SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

VORICONAZOLE 50 mg VIATRIS Film-coated tablets

VORICONAZOLE 200 mg VIATRIS Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **VORICONAZOLE 50 mg VIATRIS** film-coated tablet contains voriconazole 50 mg.

Contains sugar: lactose monohydrate 64,10 mg per tablet.

Each **VORICONAZOLE 200 mg VIATRIS** film-coated tablet contains voriconazole 200 mg.

Contains sugar: lactose monohydrate 256,40 mg per tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

VORICONAZOLE 50 mg VIATRIS:

A white to off-white, film-coated, oval, biconvex tablet debossed with “V26” on one side of the tablet and blank on the other side.

VORICONAZOLE 200 mg VIATRIS:

A white to off-white, film-coated, capsule shaped, biconvex tablet debossed with “M164” on one side of the tablet and blank on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VORICONAZOLE VIATRIS is indicated for:

- Treatment of invasive aspergillosis.
- Treatment of serious invasive infections caused by *Candida* spp (including *C. krusei*).
- Voriconazole has been used in the 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:

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.4).

1.3.1.1 Professional Information for medicines for human used

Use in Adults:

Therapy must be initiated with the specified loading dose regimen of oral **VORICONAZOLE VIATRIS** to achieve plasma concentrations on day 1 that are close to steady state.

Detailed information on dosage recommendations is provided in the following table:

	Oral	
	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*	200 mg every 12 hours	100 mg every 12 hours

infections, *Scedosporium/* *Fusarium* infections		

Dosage adjustment

If patient response to treatment 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 **VORICONAZOLE VIATRIS** if the maintenance dose of **VORICONAZOLE VIATRIS** 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 section 4.4).

When **VORICONAZOLE VIATRIS** is co-administered with adjusted doses of efavirenz, **VORICONAZOLE VIATRIS** maintenance dose should be increased to 400 mg every 12 hours (see section 4.4 and 4.5).

Treatment duration depends upon patients' clinical and mycological response.

Use in the elderly:

No dose adjustment is necessary for elderly patients.

Use in patients with renal impairment:

The pharmacokinetics of orally administered voriconazole, as in **VORICONAZOLE VIATRIS**, are not affected by renal impairment. Therefore, no adjustment is necessary for oral dosing for patients with mild to severe renal impairment.

Voriconazole, as in **VORICONAZOLE VIATRIS**, is haemodialysed with a clearance of 121 ml/min. A four-hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

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) receiving **VORICONAZOLE VIATRIS**.

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

VORICONAZOLE VIATRIS 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 toxicity (see section 4.4).

Use in children:

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

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

Children aged 2 to < 12 years:

	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

If a child is able to swallow tablets, the dose should be administered to the nearest mg/kg dose possible using whole 50 mg tablets. The pharmacokinetics and tolerability of higher doses have not been characterised in paediatric populations.

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

Duration of Treatment

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

Method of administration

VORICONAZOLE VIATRIS tablets are to be taken at least one hour before, or one hour following a meal

4.3 Contraindications

VORICONAZOLE VIATRIS is contraindicated:

- in patients with known hypersensitivity to voriconazole or to any of the excipients (see section 6.1).
- Co-administration with CYP3A4 substrates, terfenadine, 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 section 4.5).

- Coadministration with rifampicin, carbamazepine and phenobarbitone since these medicines are likely to decrease plasma voriconazole concentrations significantly (see section 4.5).
- Co-administration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations (see section 4.5, for lower doses see section 4.4).
- Co-administration with high-dose ritonavir (400 mg and above twice daily) because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose (see section 4.5, for lower doses see section 4.4).
- Co-administration with ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, since increased plasma concentrations of these medicines can lead to ergotism (see section 4.5).
- Co-administration with sirolimus since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see section 4.5).
- Co-administration with St. John's Wort (see section 4.5).
- Co-administration of voriconazole and rifabutin is contraindicated since voriconazole is likely to increase plasma concentrations of rifabutin significantly (see ‘Interactions’)
- Patients with prolonged QT syndrome
- Pregnancy and lactation
- Severe impairment of hepatic function

4.4 Special warnings and precautions for use

Hypersensitivity

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

Cardiovascular

Voriconazole has been associated with QTc interval prolongation. There have been rare cases of torsades de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concomitant medicines that may have been contributory. **VORICONAZOLE VIATRIS** should be administered with caution to patients with potentially proarrhythmic conditions, such as:

- Congenital or acquired QTc-prolongation.
- Cardiomyopathy, in particular when heart failure is present.
- Sinus bradycardia.
- Existing symptomatic arrhythmias.
- Concomitant medicines that are known to prolong QTc interval. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2). A study has been conducted in healthy volunteers which examined the effect on QTc interval of single doses of voriconazole up to 4 times the usual daily dose. No subject experienced an interval

exceeding the potentially clinically relevant threshold of 500 msec (see section 5.1).

Hepatic toxicity

Cases of serious hepatic reactions have been reported during treatment with voriconazole, as **VORICONAZOLE VIATRIS** (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy (see section 4.8).

Monitoring of hepatic function

Patients receiving **VORICONAZOLE VIATRIS** 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 **VORICONAZOLE VIATRIS** 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, **VORICONAZOLE VIATRIS** 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.

Serious dermatological adverse reactions

- Phototoxicity

In addition, **VORICONAZOLE VIATRIS** 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 **VORICONAZOLE VIATRIS** 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, **VORICONAZOLE VIATRIS** discontinuation and use of alternative antifungal agents should be considered and the patient should be referred to a dermatologist. If **VORICONAZOLE VIATRIS** is continued, however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions. VFEND 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 medicine 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, he should be monitored closely, and **VORICONAZOLE VIATRIS** discontinued if lesions progress.

Long-term treatment

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

Squamous cell carcinoma of the skin (SCC) has been reported in relation with long-term **VORICONAZOLE VIATRIS** 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 **VORICONAZOLE VIATRIS** discontinuation should be considered after multidisciplinary advice.

Visual adverse reactions

There have been reports of prolonged visual adverse reactions, including blurred vision, optic neuritis and papilloedema (see section 4.8).

Renal adverse reactions

Acute renal failure has been observed in severely ill patients undergoing treatment with **VORICONAZOLE VIATRIS**. Patients being treated with voriconazole are likely to be

treated concomitantly with nephrotoxic medicines and have concurrent conditions that may result in decreased renal function (see section 4.8).

Monitoring of renal function

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

Monitoring of pancreatic function

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

Paediatric population

Safety and effectiveness in paediatric subjects below the age of two years has not been established (see sections 4.8 and 5.1). **VORICONAZOLE VIATRIS** is indicated for paediatric patients 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 weight for age. In that case, intravenous voriconazole administration is recommended.

- Serious dermatological adverse reactions (including SCC)

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

are warranted in this population of patients. In children experiencing photoaging injuries such as lentigines or ephelides, sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

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

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

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

Rifabutin (Potent CYP450 inducer)

Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) is recommended when rifabutin is co-administered with **VORICONAZOLE VIATRIS**. Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk (see section 4.5).

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Co-administration of **VORICONAZOLE VIATRIS** and low-dose ritonavir (100 mg twice daily) should be avoided unless an assessment of the benefit/risk to the patient justifies the use of **VORICONAZOLE VIATRIS** (see sections 4.3 and 4.5).

Everolimus (CYP3A4 substrate, P-gp substrate)

Coadministration of **VORICONAZOLE VIATRIS** with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations. Currently there are insufficient data to allow dosing recommendations in this situation (see section 4.5).

Methadone (CYP3A4 substrate)

Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended when co-administered with voriconazole since methadone levels increased following coadministration of voriconazole. Dose reduction of methadone may be needed (see section 4.5).

Short-acting opiates (CYP3A4 substrate)

Reduction in the dose of alfentanil, fentanyl and other short-acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered when co-administered with **VORICONAZOLE VIATRIS** (see section 4.5). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is co-administered with voriconazole, and in an independent published study concomitant use of voriconazole with fentanyl resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl, frequent monitoring

for opiate-associated adverse reactions (including a longer respiratory monitoring period) may be necessary.

Long-acting opiates (CYP3A4 substrate)

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

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Co-administration of oral voriconazole and oral fluconazole resulted in a significant increase in C_{max} and AUC of voriconazole in healthy subjects. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for **VORICONAZOLE VIATRIS** - associated adverse reactions is recommended if **VORICONAZOLE VIATRIS** is used sequentially after fluconazole (see section 4.5).

Excipient warning

VORICONAZOLE VIATRIS contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **VORICONAZOLE VIATRIS**.

4.5 Interaction with other medicines and other forms of interaction

Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.

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

Concomitant use of the following agents with **VORICONAZOLE VIATRIS** is contraindicated”

St John’s Wort (CYP450 inducer; P-gp inducer): In an independent published study in healthy volunteers, St John’s Wort exhibited a short initial inhibitory effect followed by induction of metabolism of voriconazole as contained in **VORICONAZOLE VIATRIS**. Therefore, concomitant use of **VORICONAZOLE VIATRIS** with St John’s Wort is contraindicated (see Section 4.3)

The exposure to **VORICONAZOLE VIATRIS** is significantly reduced by the concomitant administration of the following medicines:

Rifampicin (CYP450 inducer): Rifampicin (600 mg once daily) decreased the C_{max} (maximum plasma concentration) and AUCτ (area under the plasma concentration time curve within a dose interval) of voriconazole by 93 % and 96 %, respectively. Co-administration of **VORICONAZOLE VIATRIS** and rifampicin is contraindicated (see Section 4.3).

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate): The effect of the co-administration of oral voriconazole as contained in **VORICONAZOLE VIATRIS** (200 mg twice daily) and high dose (400 mg) and low dose (100 mg) oral ritonavir was investigated in two separate studies in healthy volunteers. High doses of ritonavir (400 mg twice daily) decreased the steady state C_{max} and AUCτ of oral voriconazole as contained in **VORICONAZOLE VIATRIS** by an average of 66 % and 82 %, whereas low doses of ritonavir (100 mg twice daily) decreased the C_{max} and AUCτ of voriconazole as contained in **VORICONAZOLE VIATRIS** by an average of 24 % and 39 % respectively.

Administration of voriconazole as contained in **VORICONAZOLE VIATRIS** did not have a significant effect on mean C_{max} and AUCτ of ritonavir in the high dose study, although a minor decrease in steady state C_{max} and AUCτ of ritonavir with an average of 25 % and 13 % respectively was observed in the low dose ritonavir interaction study. One outlier subject with raised voriconazole levels was identified in each of the ritonavir interaction studies. Co-administration of **VORICONAZOLE VIATRIS** and high doses of ritonavir (400 mg and above twice daily) is contraindicated. Co-administration of **VORICONAZOLE VIATRIS** and low dose ritonavir (100 mg twice daily) should be

avoided, unless an assessment of the benefit/risk to the patient justifies the use of **VORICONAZOLE VIATRIS** (see Section 4.3 and section 4.4).

Carbamazepine and phenobarbital (potent CYP450 inducers): Although not studied, carbamazepine or phenobarbital are likely to significantly decrease plasma **VORICONAZOLE VIATRIS** concentrations. Co-administration of **VORICONAZOLE VIATRIS** with carbamazepine and phenobarbital is contraindicated (see section 4.3)

Due to minor or no significant pharmacokinetic interactions, no dosage adjustment is required with the following medicines:

Cimetidine (non-specific CYP450 inhibitor and increases gastric pH): Cimetidine (400 mg twice daily) increased voriconazole C_{max} and AUC_{τ} by 18 % and 23 %, respectively. No dosage adjustment of **VORICONAZOLE VIATRIS** is recommended.

Ranitidine (increases gastric pH): Ranitidine (150 mg twice daily) had no significant effect on the C_{max} and AUC_{τ} of voriconazole as contained in **VORICONAZOLE VIATRIS**.

Macrolide antibiotics: Erythromycin (CYP3A4 inhibitor; 1 g twice daily) and azithromycin (500 mg once daily) had no significant effect on the C_{max} and AUC_{τ} of voriconazole as contained in **VORICONAZOLE VIATRIS**.

*Concomitant use of the following medicines with **VORICONAZOLE VIATRIS** is contraindicated:*

Astemizole, cisapride, pimozide and quinidine (CYP3A4 substrates): Although not studied, co-administration of **VORICONAZOLE VIATRIS** with astemizole, cisapride, pimozide, or quinidine is contraindicated, since increased plasma concentrations of these drugs can lead to QTc prolongation and rare occurrences of *Torsades de Pointes* (see section 4.3).

Sirolimus (CYP3A4 substrate): Voriconazole as contained in **VORICONAZOLE VIATRIS** increased sirolimus (2 mg single dose) C_{max} and AUC by 556 % and 1014 % respectively. Co-administration of **VORICONAZOLE VIATRIS** and sirolimus is contraindicated (see section 4.3).

Ergot alkaloids (CYP3A4 substrates): Although not studied, **VORICONAZOLE VIATRIS** may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. Co-administration of **VORICONAZOLE VIATRIS** with ergot alkaloids is contra-indicated (see section 4.3).

*Interaction of **VORICONAZOLE VIATRIS** with the following medicines may result in increased exposure to these medicines. Therefore, careful monitoring and/or dosage adjustment should be considered.*

Ciclosporin (CYP3A4 substrate): In stable, renal transplant recipients, voriconazole as contained in **VORICONAZOLE VIATRIS** increased cyclosporin C_{max} and $AUC\tau$ by at least 13 % and 70 % respectively. When initiating **VORICONAZOLE VIATRIS** in patients

already receiving 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 VIATRIS** is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary (see 'Warnings and Special Precautions').

Tacrolimus (CYP3A4 substrate): Voriconazole as contained in **VORICONAZOLE VIATRIS** increased tacrolimus (0,1 mg/kg single dose) C_{max} and AUCτ (area under the plasma concentration time curve to the last quantifiable measurement) by 117 % and 221 %, respectively. When initiating **VORICONAZOLE VIATRIS** in patients already receiving 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 VIATRIS** is discontinued, tacrolimus levels must be carefully monitored, and the dose increased as necessary (see 'Warnings and Special Precautions').

Methadone (CYP3A4 substrate): Repeat dose administration of oral voriconazole as contained in **VORICONAZOLE VIATRIS** (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 4 days) increased the C_{max} and AUCτ of pharmacologically active R-methadone by 31 % (90 % CI: 22 %, 40 %) and 47 % (90 % CI: 38 %, 57 %), respectively, in subjects receiving a methadone maintenance dose (30 – 100 mg daily) (see 'Warnings and Special Precautions').

Short Acting Opiates (CYP3A4 substrate): In an independent publication, steady-state administration of oral voriconazole as contained in **VORICONAZOLE VIATRIS** increased the AUC∞ of a single dose of alfentanil by 6-fold. Reduction in the dose of alfentanil and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4, should be considered when co-administration with **VORICONAZOLE VIATRIS.**

Fentanyl (CYP3A4 substrate): In an independent published study, concomitant use of voriconazole as contained in **VORICONAZOLE VIATRIS** (400 mg every 12 hours on Day 1, then 200 mg every 12 hours on Day 2) with a single intravenous dose of fentanyl (5 μg/kg) resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl by 1,4-fold (range 1,12 – 1,60-fold). When **VORICONAZOLE VIATRIS** is co-administered with fentanyl, extended and frequent monitoring of patients for respiratory depression and other fentanyl-associated adverse events is recommended, and fentanyl dosage should be reduced if warranted.

Oxycodone (CYP3A4 substrate): In an independent published study, co-administration of multiple doses of oral voriconazole as contained in **VORICONAZOLE VIATRIS** (400 mg every 12 hours, on Day 1 followed by five doses of 200 mg every 12 hours on Days 2 to 4) with single 10 mg oral dose of oxycodone on Day 3 resulted in an increase in the mean C_{max} and $AUC_{0-\infty}$ of oxycodone by 1,7-fold (range 1,4- to 2,2-fold) and 3,6-fold (range 2,7- to 5,6-fold), respectively. The mean elimination half-life of oxycodone was also increased by 2,0-fold (range 1,4- to 2,5-fold). A reduction in oxycodone dosage may be needed during **VORICONAZOLE VIATRIS** treatment to avoid opioid related adverse

effects. Extended and frequent monitoring for adverse effects associated with oxycodone and other long-acting opiates metabolised by CYP3A4 is recommended.

Oral anticoagulants:

Warfarin (CYP2C9 substrate): Co-administration of voriconazole as contained in **VORICONAZOLE VIATRIS** (300 mg twice daily) with warfarin (30 mg single dose) increased maximum prothrombin time / international normalised ratio (INR) by 93 %. Close monitoring of prothrombin time/INR is recommended if warfarin and **VORICONAZOLE VIATRIS** are co-administered.

Sulphonylureas (CYP2C9 substrates): Although not studied, **VORICONAZOLE VIATRIS** may increase the plasma levels of sulphonylureas, (e.g. tolbutamide, glipizide, and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during co-administration.

Statins (CYP3A4 substrates): Although not studied clinically, voriconazole as contained in **VORICONAZOLE VIATRIS** has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, **VORICONAZOLE VIATRIS** is likely to increase plasma levels of statins that are metabolised by CYP3A4. It is recommended that dose adjustment of the statin be considered during co-administration. Increased statin levels have been associated with rhabdomyolysis.

Benzodiazepine (CYP3A4 substrates): Although not studied clinically, voriconazole as contained in **VORICONAZOLE VIATRIS** has been shown to inhibit midazolam

metabolism *in vitro* (human liver microsomes). Therefore, **VORICONAZOLE VIATRIS** is likely to increase the plasma levels of benzodiazepines that are metabolised by CYP3A4 (e.g. midazolam, triazolam and alprazolam) and lead to a prolonged sedative effect. It is recommended that dose adjustment of the benzodiazepine be considered during co-administration.

Vinca Alkaloids (CYP3A4 substrates): Although not studied, voriconazole as contained in **VORICONAZOLE VIATRIS** may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity. It is therefore recommended that dose adjustment of the vinca alkaloid be considered.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDS): Voriconazole as contained in **VORICONAZOLE VIATRIS** increased C_{max} and AUC of ibuprofen (400 mg single dose) by 20 % and 100 %, respectively. **VORICONAZOLE VIATRIS** increased C_{max} and AUC of diclofenac (50 mg single dose) by 114 % and 78 %, respectively. Frequent monitoring for adverse events and toxicity related to NSAID's is recommended. Adjustment of dosage of NSAID's may be needed.

*No significant pharmacokinetic interactions were observed when voriconazole as contained in **VORICONAZOLE VIATRIS** was co-administered with the following medicines. Therefore, no dosage adjustment for these agents is necessary.*

Prednisolone (CYP3A4 substrate): Voriconazole as contained in **VORICONAZOLE VIATRIS** increased C_{max} and AUCτ of prednisolone (60 mg single dose) by 11 % and 34 %, respectively. No dosage adjustment is recommended.

Digoxin (P-glycoprotein mediated transport): voriconazole as contained in **VORICONAZOLE VIATRIS** had no significant effect on C_{max} and AUCτ of digoxin (0,25 mg once daily)

Mycophenolic acid (UDP-glucuronyl transferase substrate): Voriconazole as contained in **VORICONAZOLE VIATRIS** had no effect on the C_{max} and AUCτ of mycophenolic acid (1 g single dose).

Two-way interactions

Efavirenz (a non-nucleoside reverse transcriptase inhibitor [CYP450 inducer; CYP3A4 inhibitor and substrate]): Standard doses of **VORICONAZOLE VIATRIS** and standard doses of efavirenz must not be co-administered. In healthy subjects' steady state efavirenz (400 mg oral once daily) decreased the steady state C_{max} and AUCτ of voriconazole as contained in **VORICONAZOLE VIATRIS** by an average of 61 % and 77 %, respectively. In the same study, voriconazole as contained in **VORICONAZOLE VIATRIS** at steady state (400 mg oral every 12 hours for 1 day, then 200 mg oral every 12 hours for 8 days) increased the steady state C_{max} and AUCτ of efavirenz by an average of 38 % and 44 %, respectively, in the same subjects.

In a separate study in healthy subjects, voriconazole as contained in **VORICONAZOLE VIATRIS** dose of 300 mg twice daily in combination with low dose efavirenz (300 mg once daily) did not lead to sufficient voriconazole exposure.

Following co-administration of voriconazole as contained in **VORICONAZOLE VIATRIS** 400 mg twice daily with efavirenz 300 mg orally once daily, in healthy subjects, the AUCτ of voriconazole was decreased by 7 % and C_{max} was increased by 23 %, compared to voriconazole 200 mg twice daily alone. The AUCτ of efavirenz was increased by 17 % and C_{max} was equivalent compared to efavirenz 600 mg once daily alone. These differences were not considered to be clinically significant.

When **VORICONAZOLE VIATRIS** is co-administered with efavirenz, the **VORICONAZOLE VIATRIS** maintenance dose should be increased to 400 mg twice daily and the efavirenz dose should be reduced by 50 %, i.e. to 300 mg once daily (see section 4.2). When treatment with **VORICONAZOLE VIATRIS** is stopped, the initial dosage of efavirenz should be restored.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Concomitant use of **VORICONAZOLE VIATRIS** and phenytoin should be avoided unless the benefit outweighs the risk. Phenytoin (300 mg once daily) decreased the C_{max} and AUCτ of voriconazole as contained in **VORICONAZOLE VIATRIS** by 49 % and 69 %, respectively. **VORICONAZOLE VIATRIS** (400 mg twice daily, see ‘section 4.2) increased C_{max} and AUCτ of phenytoin (300 mg once daily) by 67 % and 81 %,

respectively. Careful monitoring of plasma phenytoin levels is recommended when phenytoin is co-administered with **VORICONAZOLE VIATRIS**. Phenytoin may be co-administered with **VORICONAZOLE VIATRIS** if the maintenance dose of **VORICONAZOLE VIATRIS** is increased from 3 mg/kg to 5 mg /kg intravenously twice daily or from 200 mg to 400 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg), see section 4.2.

Rifabutin (CYP450 inducer): Concomitant use of **VORICONAZOLE VIATRIS** and rifabutin is contraindicated. (see Section 4.3).

Rifabutin (300 mg once daily) decreased the C_{max} and AUCτ of voriconazole as contained in **VORICONAZOLE VIATRIS** at 200 mg twice daily by 69 % and 78 %, respectively.

During co-administration with rifabutin, the C_{max} and AUCτ of voriconazole as contained in **VORICONAZOLE VIATRIS** at 350 mg twice daily were 96 % and 68 % of the levels when administered alone at 200 mg twice daily. At a voriconazole dose of 400 mg twice daily, C_{max} and AUCτ were 104 % and 87 % higher, respectively, compared with voriconazole alone at 200 mg twice daily, voriconazole at 400 mg twice daily increased C_{max} and AUCτ of rifabutin by 195 % and 331 %, respectively.

Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate): Omeprazole (40 mg once daily) increased voriconazole C_{max} and AUCτ by 15 % and 41 %, respectively. No dosage adjustment of **VORICONAZOLE VIATRIS** is recommended. Voriconazole

as contained in **VORICONAZOLE VIATRIS** increased omeprazole C_{max} and AUCτ by 116 % and 280 %, respectively. When initiating **VORICONAZOLE VIATRIS** in patients already receiving omeprazole, it is recommended that the omeprazole dose be halved. The metabolism of other proton pump inhibitors, which are CYP2C19 substrates, may also be inhibited by **VORICONAZOLE VIATRIS**.

Oral Contraceptives (CYP3A4 substrate): Co-administration of voriconazole as contained in **VORICONAZOLE VIATRIS** and an oral contraceptive (1 mg norethisterone and 0,035 mg ethinylestradiol; once daily) in healthy female subjects resulted in increases in the C_{max} and AUCτ of ethinylestradiol (36 % and 61 % respectively) and norethisterone (15 % and 53 % respectively). **VORICONAZOLE VIATRIS** C_{max} and AUCτ increased by 14 % and 46 % respectively. Oral contraceptives containing doses other than 1 mg norethisterone and 0,035 mg ethinylestradiol have not been studied. As the ratio between norethisterone and ethinylestradiol remained similar during interaction with **VORICONAZOLE VIATRIS**, their contraceptive activity would probably not be affected. Monitoring for adverse events related to oral contraceptives is recommended during co-administration.

Indinavir (CYP3A4 inhibitor and substrate): Indinavir (800 mg three times daily) had no significant effect on voriconazole C_{max} and AUCτ. Voriconazole as contained in **VORICONAZOLE VIATRIS** did not have a significant effect on C_{max} and AUCτ of indinavir (800 mg three times daily).

Other HIV protease inhibitors (CYP3A4 inhibitors)**:** *In vitro* studies suggest that voriconazole as contained in **VORICONAZOLE VIATRIS** may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir). *In vitro* studies also show that the metabolism of voriconazole as contained in **VORICONAZOLE VIATRIS** may be inhibited by HIV protease inhibitors. However, results of the combination of **VORICONAZOLE VIATRIS** with other HIV protease inhibitors cannot be predicted in humans only from *in vitro* studies. Patients should be carefully monitored for any occurrence of drug toxicity and/or loss of efficacy.

Other Non-nucleoside reverse transcriptase inhibitors (NNRTI) (CYP3A4 substrates, inhibitors or CYP450 inducers)*: In vitro* studies show that the metabolism of voriconazole as contained in **VORICONAZOLE VIATRIS** may be inhibited by delavirdine. Although not studied, the metabolism of voriconazole as contained in **VORICONAZOLE VIATRIS** may be induced by nevirapine. **VORICONAZOLE VIATRIS** may also inhibit the metabolism of NNRTIs. Due to the lack of *in vivo* studies, patients should be carefully monitored for any occurrence of drug toxicity and/or lack of efficacy during the co-administration of **VORICONAZOLE VIATRIS** and NNRTIs.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of **VORICONAZOLE VIATRIS** in pregnant women available. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. **VORICONAZOLE VIATRIS** must not be used during pregnancy (see 4.4 Contraindications).

Women of child-bearing potential

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

Breast-feeding

The excretion of voriconazole into breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with **VORICONAZOLE VIATRIS** (see 4.4 Contraindications).

Fertility

In an animal study, no impairment of fertility was demonstrated in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

VORICONAZOLE VIATRIS has moderate influence on the ability to drive and use machines. It may cause transient and reversible changes to vision, including blurring, altered/enhanced visual perception and/or photophobia. Patients must avoid potentially hazardous tasks, such as driving or operating machinery while experiencing these symptoms.

4.8 Undesirable effects

a) Summary of adverse effects

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

b) Tabulated list of adverse reactions

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.

Undesirable effects reported in subjects receiving voriconazole:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Sinusitis
	Less frequent	Pseudomembranous colitis
Neoplasms benign, malignant and unspecified	Frequency unknown	Squamous cell carcinoma

(including cysts and polyps)		
Blood and lymphatic system disorders	Frequent	Agranulocytosis, pancytopenia, thrombocytopenia, leukopenia, anaemia
	Less frequent	Bone marrow failure, lymphadenopathy, eosinophilia, disseminated intravascular coagulation
Immune system disorders	Less frequent	Hypersensitivity, anaphylactoid reaction
Endocrine disorders	Less frequent	Adrenal insufficiency, hypothyroidism, hyperthyroidism
Metabolism and nutrition disorders	Frequent	Peripheral oedema, hypoglycaemia, hypokalaemia, Hyponatraemia

Psychiatric disorders	Frequent	Depression, hallucination, anxiety, insomnia, agitation, confusional state
Nervous system disorders	Frequent	Headache, convulsion, syncope, tremor, hypertonia3, paraesthesia, somnolence, dizziness
	Less frequent	Brain oedema, encephalopathy, extrapyramidal disorder, neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia, hepatic encephalopathy, Guillain-Barre syndrome,

		nystagmus
Eye disorders	Frequent	Visual impairment, retinal haemorrhage
	Less frequent	Optic nerve disorder, papilloedema, oculogyric crisis, diplopia, scleritis, blepharitis, optic atrophy, corneal opacity
Ear and labyrinth disorders	Less frequent	Hypoacusis, vertigo, tinnitus
Cardiac disorders	Frequent	Arrhythmia supraventricular, tachycardia, bradycardia
	Less frequent	Ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia,

		electrocardiogram QT prolonged, supraventricular tachycardia, torsades de pointes, atrioventricular block complete, bundle branch block, nodal rhythm
Vascular disorders	Frequent	Hypotension, phlebitis
	Less frequent	Thrombophlebitis, lymphangitis
Respiratory, thoracic and mediastinal disorders	Frequent	Respiratory distress, acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting, abdominal pain, nausea, cheilitis, dyspepsia,

		constipation, gingivitis
	Less frequent	Peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis
Hepato-biliary disorders	Frequent	Liver function test abnormal, jaundice, jaundice cholestatic, hepatitis
	Less frequent	Hepatic failure, hepatomegaly, cholecystitis, cholelithiasis
Skin and subcutaneous tissue disorders	Frequent	Rash, dermatitis exfoliative, alopecia, rash maculopapular, pruritus, erythema
	Less frequent	Stevens-Johnson syndrome,

		phototoxicity, purpura, urticaria, dermatitis allergic, rash, macular papular, rash, eczema, toxic epidermal necrolysis, medicine reaction with eosinophilia and systemic symptoms (DRESS), angioedema, actinic keratosis, pseudoporphyria erythema multiforme, psoriasis, drug eruption
	Frequency unknown	Cutaneous lupus erythematosus ephelides, lentigo
	Frequent	Back pain

Musculoskeletal and connective tissue disorders	Less frequent	Arthritis
	Frequency unknown	Periostitis
Renal and urinary disorders	Frequent	Renal failure acute, haematuria
	Less frequent	Renal tubular necrosis, proteinuria, nephritis
General disorders and administration site conditions	Frequent	Pyrexia, chest pain, face oedema, asthenia, chills
	Less frequent	Influenza like illness
Investigations	Frequent	Increased blood creatinine
	Less frequent	Increased blood urea, increased blood cholesterol

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important.

It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In clinical trials there were three cases of accidental overdose. All occurred in paediatric patients, who received up to five times the recommended intravenous dose of voriconazole. A single adverse reaction of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics.

Mechanism of action:

Voriconazole is a broad spectrum triazole antifungal agent. Its mode of action is inhibition of fungal cytochrome P450-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis.

Microbiology

I*n 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.

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

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

5.2 Pharmacokinetic properties

The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 200 mg or 300 mg twice

daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or haematopoietic tissue), the observed pharmacokinetic characteristics of rapid and consistent absorption, accumulation and non-linear pharmacokinetics were in agreement with those observed in healthy subjects.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose from 200 mg twice daily to 300 mg twice daily leads to a 2,5 - fold increase in exposure (AUC_T). When the recommended intravenous or oral loading dose regimens are administered, plasma concentrations close to steady state are achieved within 24 hours of dosing. Without the loading dose regimens, accumulation occurs during twice daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by day 6 in the majority of subjects.

Absorption:

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

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

Distribution:

The volume of distribution at steady state for voriconazole is estimated to be 4,6 l/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58 %. Detectable voriconazole concentrations are present in the cerebrospinal fluid of patients treated with voriconazole.

Biotransformation:

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

The inter-individual variability of voriconazole pharmacokinetics is high.

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

The major metabolite of voriconazole is the N-oxide, which accounts for 72 % of the circulating radiolabelled metabolites in plasma. This metabolite has minimal antifungal activity and does not contribute to the overall efficacy of voriconazole.

Elimination:

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

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

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

Pharmacokinetics in Special Patient Groups:

Gender:

In an oral multiple dose study, C_{max} and AUC_T for healthy young females were 83 % and 113 % higher, respectively, than in healthy young males (18 – 45 years). In the same study, no significant differences in C_{max} and AUC_T were observed between healthy elderly males and healthy elderly females (≥ 65 years).

In the clinical programme, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female patients were similar. Therefore, no dosage adjustment based on gender is necessary.

Elderly:

In an oral multiple dose study C_{max} and AUC_T in healthy elderly males (≥ 65 years) were 61 % and 86 % higher, respectively, than in healthy young males (18 - 45 years). No significant differences in C_{max} and AUC_T were observed between healthy elderly females (≥ 65 years) and healthy young females (18 - 45 years).

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

Paediatric population:

The recommended doses in children and adolescent patients are based on a population pharmacokinetic analysis of data obtained from 112 immunocompromised paediatric patients aged 2 to < 12 years and 26 immunocompromised adolescent patients aged 12 to < 17 years.

Renal Impairment:

In an oral single dose (200 mg) study in subjects 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 subjects with different degrees of renal impairment (see sections 4.3 and 4.4).

Hepatic Impairment:

After an oral single dose (200 mg), AUC was 233 % higher in subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared with subjects with normal hepatic function. Protein binding of voriconazole was not affected by impaired hepatic function.

In an oral multiple dose study, AUC_T was similar in subjects with moderate hepatic cirrhosis (Child-Pugh B) given a maintenance dose of 100 mg twice daily and subjects with normal hepatic function given 200 mg twice daily. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C). See sections 4.2 and 4.4.

5.3 Preclinical safety data

Repeated-dose toxicity studies with voriconazole indicated the liver to be the target organ. Hepatotoxicity occurred at plasma exposures similar to those obtained at therapeutic doses in humans, in common with other antifungal agents. In rats, mice and dogs, voriconazole also induced minimal adrenal changes. Conventional studies of safety pharmacology, genotoxicity or carcinogenic potential did not reveal a special hazard for humans.

In reproduction studies, voriconazole was shown to be teratogenic in rats and embryotoxic in rabbits at systemic exposures equal to those obtained in humans with therapeutic doses. In the pre- and post-natal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labour and produced dystocia with consequent maternal mortality and reduced perinatal survival of pups. The effects on parturition are probably mediated by species-specific mechanisms, involving reduction of oestradiol levels, and are consistent with those observed with other azole antifungal agents. Voriconazole administration induced no impairment of male or female fertility in rats at exposures similar to those obtained in humans at therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Croscarmellose sodium (E468)

Lactose monohydrate

Magnesium stearate (E470b)

Povidone (K29/32)

Pregelatinised starch

Film-coating:

Opadry II white (colourant) [lactose monohydrate; HPMC 2910/hypromellose 15cP; titanium dioxide, triacetin]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

PVC/Aluminium blister pack (30's) comprises of clear, transparent PVC film on one side and hard tempered aluminium foil with heat seal lacquer on the other side.

Suitable number of blister strips will be placed in an outer cardboard carton.

The number of tablets per blister strip and the number of blister strips in each carton shall be based on commercial requirement**.**

6.6 Special precautions for disposal and other handling

No special precautions for disposal or other handling.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

Republic of South Africa

8 REGISTRATION NUMBERS

VORICONAZOLE 50 mg VIATRIS: 48/20.1.7/0620

VORICONAZOLE 200 mg VIATRIS: 48/20.1.7/0621

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 November 2021

10 DATE OF REVISION OF THE TEXT

1.3.1.1 Professional Information for medicines for human used