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**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)<br>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 $AUC_\tau$ 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.
$AUC_\tau$, $AUC_t$ 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<br>*[CYP3A4 substrates]* | Although not studied, increased plasma concentrations of these medicines can lead to QTc prolongation and rare occurrences of *torsades de pointes*. | Contraindicated<br>(see section 4.3) |
| Carbamazepine and long-acting barbiturates (e.g. phenobarbital (phenobarbitone), mephobarbital (mephobarbitone))<br>*[potent CYP450 inducers]* | Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations. | Contraindicated<br>(see section 4.3) |
| Efavirenz (a non-nucleoside reverse transcriptase inhibitor)<br>*[CYP450 inducer; CYP3A4 inhibitor and substrate]*<br>Efavirenz 400 mg once daily, co-administered with voriconazole 200 mg twice daily*<br><br>Efavirenz 300 mg once daily, co-administered with voriconazole 400 mg twice daily* | Efavirenz $C_{max}$ ↑ 38 %<br>Efavirenz $AUC_\tau$ ↑ 44 %<br>Voriconazole $C_{max}$ ↓ 61 %<br>Voriconazole $AUC_\tau$ ↓ 77 %<br>Compared to efavirenz 600 mg once daily,<br>Efavirenz $C_{max}$ ↔<br>Efavirenz $AUC_\tau$ ↑ 17 %<br>Compared to voriconazole 200 mg twice daily<br>Voriconazole $C_{max}$ ↑ 23 %<br>Voriconazole $AUC_\tau$ ↓ 7 %<br>The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by an NNRTI (see NNRTIs below). | Standard doses of voriconazole as in VCIDE and standard doses of efavirenz must not be co-administered<br><br>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)<br>*[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<br>*[potent CYP450 inducer]*<br>300 mg once daily<br><br>300 mg once daily (co-administered with voriconazole 350 mg twice daily)*<br><br>300 mg once daily (co-administered with voriconazole 400 mg twice daily)* | Voriconazole $C_{max}$ ↓ 69 %<br>Voriconazole $AUC_\tau$ ↓ 78 %<br>Compared to voriconazole 200 mg twice daily,<br>Voriconazole $C_{max}$ ↓ 4 %<br>Voriconazole $AUC_\tau$ ↓ 32 %<br>Rifabutin $C_{max}$ ↑ 195 %<br>Rifabutin $AUC_\tau$ ↑ 331 %<br>Compared to voriconazole 200 mg twice daily,<br>Voriconazole $C_{max}$ ↑ 104 %<br>Voriconazole $AUC_\tau$ ↑ 87 % | Concomitant use of voriconazole and rifabutin is contraindicated (see section 4.3). |
| Rifampicin (600 mg once daily)<br>*[potent CYP450 inducer]* | Voriconazole $C_{max}$ ↓ 93 %<br>Voriconazole $AUC_\tau$ ↓ 96 % | Contraindicated<br>(see section 4.3) |
| Ritonavir (protease inhibitor)<br>*[potent CYP450 inducer; CYP3A4 inhibitor and substrate]*<br>High dose (400 mg twice daily)<br><br>Low dose (100 mg twice daily)* | Ritonavir $C_{max}$ and $AUC_\tau$ ↔<br>Voriconazole $C_{max}$ ↓ 66 %<br>Voriconazole $AUC_\tau$ ↓ 82 %<br>Ritonavir $C_{max}$ ↓ 25 %<br>Ritonavir $AUC_\tau$ ↓13 %<br>Voriconazole $C_{max}$ ↓ 24 %<br>Voriconazole $AUC_\tau$ ↓ 39 % | Co-administration of voriconazole and high doses of ritonavir (400 mg and above twice daily) is contraindicated (see section 4.3).<br><br>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<br>*[CYP450 inducer; P-gp inducer]*<br>300 mg three times daily (co-administered with voriconazole 400 mg single dose) | In an independent published study,<br>Voriconazole $AUC_{0-\infty}$ ↓ 59 % | Contraindicated<br>(see section 4.3) |
| Everolimus<br>*[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). |
| Fluconazole (200 mg once daily)<br>*[CYP2C9, CYP2C19 and CYP3A4 inhibitor]* | Voriconazole $C_{max}$ ↑ 57 %<br>Voriconazole $AUC_\tau$ ↑ 79 %<br>Fluconazole $C_{max}$ ND<br>Fluconazole $AUC_\tau$ 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<br>*[CYP2C9 substrate and potent CYP450 inducer]*<br>300 mg once daily | Voriconazole $C_{max}$ ↓ 49 %<br>Voriconazole $AUC_\tau$ ↓ 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 %<br>Phenytoin $AUC_\tau$ ↑ 81 %<br>Compared to voriconazole 200 mg twice daily,<br>Voriconazole $C_{max}$ ↑ 34 %<br>Voriconazole $AUC_\tau$ ↑ 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). |
| Anticoagulants<br>Warfarin (30 mg single dose, co-administered with 300 mg twice daily voriconazole)<br>*[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)<br>*[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<br>*[CYP3A4 substrates]*<br>Sirolimus (2 mg single dose) | In an independent published study, Sirolimus $C_{max}$ ↑ 556 %<br>Sirolimus $AUC_{0-\infty}$ ↑ 1 014 % | Co-administration of voriconazole and sirolimus is contraindicated (see section 4.3). |
| Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)<br><br>Tacrolimus (0,1 mg/kg single dose) | Ciclosporin $C_{max}$ ↑ 13 %<br>Ciclosporin $AUC_\tau$ ↑ 70 %<br><br>Tacrolimus $C_{max}$ ↑ 117 %<br>Tacrolimus $AUC_t$ ↑ 221 % | 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).**<br>When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. **When voriconazole is discontinued, tacrolimus levels must be carefully monitored, and the dose increased as necessary (see section 4.4).** |
| Long-acting opiates<br>*[CYP3A4 substrates]*<br>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,<br>Oxycodone $C_{max}$ ↑ 1,7-fold<br>Oxycodone $AUC_{0-\infty}$ ↑ 3,6-fold<br>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)<br>*[CYP3A4 substrate]* | R-methadone (active) $C_{max}$ ↑ 31 %<br>R-methadone (active) $AUC_\tau$ ↑ 47 %<br>S-methadone $C_{max}$ ↑ 65 %<br>S-methadone $AUC_\tau$ ↑ 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)<br>*[CYP2C9 substrates]*<br>Ibuprofen (400 mg single dose)<br><br>Diclofenac (50 mg single dose) | S-Ibuprofen $C_{max}$ ↑ 20 %<br>S-Ibuprofen $AUC_{0-\infty}$ ↑ 100 %<br>Diclofenac $C_{max}$ ↑ 114 %<br>Diclofenac $AUC_{0-\infty}$ ↑ 78 % | Frequent monitoring for adverse reactions and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed. |
| Omeprazole (40 mg once daily)*<br>*[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]* | Omeprazole $C_{max}$ ↑ 116 %<br>Omeprazole $AUC_\tau$ ↑ 280 %<br>Voriconazole $C_{max}$ ↑ 15 %<br>Voriconazole $AUC_\tau$ ↑ 41 %<br>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.<br>When initiating voriconazole in patients already receiving omeprazole, it is recommended that the omeprazole dose be halved. |
| Oral contraceptives*<br>*[CYP3A4 substrate; CYP2C19 inhibitor]*<br>Norethisterone/ethinylestradiol (1 mg/0,035 mg once daily) | Ethinylestradiol $C_{max}$ ↑ 36 %<br>Ethinylestradiol $AUC_\tau$ ↑ 61 %<br>Norethisterone $C_{max}$ ↑ 15 %<br>Norethisterone $AUC_\tau$ ↑ 53 %<br>Voriconazole $C_{max}$ ↑ 14 %<br>Voriconazole $AUC_\tau$ ↑ 46 % | Monitoring for adverse reactions related to oral contraceptives, in addition to those for voriconazole, is recommended. |
| Short-acting opiates<br>*[CYP3A4 substrates]*<br>Alfentanil (20 µg/kg single dose)<br>Fentanyl (5 µg/kg single dose) | In an independent published study, Alfentanil $AUC_{0-\infty}$ ↑ 6-fold<br>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.<br>Extended and frequent monitoring for respiratory depression and other opiate-associated adverse reactions is recommended. |
| Statins (e.g. lovastatin)<br>*[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)<br>*[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)<br>*[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)*<br>*[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)*<br>*[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)<br>*[non-specific CYP450 inhibitor and increases gastric pH]* | Voriconazole $C_{max}$ ↑ 18 %<br>Voriconazole $AUC_\tau$ ↑ 23 % | No dose adjustment |
| Digoxin (0,25 mg once daily)<br>*[P-gp substrate]* | Digoxin $C_{max}$ ↔<br>Digoxin $AUC_\tau$ ↔ | No dose adjustment |
| Indinavir (800 mg three times daily)<br>*[CYP3A4 inhibitor and substrate]* | Indinavir $C_{max}$ ↔<br>Indinavir $AUC_\tau$ ↔<br>Voriconazole $C_{max}$ ↔<br>Voriconazole $AUC_\tau$ ↔ | No dose adjustment |
| Macrolide antibiotics<br>Erythromycin (1 g twice daily)<br>*[CYP3A4 inhibitor]*<br>Azithromycin (500 mg once daily) | Voriconazole $C_{max}$ and $AUC_\tau$ ↔<br><br>Voriconazole $C_{max}$ and $AUC_\tau$ ↔ | No dose adjustment |
| Mycophenolic acid (1 g single dose)<br>*[UDP-glucuronyl transferase substrate]* | Mycophenolic acid $C_{max}$ ↔<br>Mycophenolic acid $AUC_t$ ↔ | No dose adjustment |
| Prednisolone (60 mg single dose)<br>*[CYP3A4 substrate]* | Prednisolone $C_{max}$ ↑ 11 %<br>Prednisolone $AUC_{0-\infty}$ ↑ 34 % | No dose adjustment |
| Ranitidine (150 mg twice daily)<br>*[increases gastric pH]* | Voriconazole $C_{max}$ and $AUC_\tau$ ↔ | 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* |
| 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 | | |
| 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 | |
| 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 | |
| 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* |
| 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

MACLEODS

*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 $14\alpha$-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 ($AUC_\tau$) 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

49/20.1.7/1211

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 January 2021

## 10. DATE OF REVISION OF THE TEXT

Not applicable

PM0079-01

## PATIENT INFORMATION LEAFLET

**SCHEDULING STATUS: S4**

**VCIDE® 200 IV,** 200 mg powder for solution for infusion
**Voriconazole**
**Sugar free**
Contains 88,74 mg sodium/vial

**Read all of this leaflet carefully before you are given VCIDE**
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.
- VCIDE has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

**What is in this leaflet**
1. What VCIDE is and what it is used for
2. What you need to know before you are given VCIDE
3. How VCIDE will be given to you
4. Possible side effects
5. How to store VCIDE
6. Contents of the pack and other information

### 1. What VCIDE is and what it is used for

VCIDE is an antifungal medicine. It works by killing or stopping the growth of the fungi that cause infections.
VCIDE is used for the treatment of a wide variety of fungal infections in patients (adults and children over the age of 2).
VCIDE may also be used for the prevention of fungal infections in high-risk bone marrow transplant recipients.

### 2. What you need to know before you are given VCIDE

**VCIDE should not be administered to you:**
- if you are hypersensitive (allergic) to voriconazole or any ingredient in VCIDE (listed in section 6);
- if you have prolonged QT-syndrome (a heart rhythm disorder);
- if your liver function is severely affected;
- if you are pregnant or breastfeeding;

A list of the medicines that may affect VCIDE is shown in the section "Other medicines and VCIDE". However, the medicines in the following list must not be taken during your course of VCIDE treatment:
- Astemizole (used for allergy)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heartbeat)
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Rifampicin, rifabutin (used for treating tuberculosis)
- Efavirenz (used for treating HIV) in doses of 400 mg and above once daily
- Carbamazepine (used to treat seizures)
- Phenobarbital (phenobarbitone) (used for severe insomnia and seizures)
- Ritonavir (used for treating HIV) in doses of 400 mg and more twice daily
- Sirolimus (used in transplant patients)
- St. John's Wort (herbal supplement used for depression).

**Warnings and precautions**
*Women of childbearing potential*
If you are a woman of childbearing potential, you must always use effective contraception during treatment. See "Pregnancy and breastfeeding".
*Tell your doctor or healthcare professional before being given VCIDE, if you:*
- are allergic to other azole type medicines (for example, fluconazole or ketoconazole which are antifungal medicines. Ask your doctor or pharmacist if you are unsure);
- if there is a possibility that you can get pregnant (if you are of childbearing age). VCIDE cannot be used to treat patients who are pregnant or breastfeeding. Your doctor will advise you on effective contraception;
- are suffering from liver disease or have ever suffered from it. If you have liver disease, your doctor may prescribe a lower dose of VCIDE. Your doctor should also monitor your liver function while you are being treated with VCIDE by doing blood tests;
- you are known to have cardiomyopathy (diseased heart muscle), irregular heartbeat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QTc syndrome';
- have a metabolic disorder such as low potassium, calcium or magnesium;
- have a kidney disease. Depending on the degree of kidney disease the doctor may decide to rather give you voriconazole tablets. Your doctor should monitor your renal function while you are being treated with VCIDE by doing blood tests.

*You should also know that:*
You should avoid any sunlight and sun exposure while being treated. It is important to cover sun exposed areas of skin and use sunscreen with high sun protection factor (SPF), as an increased sensitivity of skin to the sun's UV rays can occur. These precautions are also applicable to children.
While being treated with VCIDE, tell your doctor immediately if you develop:
- sunburn
- severe skin rash or blisters
- bone pain.

If you develop skin disorders as described above, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you to be seen on a regular basis. There is a small chance that skin cancer could develop with long-term use of VCIDE.
VCIDE can cause problems with your eyes and vision, including blurred vision, altered colour sensation and light sensitivity. You should wear sunglasses to protect your eyes from bright light. Tell your doctor immediately if you have any eye/vision problems.
If you had an organ transplant and receive VCIDE, you may have inflammation and pain in the bones. See your doctor as soon as possible. He/she will decide if you should continue treatment with VCIDE and will treat you as necessary.
*Children*
Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children. If your child develops skin disorders, your doctor may refer your child to a dermatologist, who after consultation may decide that it is important for your child to be seen on a regular basis. Elevated liver enzymes were also observed more frequently in children.
**Other medicines and VCIDE**
Always tell your healthcare provider if you are taking any other medicine. (This includes all complementary or traditional medicines).
Some medicines, when taken at the same time as VCIDE, may affect the way VCIDE works or VCIDE may affect the way they work.
*VCIDE* ***must not be used*** *if you are already taking any of the following list of medicines. Tell your doctor if you take:*
- Astemizole (used for allergy)
- Terfenadine (used for allergy)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heartbeat)
- Carbamazepine (used to treat seizures)
- Phenobarbital (phenobarbitone) (used for severe insomnia and seizures)
- Efavirenz (used for treating HIV). Standard doses of VCIDE and standard doses (400 mg or more) of efavirenz must not be given together
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Rifampicin (used for treating tuberculosis)
- Ritonavir (used for treating HIV) in doses of 400 mg and more twice daily
- St. John's Wort (herbal supplement used for depression)
- Sirolimus (used in transplant patients).

*Tell your doctor if you are taking the following medicine, as treatment with VCIDE at the same time should be avoided if possible:*
- Ritonavir (used for treating HIV) in doses of 100 mg twice daily.
- Rifabutin (used for treating tuberculosis). If you are already being treated with rifabutin, VCIDE is contraindicated and may not be administered.
- Phenytoin (used to treat epilepsy). If you are already being treated with phenytoin your blood concentration of phenytoin will need to be monitored during your treatment with VCIDE and your dose may be adjusted.

*Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines and/or VCIDE are still having the desired effect:*
- Everolimus (used for treating advanced kidney cancer and in transplant patients)
- Fluconazole (used for fungal infections)
- Warfarin (used to slow down clotting of the blood)
- Benzodiazepines (for example midazolam, triazolam) (used for severe insomnia and stress)
- Ciclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Oxycodone and other long-acting opiates such as hydrocodone (used for moderate to severe pain)
- Methadone (used to treat heroin addiction)
- Non-steroidal anti-inflammatory drugs (e.g. ibuprofen, diclofenac) (used for treating pain and inflammation)
- Omeprazole (used for treating ulcers)
- Oral contraceptives (if you take VCIDE while using oral contraceptives, you may get side effects such as nausea and menstrual disorders)
- Alfentanil and fentanyl and other short-acting opiates such as sufentanil (painkillers used for surgical procedures)
- Statins (for example atorvastatin, simvastatin) (used for lowering cholesterol)
- Sulfonylureas (for example tolbutamide, glipizide, and glyburide) (used for diabetes)
- Vinca alkaloids (for example vincristine and vinblastine) (used in treating cancer)
- Other protease inhibitors (for example, saquinavir, amprenavir and nelfinavir)
- Non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz, delavirdine, nevirapine) (used for treating HIV) (some doses of efavirenz can NOT be taken at the same time as VCIDE)
- Indinavir and other HIV protease inhibitors (used for treating HIV).

Do not start taking or using a new medicine before you have discussed this with your doctor or pharmacist. Your doctor and pharmacist have more information on medicines to be careful with, or to avoid while you are given VCIDE.
**Pregnancy and breastfeeding**
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before taking VCIDE.
You should not use VCIDE when you are pregnant.
**You must use effective contraception if you are of childbearing age. Contact your doctor immediately if you become pregnant while being treated with VCIDE.**
It is not known if VCIDE is excreted in breastmilk. You should not breastfeed your baby if you receive VCIDE.
**Driving and using machines**
VCIDE may affect your vision and you may feel dizzy. You should not drive or operate machinery until you know how VCIDE affects you.
**VCIDE contains sodium**
Each vial of VCIDE contains 225,6 mg sodium chloride, which provides 88,74 mg sodium (main component of cooking/table salt). Talk to your doctor or pharmacist if you need 6 or more vials daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

### 3. How to use VCIDE

VCIDE should only be used under the supervision of a doctor.
You will not be expected to give yourself VCIDE. It will be given to you by a person who is qualified to do so.
Your doctor will decide what dose (depending on your weight) you should receive for your condition and also for how long you need to receive it. The dose and duration of treatment will depend on how your body and the infection reacts on the treatment.
Usually you will be given 6 mg VCIDE per kg body mass, every 12 hours for the first 24 hours and thereafter 4 mg/kg every 12 hours as maintenance dose. If you use efavirenz (for HIV) or phenytoin (anti-seizure medicine), your doctor may adapt your dosage. See "Other medicines and VCIDE".
Your doctor or other healthcare provider will give you VCIDE through a slow infusion (a drip for 1 to 2 hours) into one of your large veins.
Before it is used, VCIDE powder for solution for infusion will be reconstituted and diluted to the correct concentration by your hospital pharmacist or nurse.
You may be switched from the intravenous infusion to tablets once your condition improves.
If you have the impression that the effect of VCIDE is too strong or too weak, tell your doctor or pharmacist.
**If you receive more VCIDE than you should**
Since a healthcare provider will administer VCIDE, he/she will control the dosage. However, in the event of overdosage the doctor will manage the overdosage.
**If you missed a dose of VCIDE**
Since a healthcare provider will administer VCIDE, it is unlikely that the dose will be missed.
**If you stop using VCIDE**
It is important that you finish your treatment as prescribed by your doctor.
Do not expect to stop receiving VCIDE just because you feel better. If you stop receiving treatment before the course is completed, the fungus causing the disease may become resistant to VCIDE and your disease will get worse.

### 4. Possible side effects

VCIDE can have side effects.
Not all side effects reported for VCIDE are included in this leaflet. Should your general health worsen or if you experience any untoward effects while receiving VCIDE, please consult your healthcare provider for advice.
**If any of the following happens, stop using VCIDE and tell your doctor immediately:**
- Serious allergic reactions, including a shock reaction. You may have swelling of the tongue and/or throat, difficulty in swallowing, difficulties in breathing, facial swelling, severe dizziness with very fast heartbeat and heavy sweating.
- Allergic skin reactions (sometimes severe), including rapid swelling (oedema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues, itchy or sore patches of thick, red skin with silvery scales of skin, irritation of the skin and mucous membranes, life threatening skin condition that causes large portions of the epidermis, the skin's outermost layer, to detach from the layers of skin below.

These are all very serious side effects. If you have them, you may have had a serious reaction to VCIDE. You may need urgent medical attention or further hospitalisation.
**Tell your doctor immediately if you notice any of the following:**
- Jaundice (yellowing of the eyes or skin, dark urine, upper stomach pain), liver failure, gallbladder disease, gallstones.
- Deterioration of brain function that is a serious complication of liver disease.
- Inflammation of the pancreas (abdominal pain, fever, rapid pulse, nausea, shivering).
- Severe diarrhoea and nausea with fever and weakness. This is a serious condition for which you may need urgent treatment.
- Heart rhythm disturbances, including very fast heartbeat, very slow heartbeat, conduction problems (sometimes life threatening), fainting.
- Double vision, serious conditions of the eye including pain and inflammation of the eyes and eyelids, abnormal eye movement, damage to the optic nerve resulting in vision impairment, optic disc swelling.
- Disorder of blood clotting system (clotting in the blood vessels). Some signs of a blood clot in your arm or leg may be swelling, pain, a warm sensation, reddish discolouration. Some signs of a blood clot in your lungs may be sudden shortness of breath, chest pain, heart pain and coughing. Some signs of a blood clot in your brain may be sudden numbness or weakness in the face, arm or leg, confusion, trouble speaking.
- Guillain-Barre syndrome (the body's immune system attacks part of the peripheral nervous system, with resulting muscle weakness, beginning in the feet and hands).
- Liver injury, inflammation of the liver. Some signs may be yellowing of the skin and eyes, nausea and fever.
- Kidney failure, inflammation in the kidney, blood in the urine, problems urinating, changes in kidney function tests, protein in the urine.

These are all very serious side effects. If you have them, you may have had a serious reaction to VCIDE. You may need urgent medical attention or hospitalisation.
**Tell your doctor if you notice any of the following:**
*Frequent side effects*
- Sinusitis (infection of the nasal passages).
- Low numbers of some types, including severe, of red (sometimes immune-related) and/or white blood cells (sometimes with fever), low numbers of cells called platelets that help the blood to clot (a blood test will be used to check these levels).
- You get more infections than usual. This could be because of a decrease in white blood cells. Your doctor will confirm this with a blood test.
- Low blood sugar, low blood potassium or low sodium in the blood (you will only know for sure that you have these deficiencies if you go for blood tests). Tell your doctor if you have muscle cramps and feel weak.
- Easy or excessive bruising, superficial bleeding into the skin, unexpected excessive bleeding, particularly if you also take or receive blood thinning medicines such as warfarin.
- Depression, problems falling asleep, anxiety, hallucinations (false perceptions).
- Sleepiness, feeling faint and/or dizzy.
- Convulsions (fits or jerks), muscle contractions, severe headache, loss of coordination.
- Tingling or abnormal skin sensations, increase in muscle tone, inability to flex the neck forward due to rigid neck muscles.
- Bleeding in the eye, blurred vision, change in colour vision, eyes sensitive for light, night blindness, a defect of vision in which objects appear greenish, colour blindness, a defect in vision where objects appear blue, eye problems, seeing bright circles that surround a light source, night blindness, seeing small specks, dots, circles, lines, a defect of vision in which objects appear yellowish.
- Shortness of breath, shortness of breath after exercise.
- Low blood pressure (you may feel faint or dizzy).
- Inflammation of a vein (phlebitis, a condition where the veins close to the surface of the body become swollen, tender, and red and may develop blood clots).
- Nausea (feeling sick), vomiting (being sick), diarrhoea (loose bowels), stomach pain, inflammation of the lips
- Liver problems (shown in laboratory tests)
- Constipation, indigestion
- Skin rashes, hair loss
- Back pain
- Feeling tired and generally weak
- Swelling around the eyes, lips, mouth, hands or feet.

*Less frequent side effects*
- Enlarged lymph glands (sometimes painful), failure of bone marrow, increased eosinophil
- High blood cholesterol (shown in laboratory tests)
- Overactive thyroid. If you have muscle weakness, have a rapid heartbeat and increased appetite, tell your doctor
- Underactive thyroid (some signs may be weight gain, fatigue and depression).
- Abnormal sense of taste
- Decreased sensitivity to touch
- Abnormal brain function, Parkinson-like symptoms, nerve injury resulting in numbness, pain, tingling or burning in the hands or feet
- Sudden behaviour changes, problems with thinking or speech
- Problems with balance or coordination, swelling of the brain
- Eye-rolling disorder where the eyes fix upwards
- Swelling and inflammation of nerves that transmit visual information to your eye or brain. Some signs are pain with eye movement and temporary vision loss in one eye.
- Ringing in the ears, dizziness, hearing loss
- Inflammation of certain internal organs – pancreas and duodenum, swelling and inflammation of the tongue
- Inflammation of the thin tissue that lines the inner wall of the abdomen and covers the abdominal organ (you may have signs like abdominal pain, bloating, fever, nausea)
- Bullous photosensitivity (skin blisters caused by sunlight)
- Freckles and pigmented spots
- Joint and muscle pains in the legs and arm
- Movement disorders (restlessness), parkinsonism (tremor, slow movement, impaired speech or muscle stiffness)
- Sleeplessness
- Flu-like illness
- Shivering, reactions at the site of the injection, including fever, reddening of the skin, pain, hardness or swelling
- Increased blood cholesterol
- Infusion site reaction (flushing, fever, sweating, increased heart rate and shortness of breath). Your doctor may stop the infusion if this occurs.

Other significant side effects whose frequency is not known, but should be reported to your doctor immediately:
- Skin cancer
- Inflammation of the tissue surrounding the bone
- Red, scaly patches or ring-shaped skin lesions that may be a symptom of an autoimmune disease called cutaneous lupus erythematosus
- Reactions on the infusion: flushing, fever, sweating, quick heartbeat, tight chest, shortness of breath, faintness, nausea, itching and rash.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.
**Reporting of side effects**
If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA on the SAHPRA website: https://www.sahpra.org.za/Publications/Index/8.
By reporting side effects, you can help provide more information on the safety of VCIDE.

### 5. How to store VCIDE

Store all medicines out of reach of children.
Store in the original carton at or below 25 °C.
***Reconstituted solutions:***
Once reconstituted, VCIDE should be used immediately, but if necessary, may be stored for up to 72 hours at 2-8 °C or at room temperature (at or below 25 °C).
Reconstituted VCIDE needs to be diluted with a compatible infusion solution first before it is infused. Your healthcare professional will prepare and store the solution according to the directions on the professional information.

### 6. Contents of the pack and other information

**What VCIDE contains**
- The active substance is voriconazole.
  Each vial contains 200 mg voriconazole, equivalent to a 10 mg/ml solution when reconstituted by your hospital pharmacist or nurse.
- The other ingredients are hydroxypropyl-beta-cyclodextrin (HP-beta-CD), sodium chloride and hydrochloric acid (for pH adjustment).

**What VCIDE looks like and contents of the pack**
A white to off-white, lyophilised powder.
The prepared solution is clear and without visible particles.
VCIDE is packed in 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. The vials are individually packed in cardboard boxes together with the patient information leaflet.

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MACLEODS

## INLIGTINGSPAMFLET VIR DIE PASIËNT

**SKEDULERINGSTATUS: S4**

**VCIDE® 200 IV,** 200 mg poeier vir oplossing vir infusie
**Vorikonasool**
**Suikervry**
Bevat 88,74 mg natrium/flessie

**Lees die hele pamflet sorgvuldig deur voordat VCIDE aan jou gegee word**
- Hou hierdie pamflet. Dit is moontlik dat jy dit weer sal wil lees.
- Indien jy nog vrae het, raadpleeg asseblief jou dokter, apteker, verpleegster of ander gesondheidsorgverskaffer.
- VCIDE is vir jou persoonlik voorgeskryf en jy moet nie jou medisyne met ander mense deel nie. Dit kan skadelik vir hulle wees, selfs al is hulle simptome dieselfde as joune.

**Wat is in hierdie pamflet**
1. Wat VCIDE is en waarvoor dit gebruik word
2. Wat jy moet weet voordat VCIDE aan jou gegee word
3. Hoe VCIDE aan jou gegee sal word
4. Moontlike newe-effekte
5. Hoe om VCIDE te bewaar
6. Inhoud van die pakkie en ander inligting

### 1. Wat VCIDE is en waarvoor dit gebruik word

VCIDE is 'n medisyne wat teen swamme werk. Dit werk deur die swamme wat infeksies veroorsaak te vernietig, of die groei daarvan te stop.
VCIDE word vir die behandeling van 'n wye verskeidenheid van swaminfeksies by pasiënte (volwassenes en kinders ouer as 2 jaar) gebruik.
VCIDE kan ook gebruik word vir die voorkoming van swaminfeksies by hoë-risiko ontvangers van beenmurgoorplantings.

### 2. Wat jy moet weet voordat VCIDE aan jou gegee word

**VCIDE moet nie aan jou toegedien word nie:**
- as jy hipersensitief (allergies) is vir vorikonasool of vir enige bestanddeel van VCIDE (gelys in afdeling 6);
- as jy verlengde QT-sindroom het ('n afwyking van die hartritme);
- as jou lewerfunksie erg aangetas is;
- as jy swanger is of borsvoed;

'n Lys van die medisyne wat VCIDE kan beïnvloed, word in die afdeling "Ander medisynes en VCIDE" getoon. Die medisyne in die volgende lys moet egter nie tydens jou behandeling met VCIDE geneem word nie:
- Astemisool (gebruik vir allergie)
- Sisapried (gebruik vir maagprobleme)
- Pimosied (gebruik vir die behandeling van geestesiekte)
- Kinidien (gebruik vir onreëlmatige hartslag)
- Ergot alkaloïede (bv. ergotamien, dihidroërgotamien; gebruik vir migraine)
- Rifampisien, rifabutien (gebruik vir die behandeling van tuberkulose)
- Efavirens (gebruik vir die behandeling van MIV) by dosisse van 400 mg en meer, een keer daagliks
- Karbamasepien (gebruik om stuipe te behandel)
- Fenobarbitaal (fenobarbitoon) (gebruik vir erge slaaploosheid en stuipe)
- Ritonavir (gebruik vir die behandeling van MIV) by dosisse van 400 mg en meer, twee keer daagliks
- Sirolimus (gebruik by oorplantingspasiënte)
- Sint-Johanneskruid ('n kruiemiddel wat gebruik word vir depressie).

**Waarskuwings en voorsorgmaatreëls**
*Vrouens wat nog in hulle vrugbare jare is*
As jy 'n vrou is wat nog kinders kan kry moet jy altyd doeltreffende voorbehoedmiddels tydens behandeling gebruik. Kyk "Swangerskap en borsvoeding".
*Lig jou dokter of gesondheidsorgkundige in van die volgende, voordat VCIDE aan jou gegee word, indien:*
- jy allergies is vir ander medisynes van die asool-tipe (byvoorbeeld flukonasool of ketokonasool wat swamwerende middels is. Vra jou dokter of apteker as jy nie seker is nie);
- as daar 'n moontlikheid is dat jy swanger kan raak (as jy in die vrugbare ouderdom is). VCIDE kan nie gebruik word vir die behandeling van pasiënte wat swanger is of borsvoed nie. Jou dokter sal jou raad gee oor doeltreffende voorbehoeding;
- as jy tans aan 'n lewersiekte ly, of voorheen gehad het. As jy 'n lewersiekte het, kan jou dokter 'n laer dosis van VCIDE voorskryf. Jou dokter behoort ook jou lewerfunksie te moniteer deur bloedtoetse te doen terwyl jy met VCIDE behandel word;
- dit bekend is dat jy kardiomiopatie het ('n hartspieraandoening), onreëlmatige hartklop, stadige hartklop, of 'n afwyking van die elektrokardiogram (EKG) wat 'lang QTc-sindroom' genoem word;
- jy 'n metaboliese siekte het soos lae kalium, kalsium of magnesium;
- jy niersiekte het. Afhangend van die mate van niersiekte, kan die dokter besluit om eerder vorikonasool-tablette te gee. Jou dokter behoort ook jou nierfunksie te moniteer deur bloedtoetse te doen terwyl jy met VCIDE behandel word.

*Jy moet ook weet dat:*
Jy moet sonlig en blootstelling aan die son vermy terwyl jy behandel word. Dit is belangrik om velareas wat aan die son blootgestel word te bedek en om sonskerm met 'n hoë sonbeskermingsfaktor (SPF) te gebruik, want die vel kan meer gevoelig raak vir die son se UV-strale. Hierdie voorsorgmaatreëls is ook op kinders van toepassing.
Terwyl jy met VCIDE behandel word, lig jou dokter dadelik in as jy die volgende ontwikkel:
- sonbrand
- erge veluitslag of blase
- beenpyn.

As jy bogenoemde velaandoenings ontwikkel, kan jou dokter jou na 'n dermatoloog verwys, wat na konsultasie kan besluit dat dit belangrik is dat jy gereeld gesien word. Daar is 'n klein kans dat velkanker kan ontwikkel met langdurige gebruik van VCIDE.
VCIDE kan probleme met jou oë en visie, waaronder dowwe visie, verandering in kleurwaarneming en liggevoeligheid veroorsaak. Jy moet 'n sonbril dra om jou oë teen helder lig te beskerm. Lig jou dokter dadelik in as jy oog/visieprobleme het.
As jy 'n orgaanoorplanting gehad het en jy ontvang VCIDE, kan jy ontsteking en pyn in die bene hê. Spreek jou dokter so gou as wat jy kan. Hy/sy sal besluit of jy moet aanhou met die behandeling met VCIDE en sal jou behandel soos nodig.
*Kinders*
Sonbrand of ernstige velreaksie na blootstelling aan lig of son is meer gereeld by kinders ervaar. As jou kind velaandoenings ontwikkel kan jou dokter jou kind na 'n dermatoloog verwys, wat na konsultasie kan besluit dat dit belangrik is dat jou kind gereeld gesien moet word. Verhoogde lewerensieme is ook meer gereeld by kinders waargeneem.
**Ander medisynes en VCIDE**
Lig altyd jou gesondheidsorgverskaffer in as jy enige ander medisyne neem. (Dit sluit alle komplementêre of tradisionele medisyne in).
Sommige medisynes, wat gelyktydig met VCIDE geneem word, kan die werking van VCIDE beïnvloed, of VCIDE kan die werking daarvan beïnvloed.
*VCIDE* ***mag nie gebruik word nie*** *as jy alreeds een van die volgende lys medisynes gebruik. Lig jou dokter in as jy die volgende neem:*
- Astemisool (gebruik vir allergie)
- Terfenadien (gebruik vir allergie)
- Sisapried (gebruik vir maagprobleme)
- Pimosied (gebruik vir die behandeling van geestesversteuring)
- Kinidien (gebruik vir ongereelde hartslag)
- Karbamasepien (gebruik om stuipe te behandel)
- Fenobarbitaal (fenobarbitoon) (gebruik vir erge slaaploosheid en stuipe)
- Efavirens (gebruik om MIV te behandel). Standaard dosisse van VCIDE en standaard dosisse (400 mg of meer) efavirens moet nie saam gegee word nie
- Ergot alkaloïede (bv. ergotamien, dihidroërgotamien; gebruik vir migraine)
- Rifampisien (gebruik vir die behandeling van tuberkulose)
- Ritonavir (gebruik vir die behandeling van MIV) by dosisse van 400 mg en meer, twee keer daagliks
- Sint-Johanneskruid ('n kruiemiddel wat gebruik word vir depressie)
- Sirolimus (gebruik by oorplantingspasiënte).

*Lig jou dokter in as jy die volgende medisynes gebruik, aangesien gelyktydige behandeling met VCIDE vermy moet word indien moontlik:*
- Ritonavir (gebruik vir die behandeling van MIV) by dosisse van 100 mg en meer, twee keer daagliks.
- Rifabutien (gebruik vir die behandeling van tuberkulose). As jy reeds met rifabutien behandel word, is VCIDE teenaangedui en mag dit nie toegedien word nie.
- Fenitoïen (gebruik om epilepsie te behandel). As jy reeds met fenitoïen behandel word, moet jou bloedkonsentrasie van fenitoïen tydens jou behandeling met VCIDE gemoniteer word en jou dosis kan aangepas word.

*Sê vir jou dokter indien jy een van die volgende medisynes gebruik, aangesien 'n dosisaanpassing of monitering nodig kan wees om te kontroleer of die medisyne en/of VCIDE steeds die gewenste uitwerking het:*
- Everolimus (gebruik vir die behandeling van gevorderde nierkanker en by oorplantingspasiënte)
- Flukonasool ('n medisyne gebruik vir swaminfeksies)
- Warfarien (gebruik om die stolling van bloed te vertraag)
- Bensodiasepiene (byvoorbeeld midasolaam, triasolaam) (gebruik vir erge slapeloosheid en spanning)
- Siklosporien (gebruik by oorplantingspasiënte)
- Takrolimus (gebruik by oorplantingspasiënte).
- Oksikodoon en ander langwerkende opiate soos hidrokodoon (gebruik vir matig-tot-ernstige pyn)
- Metadoon (gebruik om heroïen verslawing te behandel)
- Niesteroïdale anti-inflammatoriese medisynes (bv. ibuprofeen, diklofenak) (gebruik vir die behandeling van pyn en inflammasie)
- Omeprasool (gebruik vir behandeling van maagswere)
- Orale voorbehoedmiddels (as jy VCIDE gebruik terwyl jy orale voorbehoedmiddels gebruik, kan jy newe-effekte soos naarheid en menstruele afwykings kry)
- Alfentaniel en fentaniel en ander kortwerkende opiate soos sufentaniel (pynstillers wat vir chirurgiese prosedures gebruik word)
- Statiene (byvoorbeeld atorvastatien, simvastatien) (word gebruik om cholesterol te verlaag)
- Sulfonielureum (byvoorbeeld tolbutamied, glipisied en gliburied) (gebruik vir diabetes)
- Vinka-alkaloïede (byvoorbeeld vinkristien en vinblastien) (gebruik by die behandeling van kanker)
- Ander proteaseremmers (byvoorbeeld sakinavir, amprenavir en nelfinavir)
- Nie-nukleosied-trutranskriptaseremmers (bv. efavirens, delavirdien, nevirapien) (gebruik vir die behandeling van MIV) (sommige dosisse efavirens kan NIE gelyktydig met VCIDE geneem word nie)
- Indinavir en ander MIV-proteaseremmers (gebruik om MIV te behandel).

Moenie 'n nuwe medisyne begin neem of gebruik voordat jy dit met jou dokter of apteker bespreek het nie. Jou dokter of apteker sal meer inligting hê oor die medisynes waarvoor jy versigtig moet wees, of moet vermy, terwyl VCIDE aan jou gegee word.
**Swangerskap en borsvoeding**
Indien jy swanger is of borsvoed, dink jy is dalk swanger, of beplan om 'n baba te hê, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgverskaffer vir advies voordat jy VCIDE neem.
Jy moet nie VCIDE neem as jy swanger is nie.
**As jy nog 'n vrugbare vrou is wat kinders kan hê moet jy doeltreffende voorbehoeding gebruik. Indien jy swanger raak terwyl jy met VCIDE behandel word, kontak dadelik jou dokter.**
Dit is nie bekend of VCIDE in borsmelk uitgeskei word nie. Jy moet nie jou baba borsvoed as jy VCIDE ontvang nie.
**Bestuur en gebruik van masjinerie**
VCIDE kan jou sig aantas en jy kan duiselig voel. Jy moet nie bestuur of masjinerie hanteer voordat jy nie weet hoe VCIDE jou aantas nie.
**VCIDE bevat natrium**
Elke flessie met VCIDE bevat 225,6 mg natriumchloried, wat 88,74 mg natrium (hoofkomponent van kook-/tafelsout) voorsien. Praat met jou dokter of apteker as jy 6 of meer flessies daagliks benodig vir 'n lang tydperk, veral as jy aangeraai was om 'n dieet met min sout (natrium) te volg.

### 3. Hoe om VCIDE te gebruik

VCIDE moet slegs onder toesig van 'n dokter gebruik word.
Daar sal nie van jou verwag word om VCIDE aan jouself toe te dien nie. Dit sal aan jou gegee word deur 'n persoon wat gekwalifiseer is om dit te doen.
Jou dokter sal besluit watter dosis (afhangend van jou gewig) jy vir jou toestand moet ontvang en ook vir hoe lank jy dit moet ontvang. Die dosis en duur van die behandeling sal afhang van hoe jou liggaam en die infeksie op die behandeling reageer.
Gewoonlik sal 6 mg VCIDE per kg liggaamsmassa, elke 12 uur vir die eerste 24 uur en daarna 4 mg/kg elke 12 uur as instandhoudingsdosis aan jou gegee word.
As jy efavirens (vir MIV) of fenitoïen (medisyne teen stuipe) gebruik, kan jou dokter jou dosis aanpas. Kyk ook "Ander medisynes en VCIDE".
Jou dokter of ander gesondheidsorgverskaffer sal VCIDE deur 'n stadige infusie (indruppeling vir 1 tot 2 uur) in een van jou groot are toedien.
Voordat dit gebruik word, sal VCIDE poeier vir oplossing vir infusie aangemaak en deur die hospitaalapteker of verpleegster tot die regte konsentrasie verdun word.
Jy kan van die intraveneuse infusie na die tablette oorgeskakel word sodra jou siektetoestand verbeter.
Indien jy die indruk kry dat die effek van VCIDE te sterk of te swak is, lig jou dokter of apteker in.
**Indien jy meer VCIDE ontvang as wat jy moes**
Aangesien 'n gesondheidsorgverskaffer VCIDE sal toedien, sal hy/sy die dosis beheer. In geval van oordosering sal die dokter egter die oordosering behandel.
**Indien jy 'n dosis van VCIDE oorgeslaan het**
Aangesien 'n gesondheidsorgverskaffer VCIDE sal toedien, is dit onwaarskynlik dat 'n dosis oorgeslaan sal word.
**Indien jy ophou om VCIDE te neem**
Dit is belangrik dat jy die behandeling volgens jou dokter se voorskrif voltooi.
Moenie ophou om VCIDE te neem net omdat jy beter voel nie. As jy ophou om behandeling te ontvang voordat die kursus voltooi is, kan die swam wat die siekte veroorsaak, bestand wees teen VCIDE en sal jou siekte erger word.

### 4. Moontlike newe-effekte

VCIDE kan newe-effekte hê.
Nie alle newe-effekte wat vir VCIDE aangemeld is, word by hierdie pamflet ingesluit nie. Indien jou algemene gesondheid agteruitgaan, of jy enige ongunstige effekte ervaar terwyl jy VCIDE ontvang, raadpleeg asseblief jou gesondheidsorgverskaffer.
**Indien enige van die volgende gebeur, hou op om VCIDE te neem en sê dadelik vir jou dokter:**
- Ernstige allergiese reaksies, wat 'n skok-reaksie insluit. Jy kan die volgende ervaar: 'n geswelde tong en/of keel, sukkel om te sluk of asem te haal, swelling van die gesig, erge duiseligheid met 'n baie vinnige hartklop en baie sweet.
- Allergiese velreaksies (soms erg), insluitend vinnige swelling (edeem) van die dermis, onderhuidse weefsel, slymvlies en weefsels onder die slymvlies, jeukerige of seer kolle van dik, rooi vel met silwer velskubbe, irritasie van die vel en slymvliese, 'n lewensbedreigende veltoestand wat veroorsaak dat groot dele van die epidermis, die buitenste laag van die vel, loskom van die onderlaag van die vel.

Al hierdie newe-effekte is baie ernstig. Indien jy dit ervaar, kan jy moontlik 'n ernstige reaksie op VCIDE hê. Jy kan dringende mediese aandag of verdere hospitalisering benodig.
**Sê dadelik vir jou dokter as jy enige van die volgende waarneem:**
- Geelsug (geel verkleuring van die oë of vel, donker urien, bobuikpyn), lewerversaking, galblaasaandoening, galstene.
- Agteruitgang van breinfunksie, wat 'n ernstige komplikasie van lewersiekte is.
- Ontsteking van die pankreas (buikpyn, koors, vinnige pols, naarheid, bewerigheid).
- Erge diarree en naarheid met koors en swakheid. Dit is 'n ernstige toestand waarvoor jy dringend behandeling kan benodig.
- Hartritmestoornisse, waaronder baie vinnige hartklop, baie stadige hartklop, geleidingsprobleme (soms lewensgevaarlik), floute.
- Dubbelvisie, ernstige oogtoestande, insluitend pyn en ontsteking van die oë en ooglede, abnormale oogbeweging, beskadiging van die optiese senuwee wat lei tot aantasting van sig, swelling van die optiese skyf.
- Versteuring van die bloedstollingsisteem (klonte in die bloedvate). Sommige tekens van 'n bloedklont in jou arm of been kan wees: swelling, pyn, 'n warm gevoel, rooierige verkleuring. Sommige tekens van 'n bloedklont in jou longe kan wees: skielike kortasemigheid, pyn op die bors, hartpyn en hoes. Sommige tekens van 'n bloedklont in jou brein kan wees: skielike gevoelloosheid of swakheid in die gesig, arm of been, verwarring, sukkel om te praat.
- Guillain-Barre-sindroom (die immuunstelsel van die liggaam val 'n deel van die perifere senuweestelsel aan, met gevolglike swakheid van die spiere; wat in die voete en hande begin).
- Lewerbesering, ontsteking van die lewer. Sommige tekens kan geel verkleuring van die vel en oë, naarheid en koors wees.
- Nierversaking, ontsteking in die nier, bloed in die urien, sukkel om te urineer, veranderinge in nierfunksietoetse, proteïen in die urien.

Al hierdie newe-effekte is baie ernstig. Indien jy dit ervaar, kan jy moontlik 'n ernstige reaksie op VCIDE hê. Jy kan dringende mediese aandag of hospitalisering benodig.
**Lig jou dokter in as jy enige van die volgende waarneem:**
*Gereelde newe-effekte*
- Sinusitis (infeksie van die neusgange).
- Lae tellings, ook erge lae tellings, van sommige soorte rooibloedselle (soms immuunverwant) en/of witbloedselle (soms met koors), lae seltelling van bloedplaatjies wat die bloed help stol ('n bloedtoets word gebruik om hierdie vlakke na te gaan).
- Jy kry meer infeksies as gewoonlik. Dit kan wees vanweë 'n afname in witbloedselle. Jou dokter sal dit met 'n bloedtoets bevestig.
- Lae bloedsuiker, lae kalium in die bloed of lae natrium in die bloed (jy sal net seker kan wees dat jy hierdie tekorte het as jy vir bloedtoetse gaan). Sê vir jou dokter as jy spierkrampe het en swak voel.
- Kneus maklik of baie, oppervlakkige bloeding in die vel, onverwagte buitensporige bloeding, veral as jy ook bloedverdunners soos warfarien neem of gebruik.
- Depressie, probleme om aan die slaap te raak, angs, hallusinasies (valse persepsies).
- Slaperigheid, flou gevoel en/of duiseligheid.
- Konvulsies (stuipe of rukkings), spiersametrekkings, erge hoofpyn, verlies aan koördinasie.
- Tinteling of abnormale velsensasies, toename in spiertonus, onvermoë om die nek vorentoe te buig as gevolg van stywe nekspiere.
- Bloeding in die oog, dowwe visie, verandering in kleurvisie, oë wat sensitief is vir lig, nagblindheid, 'n sigafwyking waar voorwerpe groenerig lyk, kleurblindheid, 'n gebrek aan visie waar voorwerpe blou lyk, oogprobleme, sien helder sirkels wat 'n ligbron omsirkel, nagblindheid, sien klein vlekkies, kolletjies, sirkels, lyne, 'n sigafwyking waar voorwerpe gelerig lyk.
- Kortasemigheid, kortasem na oefening.
- Lae bloeddruk (jy kan flou of duiselig voel).
- Inflammasie van 'n aar (flebitis, 'n siektetoestand waar die are naby die oppervlak van die liggaam geswel, teer en rooi word en bloedklonte kan ontwikkel).
- Naarheid (mislike gevoel), braking (opbring), diarree (los stoelgange), maagpyn, ontsteking van die lippe
- Lewerprobleme (deur laboratoriumtoetse aangetoon)
- Hardlywigheid, slegte spysvertering
- Veluitslag, haarverlies
- Rugpyn
- Voel moeg en oor die algemeen swak
- Swelling om die oë, lippe, mond, hande of voete.

*Minder gereelde newe-effekte*
- Vergrote limfkliere (soms pynlik), versaking van die beenmurg, verhoogde eosinofiele
- Hoë bloedcholesterol (deur laboratoriumtoetse aangetoon)
- Ooraktiewe skildklier. Sê vir jou dokter as jy spierswakheid, 'n vinnige hartklop en verhoogde eetlus het
- Onderaktiewe skildklier (sommige tekens kan gewigstoename, moegheid en depressie wees).
- Abnormale smaaksintuig
- Verminderde gevoeligheid vir aanraking
- Abnormale breinfunksie, Parkinson-agtige simptome, senuweebesering wat gevoelloosheid tot gevolg het, pyn, tinteling of branderigheid in die hande of voete
- Skielike gedragsveranderinge, probleme met denke of spraak
- Probleme met balans of koördinasie, swelling van die brein
- Oogtolling versteuring, waar die oë na boontoe gefikseer is
- Swelling en ontsteking van die senuwees wat die visuele inligting tussen jou oog en brein oordra. Sommige tekens kan wees pyn met oogbeweging en tydelike verlies van sig in een oog.
- Suising in die ore, duiseligheid, gehoorverlies
- Ontsteking van sekere interne organe - pankreas en duodenum, swelling en ontsteking van die tong
- Ontsteking van die dun weefsel wat die binnewand van die buik uitvoer en die abdominale orgaan bedek (jy kan tekens hê soos buikpyn, opgeblasenheid, koors, naarheid)
- Blaasagtige liggevoeligheid (velblase deur sonlig veroorsaak)
- Sproete en pigmentasievlekke
- Gewrigs- en spierpyne in die bene en arms
- Bewegingsiekte (rusteloosheid), parkinsonisme (bewing, stadige beweging, belemmerde spraak of spierstyfheid)
- Slapeloosheid
- Griepagtige siekte
- Bewing, reaksies by die plek van inspuiting, insluitend koors, rooiheid van die vel, pyn, hardheid of swelling
- Verhoogde bloed cholesterol
- Reaksie by die infusieplek (gloede, koors, sweet, harttempo neem toe en kortasemigheid). Jou dokter kan die infusie staak as dit voorkom.

Ander beduidende newe-effekte waarvan die frekwensie nie bekend is nie, maar wat dadelik aan jou dokter gerapporteer moet word:
- Velkanker
- Ontsteking van die weefsel om die been
- Rooi, skubberig kolle of ringvormige velletsels wat 'n simptoom kan wees van 'n outo-immuunsiekte genaamd lupus eritematose
- Reaksies op die infusie: gloede, koors, sweet, vinnige hartklop, benoude bors, kortasemigheid, floute, naarheid, jeuk en uitslag.

Indien jy enige newe-effekte opmerk wat nie in hierdie pamflet vermeld word nie, lig jou dokter of apteker in.
**Aanmelding van newe-effekte**
Indien jy newe-effekte ervaar, praat met jou dokter, apteker of verpleegster. Jy kan ook newe-effekte aan SAHPRA rapporteer op die SAHPRA-webwerf:
https://www.sahpra.org.za/Publications/Index/8. Deur newe-effekte aan te meld, kan jy help om meer inligting oor die veiligheid van VCIDE te verskaf.

### 5. Hoe om VCIDE te bewaar

Bewaar alle medisyne buite bereik van kinders.
Berg in die oorspronklike karton, by of onder 25 °C.
***Hersaamgestelde oplossings:***
Sodra dit hersaamgestel is, moet VCIDE dadelik gebruik word, maar indien nodig kan dit vir tot en met 72 uur by 2-8 °C of by kamertemperatuur (by of onder 25 °C) gebêre word.
Hersaamgestelde VCIDE moet eers met 'n verenigbare infusie-oplossing verdun word voordat die infusie toegedien word. Jou gesondheidsorgkundige sal die oplossing voorberei en volgens die aanwysings op die professionele inligting bewaar.

### 6. Inhoud van die pakkie en ander inligting

**Wat VCIDE bevat**
- Die aktiewe bestanddeel is vorikonasool.
  Elke flessie bevat 200 mg vorikonasool, gelykstaande aan 'n 10 mg/ml oplossing wanneer dit hersaamgestel word deur jou hospitaalapteker of verpleegster.
- Die ander bestanddele is hidroksiepropiel-beta-siklodekstrien (HP-beta-CD), natriumchloried en soutsuur (vir instelling van die pH).

**Hoe VCIDE lyk en wat die inhoud van die pakkie is**
'n Wit tot amperwit, gevriesdroogde poeier.
Die voorbereide oplossing is helder en sonder sigbare deeltjies.
VCIDE word verpak in 'n enkelgebruik 25 ml deursigtige, kleurlose, tipe-I glasflessie, toegemaak met 'n grys rubberprop en 'n aluminiumdop met 'n rooi plastiek wip-af seël. Die flessies word afsonderlik verpak in kartonhouers saam met die pasiëntinligtingsblad.

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**Hierdie pamflet was voorheen hersien in**
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