (2)	33,0 ml (2)
60	18,0 ml (1)	24,0 ml (2)	36,0 ml (2)
65	19,5 ml (1)	26,0 ml (2)	39,0 ml (2)
70	21,0 ml (2)	28,0 ml (2)	42,0 ml (3)
75	22,5 ml (2)	30,0 ml (2)	45,0 ml (3)
80	24,0 ml (2)	32,0 ml (2)	48,0 ml (3)
85	25,5 ml (2)	34,0 ml (2)	51,0 ml (3)
90	27,0 ml (2)	36,0 ml (2)	54,0 ml (3)
95	28,5 ml (2)	38,0 ml (2)	57,0 ml (3)
100	30,0 ml (2)	40,0 ml (2)	60,0 ml (3)

VORZOL does not contain an antimicrobial preservative. If the reconstituted solution is not used immediately, the reconstituted solution will remain suitable for its intended use for up to 24 hours, stored at 2 to 8 °C, if 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 VORZOL with diluents other than those described above is described in section 6.2.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz South Africa (Pty) Ltd.

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8 REGISTRATION NUMBER

49/20.1.7/1011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

30 May 2022

[1]Company Reg. No.: 1990/001979/07