1.3.1.1 Clean Proposed Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

VCIDE® 50 FC, film-coated tablets

VCIDE® 200 FC, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VCIDE 50 FC film-coated tablets contain 50 mg voriconazole

VCIDE 200 FC film-coated tablets contain 200 mg voriconazole.

Excipient with known effect:

Contains sugar (lactose monohydrate).

Each VCIDE 50 FC tablet contains 58,77 mg lactose monohydrate and each VCIDE 200 FC tablet contains 235,08 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

VCIDE 50 FC is presented as a white to off-white round biconvex film-coated tablet with code V50 on one side.

VCIDE 200 FC is presented as a white to off-white oval biconvex film-coated tablet with code V200 on one side.

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 voriconazole plasma concentrations on day 1 that are close to steady-state (see Table 1). On the basis of the high oral bioavailability (96 %), switching between intravenous and oral voriconazole administration is appropriate when clinically indicated.

Detailed information on dosage recommendations for adults is provided in Table 1 and for children in Table 2.

Table 1 Adult dosage recommendations

	Patients 40 kg and above	**Patients less than 40 kg**
Loading dose regimen for all indications (first 24 hours)	400 mg every 12 hours (for the first 24 hours)	200 mg every 12 hours (for the first 24 hours)
Maintenance dose (after first 24 hours) Prevention of breakthrough infections	200 mg every 12 hours	100 mg every 12 hours
Invasive aspergillosis, serious *Candida* infections, *Scedosporium/Fusarium* infections	200 mg every 12 hours	100 mg every 12 hours

Dosage adjustment:

If patient response is inadequate, the maintenance dose may be increased to 300 mg every 12 hours for oral administration. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily.

If patients are unable to tolerate treatment at these higher doses, reduce the oral dose by 50 mg steps to the 200 mg every 12 hours (or 100 mg every 12 hours for patients less than 40 kg) maintenance dose.

Dosage adjustments in case of co-administration:

Phenytoin may be co-administered with VCIDE if the maintenance dose of VCIDE is increased from 200 mg to 400 mg orally, every 12 hours (100 mg to 200 mg orally, every 12 hours in patients less than 40 kg), 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).

Duration of treatment:

Treatment duration depends upon patients' clinical and mycological response.

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.

If a child can swallow tablets, the dose should be administered to the nearest mg/kg dose possible using whole 50 mg tablets.

Table 2 Children dosage recommendations

	Oral
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 studied 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

The pharmacokinetics of orally administered VCIDE are not affected by renal impairment. No adjustment in oral dosage is consequently required for patients with mild to severe renal impairment.

Voriconazole is haemodialysed with a clearance of 121 mL/min. A four-hour haemodialysis session does not remove enough VCIDE to warrant dose adjustment.

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.

It is recommended that the standard loading dose regimens of 400 mg every 12 hours (orally) and a maintenance dose of 100 mg every 12 hours (orally) be used in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) taking VCIDE.

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

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 medicine toxicity (see section 4.8).

Paediatric dosage

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 should be taken at least one hour before, or one hour after a meal.

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.
- Pregnancy and lactation.
- Coadministration with the following medicines:
  - CYP3A4 substrates, astemizole, terfenadine, cisapride, pimozide or quinidine, since increased plasma concentrations of these medicines can lead to QTc prolongation and rare occurrences of *Torsades de Pointes* (see sections 4.4 and 4.5).
  - CYP3A4 substrates such as ergot alkaloids, e.g. ergotamine, dihydroergotamine, since increased plasma concentrations of these medicines can lead to ergotism (see sections 4.4 and 4.5).
  - Rifampicin, carbamazepine and phenobarbital (phenobarbitone), since these medicines are likely to decrease plasma voriconazole concentrations significantly (see sections 4.4 and 4.5).
  - Rifabutin, since VCIDE is likely to increase plasma concentrations of rifabutin significantly (see sections 4.4 and 4.5).
  - Ritonavir (high dose – 400 mg and above twice daily), because ritonavir significantly decreased plasma VCIDE concentrations in healthy subjects at this dose (see sections 4.4 and 4.5).
  - Sirolimus, since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see sections 4.4 and 4.5).
  - St. John's wort (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

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).

Cardiovascular effects

Voriconazole (as in 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 cardiomyopathy, hypokalaemia and concomitant medicinal products that may have been contributory (see section 4.5).

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

- 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.

Hepatic toxicity

Serious hepatic reactions may occur during treatment with 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.

Monitoring of hepatic function

Patients receiving VCIDE must be carefully monitored for hepatic toxicity. Clinical management should include laboratory evaluation of hepatic function (specifically AST and ALT) at the initiation of treatment with VCIDE and at least weekly for the first month of treatment. Treatment duration should be as short as possible, however, if based on the benefit-risk assessment the treatment is continued (see section 4.2), monitoring frequency can be reduced to monthly if there are no changes in the liver function tests.

If the liver function tests become markedly elevated, VCIDE should be discontinued.

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

Visual disturbances

VCIDE may cause prolonged visual adverse reactions, including blurred vision, optic neuritis and papilloedema (see section 4.8).

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

These events occurred primarily in severely ill patients who had underlying conditions and/or concomitant medications which may have caused or contributed to these events.

In clinical trials, subjects frequently 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.

These 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.

The mechanism of action is unknown, although the site of action is most likely to be within the retina.

Renal toxicity

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

- *Phototoxicity*

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).

- *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 phototoxic reactions occur, multidisciplinary advice should be sought, VCIDE discontinuation and use of alternative antifungal medicines should be considered, and the patient should be referred to a dermatologist. 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”).

- *Periostitis*

Non-infectious periostitis, with elevated fluoride and alkaline phosphatase levels, has been reported in transplant patients. If a patient develops skeletal pain and radiologic findings

compatible with periostitis, multidisciplinary advice should be obtained and discontinuation of VCIDE considered.

- *Exfoliative cutaneous reactions*

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported with the use of voriconazole. If a patient develops a rash, she/he 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.

Paediatric use

Safety and effectiveness in paediatric patients below the age of 2 years has not been established. VCIDE is indicated for children aged two years or older. A higher frequency of liver enzyme elevations was observed in the paediatric population (see section 4.8). Hepatic function should be monitored in both children and adults. Oral bioavailability may be limited in paediatric patients aged 2 to <12 years with malabsorption and very low body mass for age. Intravenous administration is recommended for these patients.

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

Serious skin reactions (including squamous cell carcinoma):

The frequency of phototoxicity reactions is higher in the paediatric population. As SCC has been reported, stringent measures for photoprotection are required 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

The following medicines may only be given with extra caution or may be contraindicated. Refer to sections 4.5 and 4.3.

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 VCIDE (see section 4.5). Clinical studies have shown that voriconazole increases plasma exposure of these medicines. 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 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 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 (see section 4.5).

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and -substrate)

Coadministration of VCIDE and low dose ritonavir (100 mg twice daily), should be avoided (see section 4.5 and for higher doses see section 4.3).

Efavirenz (CYP450-inducer; CYP3A4-inhibitor and -substrate)

When VCIDE is co-administered with efavirenz, the dose of VCIDE should be increased to 400 mg twice daily and that of efavirenz should be decreased to 300 mg once daily (see sections 4.2 and 4.5).

Fluconazole (CYP3A4, CYP2C9 and CYP2C19 inhibitor)

Coadministration of VCIDE tablets and oral fluconazole results in a significant increase in plasma exposure (C_{max} and AUC_{τ}) of voriconazole in healthy persons. 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)

Coadministration 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).

Lactose

VCIDE contains lactose and should not be given to patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

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.

VCIDE should be administered with caution in patients taking concomitant medicines that is known to prolong QTc interval. When there is also a potential for voriconazole to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide), coadministration is contraindicated (see below and section 4.3).

Interaction table

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

The direction of the arrow for each pharmacokinetic parameter is based on the 90 % confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80-125 % range.

The asterisk (*) indicates a two-way interaction.

AUC_{τ}, AUC_t and $AUC_{0-\infty}$ represent area under the curve over a dosing interval, from time zero to the time with detectable measurement and from time zero to infinity, respectively.

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

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Astemizole, cisapride, pimozide, quinidine and terfenadine *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of these medicines can lead to QTc prolongation and rare occurrences of *torsades de pointes*.	Contraindicated (see section 4.3)
Carbamazepine and long-acting barbiturates (e.g., phenobarbital (phenobarbitone), mephobarbital) *[potent CYP450 inducers]*	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	Contraindicated (see section 4.3)
Efavirenz (a non-nucleoside reverse transcriptase inhibitor) *[CYP450 inducer; CYP3A4 inhibitor and substrate]* Efavirenz 400 mg 1 X daily, co-administered with voriconazole 200 mg 2 X daily* Efavirenz 300 mg 1 X daily, co-administered with voriconazole 400 mg 2 X daily*	Efavirenz C_{max} ↑ Efavirenz AUC_T ↑ Voriconazole C_{max} ↓ Voriconazole AUC_T ↓ Compared to efavirenz 600 mg 1 X daily, Efavirenz C_{max} ↔ Efavirenz AUC_T ↑ Compared to voriconazole 200 mg 2 X daily, Voriconazole C_{max} ↑ Voriconazole AUC_T ↓	Standard doses of VCIDE and standard doses of efavirenz must not be co-administered. Voriconazole may be co-administered with efavirenz if the voriconazole maintenance dose is increased to 400 mg 2 X daily and the efavirenz dose is decreased to 300 mg 1 X daily. When voriconazole treatment is stopped, the initial dose of efavirenz should be restored (see section 4.2 and 4.4).

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Ergot alkaloids (e.g., ergotamine and dihydroergotamine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.	Contraindicated (see section 4.3)
Rifabutin *[potent CYP450 inducer]* 300 mg 1 X daily 300 mg 1 X daily (co-administered with voriconazole 350 mg 2 X daily)* 300 mg 1 X daily (co-administered with voriconazole 400 mg 2 X daily)*	Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓ Compared to voriconazole 200 mg 2 X daily, Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓ Rifabutin C_{max} ↑ Rifabutin AUC_{τ} ↑ Compared to voriconazole 200 mg 2 X daily, Voriconazole C_{max} ↑ Voriconazole AUC_{τ} ↑	Contraindicated (see section 4.3)
Rifampicin (600 mg 1 X daily) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓	Contraindicated (see section 4.3)

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]* High dose (400 mg 2 X daily) Low dose (100 mg 2 X daily)*	Ritonavir C_{max} and AUC_{τ} ↔ Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓ Ritonavir C_{max} ↓ Ritonavir AUC_{τ} ↓ Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓	Coadministration of voriconazole and high doses of ritonavir (400 mg and above 2 X daily) is contraindicated (see section 4.3). Coadministration of voriconazole and low dose ritonavir (100 mg 2 X daily) should be avoided.
St. John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg 3 X daily (co-administered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole $AUC_{0-\infty}$↓	Contraindicated (see section 4.3)
Everolimus *[CYP3A4 substrate, P-gp substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	Coadministration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see section 4.4).

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Fluconazole (200 mg 1 X daily) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	Voriconazole C_{max} ↑ Voriconazole AUC_{τ} ↑ Fluconazole C_{max} ND Fluconazole AUC_{τ} ND	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.
Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]* 300 mg 1 X daily 300 mg 1 X daily (co-administered with voriconazole 400 mg 2 X daily)*	Voriconazole C_{max} ↓ Voriconazole AUC_{τ} ↓ Phenytoin C_{max} ↑ Phenytoin AUC_{τ} ↑ Compared to voriconazole 200 mg 2 X daily, Voriconazole C_{max} ↑ Voriconazole AUC_{τ} ↑	Concomitant use of voriconazole and phenytoin should be avoided. Careful monitoring of phenytoin plasma levels is recommended. Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased from 200 mg to 400 mg oral 2 X daily (100 mg to 200 mg oral 2 X daily in patients less than 40 kg) (see section 4.2).

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Anticoagulants Warfarin (30 mg single dose, co-administered with 300 mg 2 X daily voriconazole) *[CYP2C9 substrate]* Other oral coumarins (e.g., phenprocoumon, acenocoumarol) *[CYP2C9 and CYP3A4 substrates]*	Maximum increase in prothrombin time was approximately 2-fold. Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.	Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.
Benzodiazepines (e.g., midazolam, triazolam, alprazolam) *[CYP3A4 substrates]*	Although not studied clinically, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	Dose reduction of benzodiazepines should be considered.
Immunosuppressants *[CYP3A4 substrates]* Sirolimus (2 mg single dose)	In an independent published study, Sirolimus C_{max} ↑ Sirolimus $AUC_{0-\infty}$↑	Coadministration of voriconazole and sirolimus is contraindicated (see section 4.3).

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin C_{max} ↑ Ciclosporin AUC_{τ} ↑	When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. **When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.**

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Tacrolimus (0,1 mg/kg single dose)	Tacrolimus C_{max} ↑ Tacrolimus AUC_t ↑	When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. **When voriconazole is discontinued, tacrolimus levels must be carefully monitored, and the dose increased as necessary.**
Long-acting opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose)	In an independent published study, Oxycodone C_{max} ↑ Oxycodone $AUC_{0-\infty}$↑	Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse reactions may be necessary.

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Methadone (32-100 mg 1 X daily) *[CYP3A4 substrate]*	R-methadone (active) C_{max} ↑ R-methadone (active) AUC_{T} ↑ S-methadone C_{max} ↑ S-methadone AUC_{T} ↑	Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended. Dose reduction of methadone may be needed.
Non-steroidal anti-inflammatory drugs (NSAIDs) *[CYP2C9 substrates]* Ibuprofen (400 mg single dose) Diclofenac (50 mg single dose)	S-Ibuprofen C_{max} ↑ S-Ibuprofen $AUC_{0-\infty}$↑ Diclofenac C_{max} ↑ Diclofenac $AUC_{0-\infty}$↑	Frequent monitoring for adverse reactions and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.
Omeprazole (40 mg 1 X daily)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	Omeprazole C_{max} ↑ Omeprazole AUC_{T} ↑ Voriconazole C_{max} ↑ Voriconazole AUC_{T} ↑ The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicines.	No dose adjustment of voriconazole is recommended. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose be halved.

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Oral contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ethinylestradiol (1 mg/0,035 mg 1 X daily)	Ethinylestradiol C_{max} ↑ Ethinylestradiol AUC_T ↑ Norethisterone C_{max} ↑ Norethisterone AUC_T ↑ Voriconazole C_{max} ↑ Voriconazole AUC_T ↑	Monitoring for adverse reactions related to oral contraceptives, in addition to those for voriconazole, is recommended.
Short-acting opiates *[CYP3A4 substrates]* Alfentanil (20 µg/kg single dose, with concomitant naloxone) Fentanyl (5 µg/kg single dose)	In an independent published study, Alfentanil $AUC_{0-\infty}$↑ In an independent published study, Fentanyl $AUC_{0-\infty}$↑	Dose reduction of alfentanil, fentanyl and other short-acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse reactions is recommended.
Statins (e.g., lovastatin) *[CYP3A4 substrates]*	Although not studied clinically, voriconazole 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.

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Sulfonylureas (e.g., tolbutamide, glipizide, glyburide) *[CYP2C9 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of sulfonylureas and cause hypoglycaemia.	Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.
Vinca Alkaloids (e.g., vincristine and vinblastine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of vinca alkaloids and lead to neurotoxicity.	Dose reduction of vinca alkaloids should be considered.
Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir)* *[CYP3A4 substrates and inhibitors]*	Not studied clinically. *In vitro* studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	Careful monitoring for any occurrence of medicine toxicity and/or lack of efficacy, and dose adjustment may be needed.
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (e.g., delavirdine, nevirapine)* *[CYP3A4 substrates, inhibitors or CYP450 inducers]*	Not studied clinically. *In vitro* studies show that the metabolism of voriconazole may be inhibited by NNRTIs and voriconazole may inhibit the metabolism of NNRTIs. The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by an NNRTI.	Careful monitoring for any occurrence of medicine toxicity and/or lack of efficacy, and dose adjustment may be needed.

Medicine ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with** VCIDE
Cimetidine (400 mg 2 X daily) *[non-specific CYP450 inhibitor and increases gastric pH]*	Voriconazole C_{max} ↑ Voriconazole AUC_{τ} ↑	No dose adjustment
Digoxin (0,25 mg 1 X daily) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUC_{τ} ↔	No dose adjustment
Indinavir (800 mg 3 X daily) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUC_{τ} ↔ Voriconazole C_{max} ↔ Voriconazole AUC_{τ} ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g 2 X daily) *[CYP3A4 inhibitor]* Azithromycin (500 mg 1 X daily)	Voriconazole C_{max} and AUC_{τ} ↔ Voriconazole C_{max} and AUC_{τ} ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment
Mycophenolic acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_{t} ↔	No dose adjustment
Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	Prednisolone C_{max} ↑ Prednisolone $AUC_{0-\infty}$ ↑	No dose adjustment
Ranitidine (150 mg 2 X daily) *[increases gastric pH]*	Voriconazole C_{max} and AUC_{τ} ↔	No dose adjustment

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

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

Pregnancy

Adequate information is not available on the use of 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 (see section 4.3).

Lactation

The excretion of voriconazole (as contained in VCIDE) into breastmilk has not been investigated. Breastfeeding must be stopped on initiation of treatment with VCIDE (see section 4.3).

Fertility

In an animal study, no impairment of fertility was demonstrated in male and female rats.

4.7 Effects on ability to drive and use machines

VCIDE has moderate influence on the ability to drive and use machines. It 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 while experiencing these symptoms.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were visual impairment, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema, liver function test abnormal, respiratory distress and abdominal pain. The severity of the adverse events was generally mild to moderate. No clinically significant differences were seen when the safety data were analysed by age, race, or gender.

Tabulated summary of adverse reactions

In the table below, causality adverse reactions and their frequency categories are listed by system organ class. Frequency categories are expressed as: Frequent, Less frequent and Frequency unknown (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Frequent	Less frequent	Frequency not known
Infections and infestations	sinusitis	pseudomembranous colitis	
Neoplasms benign, malignant and unspecified (including cysts and polyps)			squamous cell carcinoma*
Blood and lymphatic system disorders	agranulocytosis[1], pancytopenia, thrombocytopenia[2], leukopenia, anaemia	bone marrow failure, lymphadenopathy, eosinophilia, disseminated intravascular coagulation	

System Organ Class	Frequent	Less frequent	Frequency not known
Immune system disorders		hypersensitivity, anaphylactoid reaction	
Endocrine disorders		adrenal insufficiency, hypothyroidism, hyperthyroidism	
Metabolism and nutrition disorders	peripheral oedema, hypoglycaemia, hypokalaemia, hyponatraemia	hypercholesterolemia	
Psychiatric disorders	depression, hallucination, anxiety, insomnia, agitation, confusional state		
Nervous system disorders	headache, convulsion, syncope, tremor, hypertonia[3], paraesthesia, somnolence, dizziness	brain oedema, encephalopathy[4], extrapyramidal disorder[5], peripheral neuropathy, ataxia, hypoaesthesia, dysgeusia, hepatic encephalopathy, Guillain-Barre syndrome, nystagmus	
Eye disorders	visual impairment,[6] retinal haemorrhage	optic nerve disorder[7], papilloedema[8], oculogyric crisis, diplopia, scleritis, blepharitis, optic atrophy, corneal opacity	

System Organ Class	Frequent	Less frequent	Frequency not known
Ear and labyrinth disorders		hypoacusis, vertigo, tinnitus	
Cardiac disorders	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 rhythm	
Vascular disorders	hypotension, phlebitis	thrombophlebitis, lymphangitis	
Respiratory, thoracic and mediastinal disorders	respiratory distress,[9] acute respiratory distress syndrome, pulmonary oedema		
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea, cheilitis, dyspepsia, constipation, gingivitis	peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis	
Hepatobiliary disorders	Abnormal liver function test , jaundice, cholestatic jaundice, hepatitis[10]	cholecystitis, cholelithiasis, hepatomegaly, hepatic failure	

System Organ Class	Frequent	Less frequent	Frequency not known
Skin and subcutaneous tissue disorders	rash, exfoliative dermatitis, alopecia, maculo-papular rash, pruritus, erythema, facial oedema	Stevens-Johnson syndrome[8], phototoxicity, purpura, urticaria, allergic dermatitis, papular rash, macular rash, eczema, toxic epidermal necrolysis[8], drug reaction with eosinophilia and systemic symptoms (DRESS)[8], angioedema, 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	renal tubular necrosis, proteinuria, nephritis	
General disorders and administration site conditions	pyrexia, chest pain, face oedema,[11] asthenia, chills	influenza like illness	
Investigations	increased blood creatinine	increased blood urea, increased blood cholesterol	

*ADR identified post-marketing

[1] Includes febrile neutropenia and neutropenia.

[2] Includes immune thrombocytopenic purpura.

[3] Includes nuchal rigidity and tetany.

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

[5] Includes akathisia and parkinsonism.

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

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

[8] See section 4.4.

[9] Includes dyspnoea and exertional dyspnoea.

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

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

Paediatric population

Overall, the safety profile of voriconazole in paediatric population was similar to that in adults. However, a trend towards a higher frequency of liver enzyme elevations, reported as adverse events in clinical trials was observed in paediatric patients as compared to adults.

Post-marketing data suggest there might be a higher occurrence of skin reactions (especially erythema) in the paediatric population compared to adults. There have been post-marketing reports of pancreatitis in paediatric patients.

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. In an overdose, haemodialysis may assist in the removal of voriconazole from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives. ATC code: J02 AC03.

Mechanism of action:

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

The accumulation of 14 α-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Microbiology

In vitro, voriconazole displays broad-spectrum antifungal activity with antifungal potency against Candida species (including fluconazole resistant *C. krusei* and resistant strains of *C. glabrata* and *C. albicans*) and fungicidal activity against all *Aspergillus* species tested. In addition, voriconazole shows *in vitro* fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium* which have limited susceptibility to existing antifungal medicines.

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. Correlation of *in vitro* activity with clinical outcome is difficult owing to the complexity of the patients studied in clinical trials.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics:

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

Absorption

Voriconazole is well absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1 - 2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96 %. When multiple doses of voriconazole are administered with high fat meals C_{max} and AUC_{τ} are reduced by 34 % and 24 %, respectively.

The absorption of voriconazole is not affected by changes in gastric pH.

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 persons.

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. Poor metabolisers have, on average, 4-fold higher voriconazole exposure (AUC_{τ}) than their homozygous extensive metaboliser counterparts. Persons 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.

Linearity/non-linearity

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

It is estimated that, on average, increasing the oral dose from 200 mg twice daily to 300 mg twice daily leads to a 2,5-fold increase in exposure (AUC_{τ}).

Pharmacokinetic-pharmacodynamic relationships

A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy has not been found.

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 (see section 4.2).

Paediatrics

Average steady-state plasma concentrations in children receiving an intravenous maintenance dose of 4 mg/kg every 12 hours were similar to those in adults receiving 3 mg/kg every 12

hours. Therefore, a maintenance dose of 4 mg/kg every 12 hours is recommended for children aged between 2 to < 12 years of age.

Renal impairment

In patients with normal renal function and mild (creatinine clearance 41 – 60 mL/min) to severe (creatinine clearance < 20 ml/min) renal impairment, the pharmacokinetics of voriconazole were not significantly affected by renal impairment. The plasma protein binding of voriconazole was similar in patients with different degrees of renal impairment (see dosing and monitoring recommendations under sections 4.2 and 4.4).

Hepatic impairment

After a single oral dose (200 mg), the plasma exposure of voriconazole (AUC) was higher in persons with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared with persons 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). See dosing and monitoring recommendations under sections 4.2 and 4.4.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Pregelatinised maize starch

Lactose monohydrate

Povidone K30

Croscarmellose sodium

Colloidal anhydrous silica

Magnesium stearate

Film-coating: Opadry II White OY-LS-28908, consisting of:

Titanium dioxide (E171)

Lactose monohydrate

Hypromellose (E464)

Macrogol/PEG (E1521).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Film-coated tablets: 36 months

Bottles: Use within 30 days after first opening.

6.4 Special precautions for storage

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

6.5 Nature and contents of the container

Cartons containing transparent PVC/aluminium foil blisters of 2, 7, 10, 14, 20, 28, 30, 50, 56 or 100 film-coated tablets, together with a leaflet.

Cartons containing white opaque HDPE bottles, with child-resistant polypropylene screw caps and induction seal liners, with 30 film-coated tablets, together with a leaflet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused VCIDE should be disposed of in accordance with local requirements.

8 REGISTRATION NUMBERS

VCIDE 50 FC: 50/20.1.7/0786

VCIDE 200 FC: 50/20.1.7/0787

7 HOLDER OF CERTIFICATES OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1

Bassonia Estate Office Park (East)

1 Cussonia Drive

Bassonia Rock Ext 12

Alberton, South Africa

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 20 April 2021

10 DATE OF REVISION OF THE TEXT

Not applicable.