1.3.1.1 Proposed Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Vorispore 50 FC, film-coated tablets

Vorispore 200 FC, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg or 200 mg voriconazole.

Excipient with known effect:

Contains sugar (lactose monohydrate).

Each Vorispore 50 FC tablet contains 58,77 mg lactose monohydrate and each Vorispore 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.

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

Vorispore 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 Vorispore to achieve 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 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.

Phenytoin may be co-administered with Vorispore if the maintenance dose of Vorispore 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 Vorispore is co-administered with adapted doses of efavirenz, the maintenance dose of Vorispore 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. Ref 1 (153)

Use in the elderly

No dose adjustment is necessary for elderly patients.

Use in patients with renal impairment

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

Vorispore is haemodialysed with a clearance of 121 ml/min. A four-hour haemodialysis session does not remove enough Vorispore 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 Vorispore.

No data are available on the use of Vorispore in patients with severe chronic hepatic cirrhosis (Child-Pugh C). Ref 1 (161)

Vorispore 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, Vorispore is not recommended for children less than 2 years of age.

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.

Method of administration

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

Ref 1 (131)

4.3 Contraindications

- Hypersensitivity to voriconazole or to any of the excipients of Vorispore listed in section 6.1.
- Patients with prolonged QT- syndrome.
- Severe impairment of hepatic function.
- Coadministration with the following medicines:
  - CYP3A4 substrates, astemizole, 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 drugs can lead to ergotism (see sections 4.4 and 4.5).
  - Rifampicin, carbamazepine and phenobarbital, since these medicines are likely to decrease plasma voriconazole concentrations significantly (see sections 4.4 and 4.5).
  - Rifabutin, since Vorispore 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 Vorispore concentrations in healthy subjects at this dose (see sections 4.4 and 4.5).

- Efavirenz (doses ≥ 400 mg/day), because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations (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 Vorispore to patients with hypersensitivity to other azoles (see section 4.8).

Cardiovascular effects

Vorispore 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 concomitant medicinal products that may have been contributory (see section 4.5).

Vorispore 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 Vorispore therapy (see section 4.2).

Hepatic toxicity

Serious hepatic reactions may occur during treatment with Vorispore (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 Vorispore 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 Vorispore 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, Vorispore should be discontinued, unless the medical judgment of the risk- benefit of the treatment for the patient justifies continued use.

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

Visual disturbances

Vorispore 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. Ref 1 (58)

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 Vorispore 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*

Vorispore 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 Vorispore 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, Vorispore discontinuation and use of alternative antifungal medicines should be considered and the patient should be referred to a dermatologist. If Vorispore is continued, however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions. Vorispore 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), 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 Vorispore 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 Vorispore -treatment.

Long-term treatment

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

Squamous cell carcinoma of the skin (SCC) has been reported in relation with long-term Vorispore 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, multidisciplinary advice should be obtained and discontinuation of Vorispore considered.

Paediatric use

Safety and effectiveness in paediatric patients below the age of 2 years has not been established. Vorispore 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. Ref

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.

Prophylaxis

In case of treatment-related adverse events (hepatotoxicity, severe skin reactions including phototoxicity and SCC, severe or prolonged visual disorders and periostitis), discontinuation of Vorispore and use of alternative antifungal medicines must be considered.

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 Vorispore (see section 4.5). 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 Vorispore . Frequent monitoring for opiate-associated adverse reactions may be necessary (see section 4.5).

Ciclosporin and tacrolimus (CYP3A4 substrates)

Clinically significant medicine interactions with Vorispore 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 Vorispore . Concomitant use of Vorispore and phenytoin should be avoided unless the benefit outweighs the risk (see section 4.5).

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Coadministration of Vorispore and low dose ritonavir (100 mg twice daily), should be avoided unless an evaluation of the benefit/risk justifies the use of Vorispore (see section 4.5)

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

When Vorispore is co-administered with efavirenz, the dose of Vorispore 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)

Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) is recommended. Concomitant use of Vorispore and rifabutin should be avoided (see section 4.3 and 4.5).

Fluconazole (CYP3A4, CYP2C9 and CYP2C19 inhibitor)

Coadministration of Vorispore tablets and oral fluconazole results in a significant increase in 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 Vorispore 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

Vorispore contains lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp 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.Ref 2 (61)

Vorispore 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 Vorispore) 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 Vorispore**
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, 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 C_{max} ↑ 38 % Efavirenz AUC_τ ↑ 44 % Voriconazole C_{max} ↓ 61 % Voriconazole AUC_τ ↓ 77 % Compared to efavirenz 600 mg 1 X daily,	Use of standard doses of voriconazole with efavirenz doses of 400 mg 1 X daily or higher is **contraindicated** (see section 4.3). Voriconazole may be co-administered with efavirenz if

Medicine *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with Vorispore**
Efavirenz 300 mg 1 X daily, co-administered with voriconazole 400 mg 2 X daily*	Efavirenz C_{max} ↔ Efavirenz AUCτ ↑ 17% Compared to voriconazole 200 mg 2 X daily, Voriconazole C_{max} ↑ 23 % Voriconazole AUCτ ↓ 7 %	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).
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} ↓ 69 % Voriconazole AUCτ ↓ 78 % Compared to voriconazole 200 mg 2 X daily, Voriconazole C_{max} ↓ 4 % Voriconazole AUCτ ↓ 32 % Rifabutin C_{max} ↑ 195 % Rifabutin AUCτ ↑ 331 % Compared to voriconazole 200 mg 2 X daily, Voriconazole C_{max} ↑ 104 %	Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk. The maintenance dose of voriconazole may be increased to 5 mg/kg intravenously 2 X daily or from 200 mg to 350 mg orally 2 X daily (100 mg to 200 mg orally 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 Vorispore**
	Voriconazole AUCτ ↑ 87 %	Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) is recommended when rifabutin is co-administered with voriconazole.
Rifampicin (600 mg 1 X daily) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓ 93 % Voriconazole AUCτ ↓ 96 %	**Contraindicated** (see section 4.3)
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]* High dose (400 mg 2 X daily) Low dose (100 mg 2 X daily)*	Ritonavir C_{max} and AUCτ ↔ Voriconazole C_{max} ↓ 66 % Voriconazole AUCτ ↓ 82 % Ritonavir C_{max} ↓ 25 % Ritonavir AUCτ ↓13 % Voriconazole C_{max} ↓ 24 % Voriconazole AUCτ ↓ 39 %	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 unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
St. John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg 3 X daily (co-administered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole $AUC_{0-\infty}$ ↓ 59 %	**Contraindicated** (see section 4.3)

Medicine *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with Vorispore**
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).
Fluconazole (200 mg 1 X daily) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	Voriconazole C_{max} ↑ 57 % Voriconazole AUC_{τ} ↑ 79 % Fluconazole C_{max} ND Fluconazole AUC_{τ} ND	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.

Medicine *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with Vorispore**
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} ↓ 49 % Voriconazole AUC_{τ} ↓ 69 % Phenytoin C_{max} ↑ 67 % Phenytoin AUC_{τ} ↑ 81 % Compared to voriconazole 200 mg 2 X daily, Voriconazole C_{max} ↑ 34 % Voriconazole AUC_{τ} ↑ 39 %	Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended. Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV 2 X daily or 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 Vorispore**
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) Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)	In an independent published study, Sirolimus C_{max} ↑ 6,6-fold Sirolimus $AUC_{0-\infty}$ ↑ 11-fold Ciclosporin C_{max} ↑ 13% Ciclosporin AUC_{τ} ↑ 70%	Coadministration of voriconazole and sirolimus is **contraindicated** (see section 4.3). When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully

Medicine *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with Vorispore**
Tacrolimus (0,1 mg/kg single dose)	Tacrolimus C_{max} ↑ 117 % Tacrolimus AUC_t ↑ 221 %	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.** 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.**

Medicine *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with Vorispore**
Long-acting opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose)	In an independent published study, Oxycodone C_{max} ↑ 1,7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3,6-fold	Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse reactions may be necessary.
Methadone (32-100 mg 1 X daily) *[CYP3A4 substrate]*	R-methadone (active) C_{max} ↑ 31 % R-methadone (active) AUC_{τ} ↑ 47 % S-methadone C_{max} ↑ 65 % S-methadone AUC_{τ} ↑ 103 %	Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended. Dose reduction of methadone may be needed.
Non-steroidal anti-inflammatory drugs (NSAIDs) *[CYP2C9 substrates]* Ibuprofen (400 mg single dose) Diclofenac (50 mg single dose)	S-Ibuprofen C_{max} ↑ 20 % S-Ibuprofen $AUC_{0-\infty}$ ↑ 100 % Diclofenac C_{max} ↑ 114 % Diclofenac $AUC_{0-\infty}$ ↑ 78 %	Frequent monitoring for adverse reactions and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.

Medicine *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with Vorispore**
Omeprazole (40 mg 1 X daily)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	Omeprazole C_{max} ↑ 116 % Omeprazole AUCτ ↑ 280 % Voriconazole C_{max} ↑ 15 % Voriconazole AUCτ ↑ 41 % Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicines.	No dose adjustment of voriconazole is recommended. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose be halved.
Oral contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ethinylestradiol (1 mg/0.035 mg 1 X daily)	Ethinylestradiol C_{max} ↑ 36 % Ethinylestradiol AUCτ ↑ 61 % Norethisterone C_{max} ↑ 15 % Norethisterone AUCτ ↑ 53 % Voriconazole C_{max} ↑ 14 % Voriconazole AUCτ ↑ 46 %	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 $AUC_{0-\infty}$ ↑ 6-fold In an independent published study, Fentanyl $AUC_{0-\infty}$ ↑ 1,34-fold	Dose reduction of alfentanil, fentanyl and other short-acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse reactions is recommended.

Medicine *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with Vorispore**
Statins (e.g., lovastatin) *[CYP3A4 substrates]*	Although not studied clinically, voriconazole is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis.	Dose reduction of statins should be considered.
Sulfonylureas (e.g., tolbutamide, glipizide, glyburide) *[CYP2C9 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of sulfonylureas and cause hypoglycaemia.	Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.
Vinca Alkaloids (e.g., vincristine and vinblastine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of vinca alkaloids and lead to neurotoxicity.	Dose reduction of vinca alkaloids should be considered.
Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir)* *[CYP3A4 substrates and inhibitors]*	Not studied clinically. *In vitro* studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	Careful monitoring for any occurrence of medicine toxicity and/or lack of efficacy, and dose adjustment may be needed.

Medicine *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with Vorispore**
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.
Cimetidine (400 mg 2 X daily) *[non-specific CYP450 inhibitor and increases gastric pH]*	Voriconazole C_{max} ↑ 18 % Voriconazole AUCτ ↑ 23 %	No dose adjustment
Digoxin (0,25 mg 1 X daily) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUCτ ↔	No dose adjustment
Indinavir (800 mg 3 X daily) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUCτ ↔ Voriconazole C_{max} ↔ Voriconazole AUCτ ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g 2 X daily) *[CYP3A4 inhibitor]* Azithromycin (500 mg 1 X daily)	Voriconazole C_{max} and AUCτ ↔ Voriconazole C_{max} and AUCτ ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment

Medicine *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration with Vorispore**
Mycophenolic acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_t ↔	No dose adjustment
Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	Prednisolone C_{max} ↑ 11 % Prednisolone $AUC_{0-\infty}$ ↑ 34 %	No dose adjustment
Ranitidine (150 mg 2 X daily) *[increases gastric pH]*	Voriconazole C_{max} and AUC_τ ↔	No dose adjustment

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Lactation

The excretion of Vorispore into breastmilk has not been investigated. Breastfeeding must be stopped on initiation of treatment with Vorispore.

4.7 Effects on ability to drive and use machines

Vorispore 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.

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[1], pancytopenia, thrombocytopenia[2], leukopenia, anaemia	bone marrow failure, lymphadenopathy, eosinophilia, disseminated intravascular coagulation	
Immune system disorders		hypersensitivity, anaphylactoid reaction	
Endocrine disorders		adrenal insufficiency, hypothyroidism, hyperthyroidism	
Metabolism and nutrition disorders	oedema peripheral, hypoglycaemia, hypokalaemia, hyponatraemia		

Psychiatric disorders	depression, hallucination, anxiety, insomnia, agitation, confusional state		
Nervous system disorders	headache, convulsion, syncope, 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	
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	liver function test abnormal, jaundice, cholestatic jaundice, hepatitis[10]	cholecystitis, cholelithiasis, hepatomegaly, hepatic failure	
Skin and subcutaneous tissue disorders	rash, exfoliative dermatitis, alopecia, maculo-papular rash, pruritus, erythema, facial oedema[1]	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.

Description of selected adverse events

Altered taste perception

Treatment-related taste perversion has been reported in 12 (14 %) of patients.

Visual impairments

Visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, colour blindness, cyanopsia, eye disorder, halo vision, night

blindness, oscillopsia, photopsia, scintillating scotoma, visual acuity reduced, visual brightness, visual field defect, vitreous floaters, and xanthopsia) were frequently reported during clinical trials. These visual impairments were transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed.

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

Dermatological reactions

Dermatological reactions were frequently reported in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medicines. The majority of rashes were of mild to moderate severity. Patients have developed severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) (uncommon), toxic epidermal necrolysis (TEN) (rare), drug reaction with eosinophilia and systemic symptoms (DRESS) (rare) and erythema multiforme (rare) during treatment with Vorispore . See section 4.4.

There have been reports of photosensitivity reactions (such as ephelides, lentigo and actinic keratosis) and squamous cell carcinoma of the skin in patients treated with voriconazole (contained in Vorispore for long periods of time; the mechanism has not been established (see section 4.4).

Liver function tests

Vorispore has been associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, hepatitis and hepatic failure leading to death (see section 4.4).

Liver function test abnormalities (see Tabulated summary of adverse events) may be associated with higher plasma concentrations and/or doses. The majority of

abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

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 Vorispore 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: www.sahpra.org.za**.**

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 Vorispore .

Vorispore 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

A 20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics

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

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.

Ref 2 (139.2) p 17

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

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.

Excretion

Voriconazole is eliminated via hepatic metabolism, with less than 2 % of the dose excreted unchanged in the urine. Ref 1 (20)

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 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

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, 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 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), AUC was 233 % 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 starch maize

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

6.4 Special precautions for storage

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

6.5 Nature and contents of the container

Transparent PVC blisters with aluminum foil packed in cartons of 2, 7, 10, 14, 20, 28, 30, 50, 56 or 100 film-coated tablets, together with the professional information and patient information leaflets.

White opaque HDPE bottles with child-resistant polypropylene screw caps with an induction seal liner packed in cartons with 2, 7, 10, 14, 20, 28, 30, 50, 56 or 100 film-coated tablets, together with the professional information and patient information leaflets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

8 REGISTRATION NUMBER

Vorispore 50 FC: 50/20.1.7/0784

Vorispore 200 FC: 50/20.1.7/0785

7 HOLDER OF CERTIFICATE OF REGISTRATION

Astral Pharma (Pty) Ltd

125 Meade Street

George

6529

South Africa

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 April 2021

10 DATE OF REVISION OF THE TEXT

To be determine