Professional Information

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

VCIDE® 200 IV, 200 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg voriconazole.

After reconstitution, each ml contains 10 mg voriconazole.

Excipient with known effect:

Each vial contains 88,74 mg sodium.

Sugar free.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white lyophilised powder.

The prepared solution is clear and without visible particles.

Osmolality: 530 mOsmol/kg ± 10 %

pH 5,0 – 7,0

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

Adult dosage

Therapy should be initiated with the specified loading dose regimen of VCIDE to achieve plasma concentrations on day 1 that are close to steady-state. On the basis of the high oral bioavailability (96 %), switching between intravenous and oral administration is appropriate when clinically indicated.

Detailed information on dosage recommendations is provided in Table 1:

Table 1 Adult dosage recommendations

	Intravenous dose
Loading dose regimen for all indications (first 24 hours)	6 mg/kg every 12 hours (for the first 24 hours)
Maintenance dose (after first 24 hours) Prevention of breakthrough infections	3 mg/kg every 12 hours
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 VCIDE if the maintenance dose of VCIDE is increased to 5 mg/kg intravenously every 12 hours (see sections 4.4 and 4.5).

Efavirenz: When VCIDE is co-administered with adjusted doses of efavirenz, the maintenance dose of VCIDE should be increased to 400 mg every 12 hours (see sections 4.4 and 4.5).

Paediatric dosage

Children aged 2 to < 12 years

Limited data are available to determine the optimal posology. However, the regimen detailed in Table 2 has been used in paediatric studies:

Table 2 Children dosage

	Intravenous dose
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):

See adult dose.

Duration of treatment

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

Special populations

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, hydroxypropyl-beta-cyclodextrin (HP-beta-CD), occurs. Oral voriconazole should be administered to these patients, unless an assessment of the risk-benefit to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients and, if increases occur, consideration should be given to changing to oral voriconazole therapy (see section 5.2).

Voriconazole is haemodialysed with a clearance of 121 ml/min. A four-hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment. The intravenous vehicle, HP-beta-CD, 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.

No data are available on the use of voriconazole as in VCIDE in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

Voriconazole as in VCIDE 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 voriconazole toxicity (see section 4.8).

VCIDE is contraindicated in severe impairment of hepatic function (see section 4.3).

Paediatric population

Safety and effectiveness in paediatric patients below the age of 2 years have not been established. Therefore, VCIDE is not recommended for children less than 2 years of age.

Method of administration

VCIDE 200 IV requires reconstitution and dilution prior to administration as an intravenous infusion. For instructions on reconstitution and dilution of VCIDE before administration, see section 6.6.

VCIDE 200 IV should be administered at a maximum rate of 3 mg/kg per hour over 1 to 2 hours.

VCIDE 200 IV is not intended for bolus injection.

VCIDE 200 IV is intended for single use only.

4.3 Contraindications

- Hypersensitivity to voriconazole or to any of the excipients of VCIDE listed in section 6.1.
- Patients with prolonged QT- syndrome.
- Severe impairment of hepatic function.
- Co-administration with the following medicines:
    - CYP3A4 substrates such as astemizole, cisapride, pimozide or quinidine, since increased plasma concentrations of these medicines can lead to QTc prolongation and occurrences of *torsades de pointes* (see section 4.5)

- CYP3A4 substrates such as ergot alkaloids, e.g. ergotamine, dihydroergotamine, since increased plasma concentrations of these medicines can lead to ergotism (see section 4.5)
- Rifampicin, carbamazepine and phenobarbital (phenobarbitone), since these medicines are likely to decrease plasma voriconazole concentrations significantly (see section 4.5)
- Rifabutin, since voriconazole is likely to increase plasma concentrations of rifabutin significantly (see section 4.5)
- Ritonavir (high dose – 400 mg twice daily), because ritonavir significantly decreased plasma VCIDE concentrations in healthy persons at this dose (see section 4.5)
- Efavirenz (doses ≥ 400 mg/day). Co-administration of standard doses of voriconazole as in VCIDE with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy persons at these doses. Voriconazole as in VCIDE also significantly increases efavirenz plasma concentrations (see section 4.5)
- Sirolimus, since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see section 4.5)
- St. John's wort (see section 4.5)

- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

Women of childbearing potential

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

Hypersensitivity

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

***Infusion – related reaction**:*

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

Duration of IV treatment

The duration of treatment with the intravenous formulation should not be longer than 6 months.

Cardiovascular

VCIDE has been associated with QTc-interval prolongation. There have been cases of *torsades de pointes* in patients who had risk factors, such as a history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and who took some other medicines concomitantly (see section 4.5).

VCIDE should be administered with caution to patients with potentially pro-dysrhythmic conditions, such as:

- Congenital or acquired QTc prolongation.
- Cardiomyopathy, in particular when heart failure is present.
- Sinus bradycardia.
- Existing symptomatic dysrhythmias.

- Concomitant treatment with medicines known to prolong QTc-interval (see "Concomitant administration" below and section 4.5). Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during VCIDE therapy (see section 4.2).

Hepatic toxicity

Serious hepatic reactions may occur, less frequently, during treatment with voriconazole as in VCIDE (see section 4.8). These reactions include clinical hepatitis, cholestasis and fulminant hepatic failure including fatalities which mostly occurred 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 VCIDE must be carefully monitored for more severe hepatic injury. Clinical management should include laboratory evaluation of hepatic function (specifically AST, ALT and bilirubin) at the initiation of treatment with VCIDE and at least weekly for the first month of treatment. Treatment duration should be as short as possible; however, 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, VCIDE should be discontinued.

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

Visual disturbances

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

In clinical trials, voriconazole as in VCIDE treatment-related visual disturbances were very common. In these studies, approximately 21 % of patients 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 in VCIDE. The visual disturbances were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual disturbances may be associated with higher plasma concentrations and/or doses.

There have been post-marketing reports of 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 in VCIDE on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude. The ERG measures electrical currents in the retina. The ERG changes did not progress over 29 days of treatment and were fully reversible on withdrawal of voriconazole as in VCIDE.

The long-term effect of voriconazole as in VCIDE (median 169 days; range 5 to 353 days) on visual function was evaluated in subjects with paracoccidioidomycosis. Voriconazole as in VCIDE 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. Seventeen of thirty-five patients on

voriconazole as in VCIDE 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 in VCIDE therapy.

Renal adverse events

Acute renal failure has been reported in severely ill patients treated with voriconazole. Patients treated with VCIDE are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may contribute to 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.

Serious dermatological adverse reactions

Photosensitivity

VCIDE has been associated with phototoxicity including reactions such as ephelides, lentigo, actinic keratosis and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during VCIDE treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

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

Squamous cell carcinoma of the skin (SCC)

Squamous cell carcinoma of the skin has been reported in patients, some of whom have reported prior phototoxic reactions. If VCIDE is continued, however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions. VCIDE should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified (see below the section under “Long-term treatment”).

Exfoliative cutaneous reactions

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported with the use of voriconazole. If patients develop a rash, they should be monitored closely and VCIDE discontinued if lesions progress.

Monitoring of pancreatic function

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

Long-term treatment

Long-term exposure (treatment or prophylaxis), exceeding 6 months, requires careful assessment of the benefit-risk balance. Medical practitioners should therefore consider the need to limit the exposure to VCIDE (see section 4.2).

Squamous cell carcinoma of the skin (SCC) has been reported in relation with long-term voriconazole treatment.

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, discontinuation of VCIDE should be considered.

Paediatric use

Safety and effectiveness in paediatric patients below the age of 2 years has not been established. A higher frequency of liver enzyme elevations was observed in the paediatric population. Hepatic function should be monitored. Intravenous VCIDE administration is recommended in paediatric patients aged 2 to < 12 years with

malabsorption and very low body mass for age, as oral bioavailability may be limited in their case.

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

The frequency of phototoxicity reactions is higher in the paediatric population. As 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 discontinuation of treatment.

Concomitant administration of other medicines

Methadone (CYP3A4 substrate)

Increased plasma concentrations of methadone are associated with toxicity, including QT-prolongation. Frequent monitoring of adverse incidents and toxicity related to methadone, is recommended during concomitant administration. A reduction in dosage of methadone may be necessary (see section 4.5).

Short-acting opiates (CYP3A4 substrate)

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

Long-action opiates (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, as in VCIDE. Frequent monitoring for opiate-associated adverse reactions may be necessary (see section 4.5).

Ciclosporin and tacrolimus (CYP3A4 substrates)

Clinically significant medicine interactions with voriconazole, as in VCIDE, may occur in patients who are receiving treatment with ciclosporin or tacrolimus (see section 4.5).

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

Careful monitoring of phenytoin levels is recommended when phenytoin is co-administered with VCIDE. Concomitant use of VCIDE and phenytoin should be avoided unless the benefit outweighs the risk (see section 4.5).

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Co-administration of voriconazole, as in VCIDE, and low dose ritonavir (100 mg twice daily), should be avoided unless an evaluation of the benefit/risk justifies the use of voriconazole, as in VCIDE (see section 4.5 and for higher doses see section 4.3).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

When voriconazole, as in VCIDE, is co-administered with efavirenz, the dose of voriconazole should be increased to 400 mg twice daily and that of efavirenz should be decreased to 300 mg once daily (see section 4.5).

Rifabutin (Potent CYP450 inducer)

Concomitant use of voriconazole, as in VCIDE, and rifabutin is contraindicated (see section 4.3 and 4.5).

Fluconazole (CYP3A4, CYP2C9 and CYP2C19 inhibitor)

It was reported that co-administration of voriconazole, as in VCIDE, tablets and oral fluconazole results in a significant increase in C_{max} and AUC_{τ} of voriconazole in healthy subjects. Specific recommendations are not possible for adjustments of the

dose and/or frequency of voriconazole and fluconazole. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole (see section 4.5).

Everolimus (CYP3A4 substrate, P-gp substrate)

Co-administration of VCIDE with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations. There are insufficient data to allow dosing recommendations in this situation (see section 4.5).

Sodium content

Each vial of VCIDE contains 225,6 mg sodium chloride, which provides 88,74 mg sodium per vial.

The sodium content should be taken into account by patients on a controlled sodium diet.

4.5 Interactions 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.

Interaction table

Interactions between voriconazole and other medicines are listed in the table below ("ND" is the abbreviation for not determined).

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.

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
Astemizole, cisapride, pimozide, quinidine and terfenadine *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of these medicines 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 (phenobarbitone), mephobarbital (mephobarbitone)) *[potent CYP450 inducers]*	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	Contraindicated (see section 4.3)

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
Efavirenz (a non-nucleoside reverse transcriptase inhibitor) *[CYP450 inducer; CYP3A4 inhibitor and substrate]* Efavirenz 400 mg once daily, co-administered with voriconazole 200 mg twice daily*	Efavirenz C_{max} ↑ 38 % Efavirenz AUCτ ↑ 44 % Voriconazole C_{max} ↓ 61 % Voriconazole AUCτ ↓ 77 %	Standard doses of voriconazole as in VCIDE and standard doses of efavirenz must not be co-administered
Efavirenz 300 mg once daily, co-administered with voriconazole 400 mg twice daily*	Compared to efavirenz 600 mg once daily, Efavirenz C_{max} ↔ Efavirenz AUCτ ↑ 17 % Compared to voriconazole 200 mg twice daily, Voriconazole C_{max} ↑ 23 % Voriconazole AUCτ ↓ 7 % The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by an NNRTI (see NNRTIs below).	Voriconazole may be co-administered with efavirenz if the voriconazole maintenance dose is increased to 400 mg twice daily and the efavirenz dose is decreased 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).

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
Rifabutin *[potent CYP450 inducer]* 300 mg once daily	Voriconazole C_{max} ↓ 69 % Voriconazole AUCτ ↓ 78 %	Concomitant use of voriconazole and rifabutin is contraindicated (see section 4.3).
300 mg once daily (co-administered with voriconazole 350 mg twice daily)*	Compared to voriconazole 200 mg twice daily, Voriconazole C_{max} ↓ 4 % Voriconazole AUCτ ↓ 32 %	
300 mg once daily (co-administered with voriconazole 400 mg twice daily)*	Rifabutin C_{max} ↑ 195 % Rifabutin AUCτ ↑ 331 % Compared to voriconazole 200 mg twice daily, Voriconazole C_{max} ↑ 104 % Voriconazole AUCτ ↑ 87 %	
Rifampicin (600 mg once daily) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓ 93 % Voriconazole AUCτ ↓ 96 %	Contraindicated (see section 4.3)
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]* High dose (400 mg twice daily)	Ritonavir C_{max} and AUCτ ↔ Voriconazole C_{max} ↓ 66 % Voriconazole AUCτ ↓ 82 %	Co-administration of voriconazole and high doses of ritonavir (400 mg and above twice daily) is contraindicated (see section 4.3).

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
Low dose (100 mg twice daily)*	Ritonavir C_{max} ↓ 25 % Ritonavir AUCτ ↓13 % Voriconazole C_{max} ↓ 24 % Voriconazole AUCτ ↓ 39 %	Co-administration of voriconazole and low dose ritonavir (100 mg twice daily) should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole (see section 4.4).
St. John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg three times daily (co-administered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole $AUC_{0-\infty}$ ↓ 59 %	Contraindicated (see section 4.3)
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).

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
Fluconazole (200 mg once daily) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	Voriconazole C_{max} ↑ 57 % Voriconazole AUCτ ↑ 79 % 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 once daily	Voriconazole C_{max} ↓ 49 % Voriconazole AUCτ ↓ 69 %	Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended.
300 mg once daily (co-administered with voriconazole 400 mg twice daily)*	Phenytoin C_{max} ↑ 67 % Phenytoin AUCτ ↑ 81 % Compared to voriconazole 200 mg twice daily, Voriconazole C_{max} ↑ 34 % Voriconazole AUCτ ↑ 39 %	Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV twice daily or from 200 mg to 400 mg oral twice daily (100 mg to 200 mg oral twice daily in patients less than 40 kg) (see section 4.2).

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
Anticoagulants Warfarin (30 mg single dose, co-administered with 300 mg twice daily voriconazole) *[CYP2C9 substrate]*	Maximum prothrombin time / international normalised ratio (INR) increased by 93 %	Close monitoring of prothrombin time or international normalised ratio is recommended when warfarin and VCIDE are co-administered.
Benzodiazepines (e.g. midazolam, triazolam, alprazolam) *[CYP3A4 substrates]*	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.
Immunosuppressants *[CYP3A4 substrates]* Sirolimus (2 mg single dose)	In an independent published study, Sirolimus C_{max} ↑ 556 % Sirolimus $AUC_{0-\infty}$ ↑ 1 014 %	Co-administration of voriconazole and sirolimus is contraindicated (see section 4.3).

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
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 (see section 4.4).**
Tacrolimus (0,1 mg/kg single dose)	Tacrolimus C_{max} ↑ 117 % Tacrolimus AUC_t ↑ 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**

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
		monitored, and the dose increased as necessary (see section 4.4).
Long-acting opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose) co-administered with voriconazole 400 mg every 12 hours for 1 day, followed by 200 mg every 12 hours on days 2 to 4	In an independent published study, Oxycodone C_{max} ↑ 1,7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3,6-fold The mean elimination half-life of oxycodone increased by 2,0-fold.	Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g. hydrocodone) should be considered. Extended and frequent monitoring for opiate-associated adverse reactions may be necessary.
Methadone (30-100 mg once daily) *[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 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) Diclofenac (50 mg single dose)	S-Ibuprofen C_{max} ↑ 20 % S-Ibuprofen $AUC_{0-\infty}$ ↑ 100 % Diclofenac C_{max} ↑ 114 % Diclofenac $AUC_{0-\infty}$ ↑ 78 %	Frequent monitoring for adverse reactions and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
Omeprazole (40 mg once daily)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	Omeprazole C_{max} ↑ 116 % Omeprazole AUC$_\tau$ ↑ 280 % Voriconazole C_{max} ↑ 15 % Voriconazole AUC$_\tau$ ↑ 41 % Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicines.	No dose adjustment of voriconazole is recommended. When initiating voriconazole in patients already receiving omeprazole, it is recommended that the omeprazole dose be halved.
Oral contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ethinylestradiol (1 mg/0,035 mg once daily)	Ethinylestradiol C_{max} ↑ 36 % Ethinylestradiol AUC$_\tau$ ↑ 61 % Norethisterone C_{max} ↑ 15 % Norethisterone AUC$_\tau$ ↑ 53 % Voriconazole C_{max} ↑ 14 % Voriconazole AUC$_\tau$ ↑ 46 %	Monitoring for adverse reactions related to oral contraceptives, in addition to those for voriconazole, is recommended.

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
Short-acting opiates *[CYP3A4 substrates]* Alfentanil (20 µg/kg single dose) Fentanyl (5 µg/kg single dose)	 In an independent published study, Alfentanil $AUC_{0-\infty}$ ↑ 6-fold In an independent published study, Fentanyl $AUC_{0-\infty}$ ↑ 1,34-fold	Dose reduction of alfentanil, fentanyl and other short-acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g. sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse reactions is recommended.
Statins (e.g. lovastatin) *[CYP3A4 substrates]*	Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase 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.

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
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 CYP450 inducers]*	Not studied clinically. *In vitro* studies show that the metabolism of voriconazole may be inhibited by delavirdine. Although not studied, metabolism of voriconazole may be induced by nevirapine. Voriconazole may inhibit the metabolism of NNRTIs.	Careful monitoring for any occurrence of medicine toxicity and/or lack of efficacy during the co-administration of voriconazole and NNRTIs and dose adjustment may be needed.
Cimetidine (400 mg twice daily) *[non-specific CYP450 inhibitor and increases gastric pH]*	Voriconazole C_{max} ↑ 18 % Voriconazole AUC$_\tau$ ↑ 23 %	No dose adjustment
Digoxin (0,25 mg once daily) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUC$_\tau$ ↔	No dose adjustment

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration with VCIDE**
Indinavir (800 mg three times daily) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUC_{τ} ↔ Voriconazole C_{max} ↔ Voriconazole AUC_{τ} ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g twice daily) *[CYP3A4 inhibitor]* Azithromycin (500 mg once daily)	 Voriconazole C_{max} and AUC_{τ} ↔ Voriconazole C_{max} and AUC_{τ} ↔	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} ↑ 11 % Prednisolone $AUC_{0-\infty}$ ↑ 34 %	No dose adjustment
Ranitidine (150 mg twice daily) *[increases gastric pH]*	Voriconazole C_{max} and AUC_{τ} ↔	No dose adjustment

4.6 Fertility, pregnancy and lactation

Pregnancy

Adequate information is not available on the use of voriconazole as in VCIDE in pregnant women. Studies in animals have shown reproductive toxicity and teratogenicity. The potential risk to humans is unknown. VCIDE should not be used during pregnancy.

Lactation

The excretion of voriconazole as in VCIDE into breastmilk has not been investigated. Breastfeeding must be stopped on initiation of treatment with VCIDE.

4.7 Effects on ability to drive and use machines

VCIDE may affect vision and dizziness has also been reported (see sections 4.4 and 4.8). Patients should be advised to avoid potentially hazardous tasks, such as driving or operating machinery until they know how VCIDE affects them.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated summary of adverse reactions

System Organ Class	**Frequent**	**Less frequent**	**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*

System Organ Class	Frequent	Less frequent	Frequency not known (cannot be estimated from available data)
Blood and lymphatic system disorders	Agranulocytosis (includes febrile neutropenia and neutropenia) , pancytopenia, thrombocytopenia (includes immune thrombocytopenic purpura), leukopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic)	Bone marrow failure, lymphadenopathy, eosinophilia, disseminated intravascular coagulation	
Immune system disorders		Hypersensitivity, anaphylactoid reaction, angioedema	
Endocrine disorders		Adrenal insufficiency, hypothyroidism, hyperthyroidism	
Metabolism and nutrition disorders	Oedema peripheral hypoglycaemia, hypokalaemia, hyponatraemia	Hypercholesterolaemia	
Psychiatric disorders	Depression, hallucination, anxiety, insomnia, agitation, confusional state		

System Organ Class	**Frequent**	**Less frequent**	**Frequency not known (cannot be estimated from available data)**
Nervous system disorders	Headache, convulsion, syncope, tremor, hypertonia (includes nuchal rigidity and tetany) paraesthesia, somnolence, dizziness	Brain oedema, encephalopathy (includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy), extrapyramidal disorder (includes akathisia and parkinsonism), peripheral neuropathy, ataxia, hypoaesthesia, dysgeusia, hepatic encephalopathy, Guillain-Barre syndrome, nystagmus, insomnia, hepatic coma	
Eye disorders	Visual impairment (including altered/enhanced visual perception, blurred vision, colour vision change, photophobia, chloropsia, colour blindness, cyanopsia, eye disorder, halo vision, night blindness, vitreous floaters, xanthopsia), retinal haemorrhage	Optic nerve disorder (prolonged optic neuritis), papilloedema, oculogyric crisis, diplopia, scleritis, blepharitis, optic atrophy, optic neuritis, corneal opacity	
Ear and labyrinth disorders		Hypoacusis, vertigo, tinnitus	

System Organ Class	**Frequent**	**Less frequent**	**Frequency not known (cannot be estimated from available data)**
Cardiac disorders	Atrial dysrhythmia, ventricular dysrhythmia, supraventricular tachycardia, bradycardia	Ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, prolonged QT interval, supraventricular tachycardia, *torsades de pointes*, complete atrioventricular block, bundle branch block, nodal dysrhythmia	
Vascular disorders	Hypotension, phlebitis	Thrombophlebitis, lymphangitis	
Respiratory, thoracic and mediastinal disorders	Respiratory distress (includes dyspnoea and exertional dyspnoea), acute respiratory distress syndrome, pulmonary oedema		
Gastrointestinal disorders	Diarrhoea, vomiting, abdominal pain, nausea, cheilitis, dyspepsia, constipation, gingivitis	Peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis, pseudomembranous colitis	

System Organ Class	**Frequent**	**Less frequent**	**Frequency not known (cannot be estimated from available data)**
Hepatobiliary disorders	Liver function test abnormal (including AST, ALT, alkaline phosphatase, GGT, LDH, bilirubin), jaundice, cholestatic jaundice, hepatitis (includes medicine-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity)	Cholecystitis, cholelithiasis, hepatomegaly, hepatic failure	
Skin and subcutaneous tissue disorders	Rash, exfoliative dermatitis, alopecia, maculo-papular rash, pruritus, erythema, facial oedema	Severe cutaneous adverse reactions (SCARS), including Stevens-Johnson syndrome, phototoxicity, purpura, urticaria, allergic dermatitis, papular rash, macular rash, eczema, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), actinic keratosis*, pseudoporphyria, erythema multiforme, psoriasis, drug eruption	Cutaneous lupus erythematosus*, ephelides*, lentigo*

System Organ Class	Frequent	Less frequent	Frequency not known (cannot be estimated from available data)
Musculoskeletal and connective tissue disorders	Back pain	Arthritis	Periostitis*
Renal and urinary disorders	Renal failure acute, haematuria, increased creatinine	Renal tubular necrosis, proteinuria, nephritis	
General disorders and administration site conditions	Pyrexia, chest pain, face oedema (includes periorbital oedema, lip oedema, and oedema mouth), asthenia, chills, peripheral oedema	Infusion site reaction, influenza like illness	
Investigations		Increased blood urea, increased blood cholesterol	
Injury, poisoning and procedural complications			Infusion related reactions including flushing, fever, sweating, tachycardia, chest tightness, dyspnoea, faintness, nausea, pruritus and rash

*ADR identified post-marketing

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of VCIDE is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA on the SAHPRA website: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

There is no known antidote to VCIDE.

VCIDE is haemodialysed with a clearance of 121 ml/min and hydroxypropyl-beta-cyclodextrin (HP-beta-CD), is haemodialysed with a clearance of 55 ml/min. In an overdose, haemodialysis may assist in the removal of voriconazole and HP-beta-CD from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics

Voriconazole is a broad-spectrum triazole antifungal medicine. It inhibits fungal cytochrome P450-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis.

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*.

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.

Clinical isolates with decreased susceptibility to voriconazole have been identified. Correlation of *in vitro* activity with clinical outcome is difficult owing to the complexity of the patients studied in clinical trials.

Resistance

Clinical isolates with decreased susceptibility to voriconazole have been identified.

In vitro data showed a slight increase of resistance of *C. glabrata* to voriconazole.

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.

In vitro sensitivity does not necessarily imply clinical sensitivity.

5.2 Pharmacokinetic properties

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose.

Absorption

The recommended loading dose regimens yield plasma concentrations close to steady-state within the first 24 hours of dosing. Without the loading dose regimens, accumulation occurs during twice daily multiple dosing, with steady-state plasma voriconazole concentrations achieved by day 6 in most patients.

Distribution

The estimated volume of distribution of voriconazole at steady-state is 4,6 ℓ/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58 %.

Detectable voriconazole concentrations are present in the cerebrospinal fluid of patients treated with voriconazole.

Metabolism

Voriconazole is metabolised by the hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.

The inter-individual variability of voriconazole pharmacokinetics is high.

The CYP2C19 enzyme is significantly involved in the metabolism of voriconazole and exhibits genetic polymorphism. For example, 15 – 20 % of Asian populations may be expected to be poor metabolisers. For Caucasians and Blacks the prevalence of poor metabolisers is 3 - 5 %. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on average, 4-fold higher voriconazole exposure (AUC_{τ}) than their homozygous extensive metaboliser counterparts. Patients 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.

Elimination

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

Approximately 80 % of the radioactivity is recovered in the urine after multiple intravenous dosing with a radiolabelled dose of voriconazole 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 about 6 hours following a 200 mg dose (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 has not been recorded.

Positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances were identified.

Pharmacokinetics in special patient groups

Gender

The safety profile and plasma concentrations observed in male and female patients are similar. Therefore, no dosage adjustment based on gender is necessary.

Elderly

A relationship between plasma concentrations and age is observed. However, the safety profile of voriconazole in young and elderly patients was similar. No dosage adjustment is therefore necessary for the elderly.

Paediatrics

It was reported that in a population pharmacokinetic analysis, average steady-state plasma concentrations in children who received an intravenous maintenance dose of 4 mg/kg every 12 hours were similar to those in adults receiving 3 mg/kg every 12 hours, with medians of 1 186 ng/ml in children and 1 155 ng/ml in adults. 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, HP-beta-CD, may occur. See dosing and monitoring recommendations under sections 4.2 and 4.4.

Hepatic impairment

It was reported that after a single oral dose (200 mg), AUC was 233 % higher in patients 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.

No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl-beta-cyclodextrin (HP-beta-CD)

Sodium chloride

Hydrochloric acid (for pH adjustment).

6.2 Incompatibilities

VCIDE must not be infused into the same line or cannula concomitantly with other medicine infusions, including parenteral nutrition (see total parenteral nutrition (TPN) in section 6.6).

Sodium bicarbonate

Sodium bicarbonate 4,2 % IV infusion is not compatible with VCIDE and must not be used as a diluent. Compatibility with other concentrations is unknown.

Blood products and concentrated electrolytes

VCIDE should not be co-infused with any blood product or any short-term infusion of concentrated electrolytes, even if the two infusions flow through separate intravenous lines (or cannulas). Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected before commencing VCIDE therapy.

6.3 Shelf life

Powder for solution for infusion:

36 months

Prepared solution for infusion:

Chemical and physical in-use stability has been demonstrated for 72 hours at room temperature (at or below 25 °C) and at 2-8 °C (in a refrigerator).

From a microbiological point of view, the product should 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 2-8 °C (in a refrigerator), unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in the original carton at or below 25 °C.

For storage instructions after reconstitution, see section 6.3.

6.5 Nature and contents of the container

A single use 25 ml clear, colourless, glass type I vial, closed with a grey rubber stopper and an aluminium cap with a red plastic flip-off seal.

Single vials are individually packed in cardboard boxes together with the patient information leaflets.

6.6 Special precautions for disposal and other handling

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

Preparation of the infusion

The vial contents are reconstituted with either 19 ml of water for injection or 19 ml of sodium chloride 9 mg/ml (0,9 %) solution for injection to obtain a clear solution containing 10 mg/ml of voriconazole and an extractable volume of 20 ml (see Table 3 below).

Discard the VCIDE vial if vacuum does not pull the diluent into the vial. It is recommended that a standard 20 ml (non-automated) syringe be used to ensure that the exact amount (19,0 ml) of water for injection or sodium chloride 9 mg/ml (0,9 %)

solution for injection is dispensed. VCIDE is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used.

For administration, the required volume of the reconstituted solution is added to a recommended compatible infusion solution (see Table 4) to obtain, where appropriate, a final voriconazole solution containing 0,5 to 5 mg/ml.

Table 3 Required volumes of 10 mg/ml VCIDE concentrate

Body mass (kg)	**3 mg/kg dose (no. of vials)**	**4 mg/kg dose (no. of vials)**	**6 mg/kg dose (no. 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 ml (1)	18 ml (1)
35	10,5 ml (1)	14 ml (1)	21 ml (2)
40	12,0 ml (1)	16 ml (1)	24 ml (2)
45	13,5 ml (1)	18 ml (1)	27 ml (2)
50	15,0 ml (1)	20 ml (1)	30 ml (2)
55	16,5 ml (1)	22 ml (2)	33 ml (2)
60	18,0 ml (1)	24 ml (2)	36 ml (2)
65	19,5 ml (1)	26 ml (2)	39 ml (2)
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)

Compatible solutions

The reconstituted solution can be diluted with the following intravenous solutions:

Table 4 Compatible intravenous solutions

0,9 % Sodium chloride solution
Compound sodium lactate solution
5 % Glucose and Ringer's lactate solution
5 % Glucose and 0,45 % sodium chloride solution
5 % Glucose solution
5 % Glucose in 20 mmol potassium chloride solution
0,45 % Sodium chloride solution
5 % Glucose and 0,9 % sodium chloride solution

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

Intravenous solution containing (non-concentrated) electrolytes

VCIDE may 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)

VCIDE may be infused at the same time as TPN but should be infused through a separate line. If it is infused through a multiple-lumen catheter, TPN must be administered through another portal than that used for VCIDE.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Not applicable