PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VORIFEND IV, 200 mg lyophilised powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VORIFEND IV vial contains 200 mg Voriconazole.

When reconstituted as directed, each ml contains 10 mg Voriconazole.

VORIFEND IV is sugar free.

Excipients with known effect:

Each vial contains 225,60 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Before reconstitution, it is a white to off white lyophilised powder.

The reconstituted solution is clear, colourless and free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VORIFEND IV is used in the treatment of:

- invasive aspergillosis.
- serious invasive infections caused by *Candida* spp (including *C. krusei*).
- serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp.

VORIFEND IV is also indicated for the 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:

It is recommended that VORIFEND IV is administered at a maximum rate of 3 mg/kg per hour over 1 to 2 hours.

For reconstitution directions refer to section 6.6 Special precautions for disposal and other handling.

Use in Adults:

Therapy must be initiated with the specified loading dose regimen for VORIFEND IV to achieve plasma concentrations on Day 1 that are close to steady state.

Dosage recommendations

Loading Dose Regimen for all indications (first 24 hours):

6 mg/kg every 12 hours (for the first 24 hours)

Maintenance Dose (after first 24 hours):

Prevention of breakthrough infections

3 mg/kg every 12 hours

Invasive aspergillosis, serious Candida infections, Scedosporium/Fusarium infections

4 mg/kg every 12 hours.

Dosage adjustment

If patient response is inadequate, the maintenance dose may be increased to 4 mg/kg every 12 hours for intravenous administration.

If patients are unable to tolerate treatment at these higher doses, reduce the intravenous dose to the original maintenance dose, 3 mg/kg every 12 hours.

Duration of treatment:

Treatment duration depends upon patients' clinical and mycological response.

Use in Children:

Safety and effectiveness in paediatric subjects below the age of 2 years has not been established. Therefore, VORIFEND IV 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 ages 2 to < 12 years:

Dosage recommendations

Loading Dose Regimen (first 24 hours):

6 mg/kg every 12 hours (for the first 24 hours).

Maintenance Dose (after first 24 hours):

4 mg/kg every 12 hours.

The pharmacokinetics and tolerability of higher doses have not been characterised in paediatric populations.

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

Duration of treatment

Treatment duration depends on the patient's clinical and mycological response. The duration of voriconazole (as contained in VORIVEND IV) treatment in the clinical studies ranged from 12 weeks to more than 6 months.

Dosage adjustments in case of co-administration

Phenytoin may be co-administered with VORIFEND IV if the maintenance dose of VORIFEND IV is increased to 5 mg/kg intravenously every 12 hours.

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

Special populations

Elderly patients

No dose adjustment is necessary for elderly patients.

Use in patients with renal impairment

In patients with moderate to severe renal dysfunction (creatinine clearance < 50 ml/min), accumulation of the intravenous vehicle, hydroxypropylbetadex, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the risk benefit to the patient justifies the use of intravenous VORIFEND IV. Serum creatinine levels should be closely monitored in these patients and, if increases occur, consideration should be given to changing to oral voriconazole.

Voriconazole is haemodialysed with a clearance of 121 ml/min. A four-hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment. The intravenous vehicle, hydroxypropylbetadex, is haemodialysed with a clearance of 37,5 ± 24 ml/min.

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 be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving VORIFEND IV.
VORIFEND IV has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

VORIFEND IV has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice.
Patients with hepatic impairment must be carefully monitored for voriconazole toxicity (also see section 4.8).

Method of administration

VORIFEND IV requires reconstitution and dilution prior to administration as an intravenous infusion. It is not for bolus injection. For reconstitution directions see section 6.6.

4.3 Contraindications

VORIFEND IV is contraindicated in patients with known hypersensitivity to voriconazole or to any of the excipients listed in section 6.1.

Co-administration of the CYP3A4 substrates, astemizole, cisapride, pimozide, quinidine or terfenadine with VORIFEND IV is contraindicated since increased plasma concentrations of these medicinal products can lead to QTc prolongation and the risk of cardiac dysrhythmias including occurrences of *Torsades de Pointes* (see section 4.5).

Co-administration of VORIFEND IV with rifampicin, carbamazepine and phenobarbitone is contraindicated since these medicines are likely to decrease plasma voriconazole concentrations significantly (see section 4.5).

Co-administration of VORIFEND IV with high dose ritonavir (400 mg and above twice daily) is contraindicated because ritonavir significantly decreased plasma VORIFEND IV concentrations in healthy subjects at this dose (see section 4.5).

Co-administration of ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, is contraindicated since increased plasma concentrations of these medicines can lead to ergotism (see section 4.5).

Co-administration of VORIFEND IV and sirolimus is contraindicated, since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see section 4.5).

Co-administration of VORIFEND IV and rifabutin is contraindicated since VORIFEND IV is likely to increase plasma concentrations of rifabutin significantly (see section 4.5).

Co-administration of VORIFEND IV with St John’s Wort is contraindicated (see section 4.5).

Patients with prolonged QT syndrome.

Pregnancy and lactation.

Severe impairment of hepatic function.

4.4 Special warnings and precautions for use

Women of child-bearing potential

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

Hypersensitivity

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

Cardiovascular

Voriconazole, as contained in VORIFEND IV, has been associated with QTc interval prolongation. There have been cases of torsades de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concomitant medicinal products that may have been contributory. VORIFEND IV is contraindicated in patients with prolonged QT syndrome. VORIFEND IV should be administered with caution to patients with other potentially prodyshythmic conditions, such as:

• Cardiomyopathy, in particular when heart failure is present.

• Sinus bradycardia.

• Existing symptomatic dyshythmias.

• Concomitant medicinal products 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).

Infusion-related reaction

During infusion of the intravenous formulation of VORIFEND IV in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest

tightness, dyspnoea, faintness, nausea, pruritus, and rash have occurred. Symptoms appeared immediately upon initiating the infusion. Depending on the severity of the symptoms, consideration should be given to stopping treatment.

Liver function tests

Liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests are either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

VORIFEND IV has been infrequently associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, and rare cases of hepatitis and hepatic failure leading to death (see section 4.8).

Monitoring of hepatic function

Patients at the beginning of therapy with VORIFEND IV and patients who develop abnormal liver function tests during VORIFEND IV therapy must be routinely monitored for the development of more severe hepatic injury.

Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VORIFEND IV should be considered if clinical signs and symptoms are consistent with liver disease development

Serious dermatological adverse reactions

• Phototoxicity

VORIFEND IV 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 VORIFEND IV 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, VORIFEND IV discontinuation and use of alternative antifungal medicines should be considered and the patient should be referred to a dermatologist. If VORIFEND IV is continued, however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions. VORIFEND IV 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 he/she should be monitored closely and VORIFEND IV discontinued if lesions progress.

Periostitis

Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients.

If a patient develops skeletal pain and radiologic findings compatible with periostitis VORIFEND IV discontinuation should be considered after multidisciplinary advice.

Visual adverse events

There have been reports of irreversible visual adverse events, including optic neuritis and papilloedema.

Altered/enhanced visual perception, blurred vision, colour vision change or photophobia may occur with VORIFEND IV treatment. These visual disturbances may be transient and fully reversible, with the majority spontaneously resolving within 60 minutes (see section 4.8).

Patients with renal adverse events

Acute renal failure may occur in severely ill patients treated with VORIFEND IV and renal function should be monitored during treatment. Patients being treated with VORIFEND IV are likely to be treated concomitantly with nephrotoxic medications 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

Adults and children with risk factors for acute pancreatitis (e.g. recent chemotherapy, haematopoietic stem cell transplantation [HSCT]), should be monitored for development of pancreatitis during VORIFEND IV treatment.

Paediatric use

Safety and effectiveness in paediatric subjects below the age of two years has not been established.

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.

• 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.

Post-marketing data show a higher occurrence of skin reactions in the paediatric population compared to adults.
There have also been post-marketing reports of pancreatitis in paediatric patients. (see section 4.8).

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 voriconazole and use of alternative antifungal medicines must be considered.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)
Careful monitoring of phenytoin levels is recommended when phenytoin is co-administered with VORIFEND IV.
Concomitant use of VORIFEND IV and phenytoin should be avoided unless the benefit outweighs the risk (see section 4.5).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)
When VORIFEND IV is co-administered with efavirenz the dose of VORIFEND IV should be increased to 400 mg twice daily and that of efavirenz should be decreased to 300 mg once daily (see section 4.5).

QT interval prolongation
VORIFEND IV may prolong the QT interval without a clear relationship to plasma concentration. VORIFEND IV should not be used concomitantly with other medicines which prolong the QT interval.

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. Concomitant use of voriconazole and rifabutin is contraindicated (see sections 4.3 and 4.5).

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Co-administration of VORIFEND IV and low dose ritonavir (100 mg twice daily) should be avoided (see section 4.5 and for higher doses see section 4.3).

Everolimus (CYP3A4 substrate, P-gp substrate)

Coadministration of voriconazole 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 events and toxicity related to methadone, including QTc prolongation, is recommended during co-administration. Dose reduction of methadone may be needed (see section 4.5).

Short Acting Opiates (CYP3A4 substrate)

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-administered with VORIFEND IV. As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is co-administered with VORIFEND IV, frequent monitoring for opiate-associated adverse events (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 metabolising by CYP3A4 (e.g. hydrocodone) should be considered when co-administered with VORIFEND IV. Frequent monitoring for opiate-associated adverse events may be necessary (see section 4.5).

Ciclosporin and tacrolimus (CYP3A4 substrates)

Clinically significant medicine interactions with VORIFEND IV may occur in patients who are receiving treatment with ciclosporin or tacrolimus (see section 4.5).

Sodium content

Each vial of VORIFEND IV contains 225,60 mg of sodium chloride. This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

This section addresses the effects of other medicinal products on VORIFEND IV, the effects of VORIFEND IV on other medicinal products and two-way interactions. The interactions for the first two sections are presented in the following order: contraindications, those requiring dosage adjustment and careful clinical and/or biological monitoring and finally those that have no significant pharmacokinetic interaction but that may be of clinical interest in this therapeutic field.

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 VORIFEND IV to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.

VORIFEND IV should be administered with caution in patients with concomitant medication

that is known to prolong QTc interval. When there is also a potential for VORIFEND IV to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide), co-administration is contraindicated (see below and section 4.3).

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

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

Efavirenz (a non-nucleoside reverse transcriptase inhibitor)
(CYP450 inducer; CYP3A4 inhibitor and substrate):
When VORIFEND IV is co-administered with efavirenz, the VORIFEND IV 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 VORIFEND IV treatment is stopped, the initial dose of efavirenz should be restored (see section 4.2 and section 4.4).

Ergot alkaloids (e.g., ergotamine and dihydroergotamine) (CYP3A4 substrates):
Although not studied, voriconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. Co-administration of VORIFEND IV with ergot alkaloids is contraindicated (see section 4.3).

Rifabutin (CYP450 inducer):

Concomitant use of voriconazole and rifabutin is contraindicated (see section 4.3). In clinical trials, rifabutin (300 mg once daily) decreased plasma concentrations of voriconazole at a dose of 200 mg twice daily.

Co-administration with rifabutin 300 mg once a day and voriconazole 400 mg twice daily, increased plasma concentrations of rifabutin and voriconazole, compared to voriconazole alone at 200 mg twice daily.

Rifampicin (CYP450 inducer):

Rifampicin (600 mg once daily) decreased plasma concentration of voriconazole. Co-administration of VORIFEND IV and rifampicin is contraindicated (see section 4.3).

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

Co-administration of voriconazole and high doses of ritonavir (400 mg and above twice daily) is contraindicated. Co-administration of VORIFEND IV and low dose ritonavir (100 mg twice daily) should be avoided (see section 4.3 and section 4.4).

St John's Wort (CYP450 inducer; P-gp inducer):

In an independent published study, St John's Wort 300 mg three times daily and 400 mg voriconazole single dose decreased the plasma concentrations of voriconazole. Therefore, concomitant use of VORIFEND IV with St John's Wort is contraindicated (see section 4.3).

Everolimus [CYP3A4 substrate, P-gp substrate]

Co-administration of with VORIFEND IV and everolimus is not recommended because voriconazole is expected to significantly increase plasma concentrations of everolimus (see section 4.4).

Fluconazole (200 mg QD) [CYP2C9, CYP2C19 and CYP3A4 inhibitor]

The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.

Phenytoin [CYP2C9 substrate and potent CYP450 inducer]:

Concomitant use of VORIFEND IV and phenytoin should be avoided. Careful monitoring of plasma phenytoin levels is recommended when phenytoin is co-administered with VORIFEND IV. Phenytoin (300 mg once daily) decreased the plasma concentration of voriconazole.

Concomitant use of voriconazole (400 mg twice daily) and phenytoin (300 mg once daily), increases the plasma concentration of phenytoin.

Phenytoin may be co-administered with VORIFEND IV if the maintenance dose of voriconazole is increased to 5 mg/kg IV twice daily (see section 4.2).

Oral anticoagulants:

Warfarin (CYP2C9 substrate):

Co-administration of voriconazole (300 mg twice daily) with warfarin (30 mg single dose) increased prothrombin time by a maximum of approximately 2-fold. Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.

Other oral coumarins (e.g., phenprocoumon, acenocoumarol)

[CYP2C9 and CYP3A4 substrates]

Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.

Benzodiazepines (CYP3A4 substrates): Although not studied clinically, VORIFEND IV 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 (CYP3A4 substrate):

Co-administration of VORIFEND IV and sirolimus (2 mg single dose) is contraindicated (see section 4.3).

Ciclosporin (CYP3A4 substrate):

In and independent published study, voriconazole increased plasma concentrations of cyclosporine. When initiating VORIFEND IV 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 VORIFEND IV is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.

Tacrolimus (CYP3A4 substrate):

Voriconazole increased plasma concentrations of tacrolimus. When initiating VORIFEND IV 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 VORIFEND IV is discontinued, tacrolimus levels must be carefully monitored, and the dose increased as necessary.

Long-Acting Opiates [CYP3A4 substrates]

Oxycodone (CYP3A4 substrate):

In an independent published study, co-administration of voriconazole and oxycodone the plasma concentrations of oxycodone increased.

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 (CYP3A4 substrate):

Repeat dose administration of oral voriconazole increased plasma concentration of the pharmacologically active R-methadone and S-methadone in subjects receiving a methadone maintenance dose (30 – 100 mg daily). 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) (CYP2C19 substrates):

Voriconazole increased plasma concentration of ibuprofen (400 mg single dose).

Voriconazole increased the plasma concentrations of diclofenac (50 mg single dose).

Frequent monitoring for adverse events and toxicity related to NSAID's is recommended.

Adjustment of dosage of NSAID's may be needed.

Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate): Omeprazole (40 mg once daily) increased plasma concentrations of voriconazole. No dosage adjustment of VORIFEND IV is recommended. Voriconazole increased plasma concentrations of omeprazole. When initiating VORIFEND IV 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 resulting in increased plasma concentrations of these medicines.

Oral Contraceptives (CYP3A4 substrates):

Co-administration of voriconazole and an oral contraceptive (1 mg norethisterone and 0,035 mg ethinylestradiol once daily) increased the plasma concentrations of norethisterone and ethinylestradiol. The plasma concentration of voriconazole also increased. Monitoring for adverse events related to oral contraceptives, in addition to those for voriconazole is recommended during co-administration.

Short Acting Opiates (CYP3A4 substrate):

Alfentanil (20 µg/kg single dose, with concomitant naloxone).

In an independent publication, voriconazole increased plasma concentration 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 (e.g., sufentanil), should be considered when co-administered with VORIFEND IV.

Fentanyl (5 µg/kg single dose).

In an independent publication, voriconazole increased plasma concentration of a single dose of fentanyl by 1,34-fold.

Extended and frequent monitoring for respiratory depression and other opiate-associated adverse reactions is recommended.

Statins (CYP3A4 substrates):

Although not studied clinically, voriconazole is likely to increase plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis. Dose reduction of statins should be considered.

Sulphonylureas (e.g., tolbutamide,glipizide, glyburide) (CYP2C9) substrates):
Although not studied, voriconazole may increase the plasma concentrations of sulphonylureas and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during co-administration. Dose reduction of sulfonylureas should be considered.

Vinca Alkaloids (CYP3A4 substrates):
Although not studied, voriconazole may increase the plasma concentrations 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.

Other HIV protease inhibitors (CYP3A4 substrates and inhibitors):
In vitro studies suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir) and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors. Patients should be carefully monitored for any occurrence of medicine toxicity and/or loss of efficacy and dose adjustments may be needed.

Other Non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g., delavirdine, nevirapine) (CYP3A4 substrates, inhibitors or CYP450 inducers)
In vitro studies show that the metabolism of voriconazole may be inhibited by NNRTI's and voriconazole may inhibit the metabolism of NNRTI's.
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 (non-specific CYP450 inhibitor and increases gastric pH): Cimetidine (400 mg twice daily) increased the plasma concentration of voriconazole. No dosage adjustment of VORIFEND IV is recommended.

Digoxin (P-glycoprotein mediated transport):
Voriconazole had no significant effect the plasma concentrations of digoxin (0,25 mg once daily). No dose adjustment required.

Indinavir (CYP3A4 inhibitor and substrate):
Indinavir (800 mg three times daily) had no significant effect on the plasma concentration of voriconazole. No dose adjustment required.

Macrolide antibiotics: Erythromycin (CYP3A4 inhibitor; 1 g twice daily) and azithromycin (500 mg once daily):
The effect of voriconazole on either erythromycin or azithromycin is unknown. No dose adjustment required.

Mycophenolic acid (UDP-glucuronyl transferase substrate):
Voriconazole had no effect on the plasma concentration of mycophenolic acid (1 g single dose). No dosage adjustment is recommended.

Prednisolone (CYP3A4 substrate):
Voriconazole increased the plasma concentration of prednisolone (60 mg single dose). No dosage adjustment is recommended.

Ranitidine (increases gastric pH):
Ranitidine (150 mg twice daily) had no significant effect on the plasma concentration of voriconazole. No dosage adjustment is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

No adequate information on the use of VORIFEND IV in pregnant women is available.

Studies in animals have shown reproductive toxicity and teratogenicity. The potential risk to humans is unknown.

VORIFEND IV must not be used during pregnancy (see section 4.3).

Breastfeeding

The excretion of VORIFEND IV into breastmilk has not been investigated. Breastfeeding must be stopped on initiation of treatment with VORIFEND IV (see section 4.3).

Fertility

Women of childbearing potential must always use effective contraception during treatment (see section 4.4).

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

4.7 Effects on ability to drive and use machines

VORIFEND IV 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 whilst experiencing these symptoms.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were visual impairment, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema, liver function test abnormalities, respiratory distress and abdominal pain. The severity of the adverse events was generally mild to moderate.

Tabulated list of adverse reactions

Infections and Infestations

Frequent: Sinusitis.

Less frequent: Pseudomembranous colitis.

Neoplasms benign and malignant (including cysts and polyps)

Frequency unknown: Squamous cell carcinoma of the skin.

Blood and lymphatic system disorders:

Frequent: Thrombocytopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic), leukopenia, pancytopenia and agranulocytosis.

Less frequent: Lymphadenopathy, eosinophilia, disseminated intravascular coagulation, bone marrow depression.

Immune system disorders

Less frequent: Allergic reaction, anaphylactoid reaction.

Endocrine disorders

Less frequent: Adrenal cortex insufficiency, hyperthyroidism, hypothyroidism.

Metabolism and nutrition disorders:

Frequent: Hypokalaemia, hypoglycaemia, peripheral oedema, hyponatraemia.

Less frequent: Hypercholesterolaemia.

Psychiatric disorders:

Frequent: Hallucinations, confusion, depression, anxiety, agitation, insomnia.

Nervous system disorders:

Frequent: Headache, dizziness, tremor, paraesthesia, convulsion, syncope, hypertonia, somnolence.

Less frequent: Ataxia, brain oedema, hypoaesthesia, nystagmus, altered taste perception, Guillain-Barre syndrome, oculogyric crisis, extrapyramidal syndrome, hepatic coma, insomnia, encephalopathy, somnolence during infusion, peripheral neuropathy, hepatic encephalopathy.

Eye disorders:

Frequent: Visual disturbances (including altered/enhanced visual perception, blurred vision, colour vision change, photophobia), retinal haemorrhage.

Less frequent: Blepharitis, optic neuritis, papilloedema, scleritis, diplopia, corneal opacity, optic atrophy, oculogyric crisis.

Ear and labyrinth disorders:

Less frequent: Vertigo, hypoacusis, tinnitus.

Cardiac disorders:

Frequent: Lung oedema, supraventricular dysrhythmia, tachycardia, bradycardia.

Less frequent: Atrial dysrhythmia, ventricular dysrhythmia, ventricular fibrillation, supraventricular tachycardia, prolonged QT interval, atrioventricular (AV) complete block, bundle branch block, nodal dysrhythmia, ventricular tachycardia (including *Torsades de Pointes*), ventricular extrasystoles.

Vascular disorders:

Frequent: Hypotension, thrombophlebitis, phlebitis.

Less frequent: Lymphangitis.

Respiratory, thoracic and mediastinal disorders:

Frequent: Respiratory distress (including dyspnea and exertional dyspnea) acute respiratory distress syndrome, pulmonary oedema.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea, abdominal pain, cheilitis, gastroenteritis, dyspepsia, constipation, gingivitis.

Less frequent: Duodenitis, glossitis, pancreatitis, tongue oedema, peritonitis, pseudomembranous colitis.

Hepatobiliary disorders:

Frequent: Elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, LDH, bilirubin), jaundice, cholestatic jaundice, hepatitis.

Less frequent: Cholecystitis, cholelithiasis, enlarged liver, hepatic failure.

Skin and subcutaneous tissue disorders:

Frequent: Rash, facial oedema, pruritus, maculopapular rash, photosensitivity, skin reaction, alopecia, exfoliative dermatitis, purpura, erythema.

Less frequent: Fixed drug eruption, eczema, psoriasis, Stevens-Johnson syndrome, urticaria, angioedema, discoid lupus erythematosis, erythema multiforme, toxic epidermal necrolysis, pseudoporphyria, allergic dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS), actinic keratosis.

Frequency unknown: Ephelides, lentigo.

Musculoskeletal and connective tissue disorders:

Frequent: Back pain.

Less frequent: Arthritis.

Frequency unknown: Periostitis.

Renal and urinary disorders:

Frequent: Increased creatinine, acute kidney failure, haematuria

Less frequent: Increased blood urea, albuminuria, nephritis, kidney. tubular necrosis, proteinuria.

General disorders and administration site conditions:

Frequent: Fever, peripheral oedema, chills, asthenia, chest pain, injection site reaction/inflammation, flu syndrome.

Investigations:

Frequent: Increased blood creatinine.

Less frequent: Increase 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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "*6.04 Adverse Drug Reaction Reporting Form*", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is no known antidote for VORIFEND IV.

Voriconazole is haemodialysed with a clearance of 121 ml/min. The intravenous vehicle, hydroxypropylbetadex, is haemodialysed with a clearance of 37,5 ± 24 ml/min.

In an overdose, haemodialysis may assist in the removal of VORIFEND IV and hydroxypropylbetadex from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics.

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives.

ATC Code: J02 AC03.

Mechanism of action

Voriconazole is a broad spectrum triazole antifungal medicine. It's mode of action is inhibition of fungal cytochrome P450-mediated 14 alpha-lanosterol demethylation, an essential step in ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Microbiology

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*), all fungicidal activity against all *Aspergillus* species tested.

In addition, voriconazole shows fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium*, which have limited susceptibility to existing antifungal medicines.

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

General Pharmacokinetic Characteristics

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

When the recommended intravenous dose regimens are administered, plasma concentrations close to steady state are achieved 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 being achieved by day 6.

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4,6 l/kg, suggesting extensive distribution into tissue. 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.

CYP2C19 is significantly involved in the metabolism of voriconazole and exhibits genetic polymorphism.

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

Elimination

Voriconazole is eliminated via hepatic metabolism with less than 2 % of the dose excreted unchanged in the urine. Approximately 80 % of the radioactivity is recovered in the urine after multiple intravenous dosing. The majority of the total radioactivity is excreted in the first 96 hours after dosing.

The terminal half life is approximately 6 hours. Because of non-linear pharmacokinetics, the terminal half-life is not useful in the prediction of the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic Relationships

A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy in therapeutic studies was not found.

Pharmacokinetics in Special Patient Groups

Gender

No dosage adjustment based on gender is necessary.

Elderly

A relationship between plasma concentrations and age was observed.

The safety profile of voriconazole in young and elderly patients is similar and, therefore, no dosage adjustment is necessary for the elderly. (see section 4.2).

Paediatric population

A population pharmacokinetic analysis found that average steady state plasma concentrations in children receiving a maintenance dose of 4 mg/kg every 12 hours were similar to those in adults receiving 3 mg/kg every 12 hours. Therefore, a maintenance dose of 4 mg/kg every 12 hours is recommended for children aged between 2 to < 12 years of age.

Renal impairment

In patients with mild, moderate to severe renal dysfunction, successive infusions may result in accumulation of the intravenous vehicle, hydroxypropylbetadex until steady state is reached. See dosing and monitoring recommendations under sections 4.2 and section 4.4.

Hepatic impairment

Protein binding of voriconazole is not affected by impaired hepatic function.

No pharmacokinetic data are available for patients with severe hepatic cirrhosis. See dosing and monitoring recommendations under sections 4.2 and section 4.4.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex

Sodium chloride

Hydrochloric acid

Water for injection

6.2 Incompatibilities

VORIFEND IV must not be infused into the same line or cannula concomitantly with other medicine infusions, including parenteral nutrition. The bag should be checked to ensure that the infusion is complete. When the VORIFEND IV infusion is complete, the line may be used for administration of other intravenous products.

Blood products and short-term infusion of concentrated solutions of electrolytes:

VORIFEND IV must not be administered simultaneously with any blood product or any short-term infusion of concentrated solutions of electrolytes, even if the two infusions are running in separate lines (or cannulas). Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of voriconazole therapy (see sections 4.2 and 4.4).

Total parenteral nutrition:

VORIFEND IV can be infused at the same time as total parenteral nutrition (TPN) but must be infused in a separate line. If infused through a multiple-lumen catheter, TPN needs to be administered using a different port from the one used for VORIFEND IV. VORIFEND IV must not be diluted with 4,2 % Sodium Bicarbonate Infusion. Compatibility with other concentrations is unknown. VORIFEND IV must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials: 3 years.

Once reconstituted, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 – 8 °C (in a refrigerator), unless reconstitution has taken place in controlled and validated aseptic conditions. Chemical and physical in-use stability has been demonstrated at room temperate and at 2 – 8 °C (refrigerated) for 72 hours.

6.4 Special precautions for storage

Unopened vials: store at or below 25 °C in the original package to protect from light.

For storage conditions after reconstitution and dilution of VORIFEND IV, see section 6.3.

6.5 Nature and contents of container

Vorifend IV powder for solution for infusion is packed in a 25 ml type I colourless glass vial, sealed with a grey rubber stopper and an aluminium cap with plastic sub-cap of red colour. Supplied in packs of 1 vial packed in a cardboard box accompanied with an instruction leaflet.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

The powder is reconstituted with either 19 ml of water for injection or 19 ml of 9 mg/ml (0,9 %) sodium chloride for infusion to obtain an extractable volume of 20 ml of clear solution containing 10 mg/ml of voriconazole. Discard the VORIFEND IV vial if vacuum does not pull the diluent into the vial. VORIFEND IV is for single use only and any unused solution should be discarded and only clear solutions without particles should be used.

For administration, the required volume of the reconstituted solution is added to a recommended compatible infusion solution (tabulated below) to obtain a final VORIFEND IV solution containing 0,5 – 5 mg/ml.

Required Volumes of 10 mg/ml VORIFEND IV Concentrate

Body Weight (kg)	**Volume of VFEND Concentrate (10 mg/ml) required for:**		
	3 mg/kg dose (number of vials)	**4 mg/kg dose (number of vials)**	**6 mg/kg dose (number of vials)**
10	-	4,0 ml (1)	-
15	-	6,0 ml (1)	-
20	-	8,0 ml (1)	-
25	-	10,0 ml (1)	-
30	9,0 ml (1)	12,0 ml (1)	18,0 ml (1)
35	10,5 ml (1)	14,0 ml (1)	21,0 ml (2)
40	12,0 ml (1)	16,0 ml (1)	24,0 ml (2)
45	13,5 ml (1)	18,0 ml (1)	27,0 ml (2)
50	15,0 ml (1)	20,0 ml (1)	30,0 ml (2)
55	16,5 ml (1)	22,0 ml (2)	33,0 ml (2)
60	18,0 ml (1)	24,0 ml (2)	36,0 ml (2)
65	19,5 ml (1)	26,0 ml (2)	39,0 ml (2)
70	21,0 ml (2)	28,0 ml (2)	42,0 ml (3)
75	22,5 ml (2)	30,0 ml (2)	45,0 ml (3)
80	24,0 ml (2)	32,0 ml (2)	48,0 ml (3)
85	25,5 ml (2)	34,0 ml (2)	51,0 ml (3)
90	27,0 ml (2)	36,0 ml (2)	54,0 ml (3)
95	28,5 ml (2)	38,0 ml (2)	57,0 ml (3)
100	30,0 ml (2)	40,0 ml (2)	60,0 ml (3)

VORIFEND IV does not contain an antimicrobial preservative. If the reconstituted solution is not used immediately, the reconstituted solution will remain suitable for its intended use for up to 24 hours, stored at 2 – 8 °C, if reconstitution has taken place in controlled and validated aseptic conditions.

The reconstituted solution can be diluted with:

0,9 % Sodium Chloride Solution

Compound Sodium Lactate Solution

5 % Glucose and Lactate Ringer's Solution

5 % Glucose and 0,45 % Sodium Chloride Solution

5 % Glucose Solution

5 % Glucose in 20 mmol Potassium Chloride Solution

0,45 % Sodium Chloride Solution

5 % Glucose and 0,9 % Sodium Chloride Solution

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

If the required volume of VORIFEND IV concentrate as described in the table above requires the use of multiple vials in order to provide the appropriate dose for a given body weight, then multiple infusion vials should be used. The instructions should be followed for reconstitution, dilution and administration of each combination. Each combination is for single use only.

If multiple vials are required, each individual vial used must be administered using a separate sterile sodium chloride bag.

For administration, the twist-off port at the bottom of the infusion bag should be opened and the infusion line connected and primed. The contents of the infusion bag are now ready for infusion to the patient.

The infusion bag should be checked to ensure that the entire contents of the bag have been infused, especially if the same intravenous line is to be used for sequential infusion of other drugs. Other additives should not be introduced into the infusion bag.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

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Centurion

0157

8. REGISTRATION NUMBER(S)

52/20.1.7/0021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 October 2021

10. DATE OF REVISION OF THE TEXT