APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VONDIP IV 200 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 25 mL vial contains voriconazole 200 mg.

When reconstituted as directed, each mL contains voriconazole 10 mg.

Once reconstituted further dilution is required before administration.

VONDIP IV 200 mg is sugar free.

Each vial contains 88,74 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white lyophilised powder.

After reconstitution with 19 mL of Water for Injections:

A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of invasive aspergillosis
- treatment of serious invasive infections caused by *Candida* spp. (including *C. krusei*)
- treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.
- prevention of breakthrough of fungal infections in febrile high- risk patients (allogeneic bone marrow transplants, relapsed leukaemia patients) where liposomal amphotericin B cannot be used.
- prophylaxis of invasive fungal infections in high risk allogeneic haematopoietic stem cell transplant (HSCT) recipients.

4.2 Posology and method of administration

Posology

It is recommended that VONDIP IV 200 mg is administered at a maximum rate of 3 mg/kg per hour over 1 to 2 hours.

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).

Use in Adults:

Therapy must be initiated with the specified loading dose regimen of intravenous VONDIP IV 200 mg to achieve plasma concentration on Day 1 that are close to steady state. On the

basis of the high oral bioavailability (96 %), switching between intravenous and oral administration is appropriate when clinically indicated. (This product does not have an oral dosage form).

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 - 4 mg/kg every 12 hours
- Prophylaxis of invasive fungal infections – 3 - 4 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.

Prophylaxis in adults and children:

Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. It may only be continued up to 180 days after transplantation in case of continuing immunosuppression
or graft versus host disease (GvHD)

Dosage

The recommended dosing regimen for prophylaxis is the same as for treatment in the respective age groups.

Duration of prophylaxis

The safety and efficacy of voriconazole use for longer than 180 days has not been adequately studied in clinical trials.

Phenytoin:

Phenytoin may be co-administered with VONDIP IV 200 mg if the maintenance dose of VONDIP IV 200 mg is increased to 5 mg/kg intravenously every 12 hours (see section 4.8).

Efavirenz:

When VONDIP IV 200 mg is co-administered with adjusted doses of efavirenz, VONDIP IV 200 mg maintenance dose should be increased to 400mg every 12 hours (see section 4.4).

Treatment duration depends upon patients clinical and mycological response.

Special populations

Elderly:

No dose adjustment is necessary for elderly patients.

Renal impairment:

Hydroxypropylbetadex cyclodextrin (HP-β-CD) at high doses can cause vacuolation of the kidney tubular cells without loss of kidney function in animals. This transient increase in size of apical vacuoles is also observed as an adaptive response to the excretion of osmotic agents such as glucose, mannitol and dextran at extremely high concentrations. Longer treatments cause these mostly reversible effects, at lower doses of HP-β-CD, indicating that duration of exposure may be of importance.

HP-β-CD is considered safe at relatively high doses and used most widely in parental products.

Amounts of ca 250 mg/kg/day are found safe in humans older than 2 years, when given 21 days (HP-β-CD). Because of their renal function, children less than 2 years old may theoretically be less vulnerable to renal toxicity, whereas it is likely to lead to higher blood levels (slower elimination). However, in juvenile rats toxicological effects of HP-β-CD were not worse than in adult rats, and a few cases on the use of intravenous products with high doses of HP-β-CD in neonates and young children have been reported without signs of toxicity.

In patients with moderate to severe renal dysfunction (creatinine clearance < 50 mL/min), accumulation of the intravenous vehicle, sulfobutylether beta cyclodextrin sodium (SBECD),

occurs.

Serum creatinine levels should be closely monitored in these patients and, if increases occur, consideration should be given to changing VONDIP IV 200 mg therapy.

VONDIP IV 200 mg is haemodialyzed with a clearance of 121 mL/min. A four-hour haemodialysis session does not remove a sufficient amount of VONDIP IV 200 mg to warrant a dose adjustment.

Impaired hepatic function:

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.

VONDIP IV 200 mg has not been studied in patients with severe chronic hepatic cirrhosis (Child- Pugh C).

VONDIP IV 200 mg 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 drug toxicity (see section 4.8).

Paediatric population

Use in children

Safety and efficacy in paediatric subjects below the age of 2 years has not been established.

Therefore, VONDIP IV 200 mg is not recommended for children less than 2 years of age (see section 4.4).

Children aged 2 to < 12 years:

Limited data are currently available to determine the optimal posology.

However, the following regimen has been used in paediatric studies:

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 the paediatric population.

Adolescents (12 to 16 years of age):

VONDIP IV 200 mg should be dosed as adults.

Duration of treatment:

Treatment duration depends on the patient's clinical and mycological response. The duration of VONDIP IV 200 mg treatment in the clinical studies ranged from 12 weeks to more than 6 months.

Method of administration

VONDIP IV 200 mg requires re-constitution and dilution before administration as an infusion. Not for bolus injection (see section 6.6).

4.3 Contraindications

- Hypersensitivity to voriconazole or to any of the ingredients of VONDIP IV 200 mg (see section 6.1)
- co-administration with CYPA34 substrates astemizole, cisapride, pimozide, terfenadine, ivabradine or quinidine is contraindicated since increased plasma concentrations of these medicines can lead to QTc prolongation, and rarely Torsade's de Pointes (see section 4.5)
- concurrent administration of VONDIP IV 200 mg with carbamazepine, phenobarbitone and rifampicin is likely to significantly decrease plasma concentrations of voriconazole (see section 4.5)
- when administered with high doses of ritonavir (400 mg and above twice daily) ritonavir significantly decreases voriconazole plasma concentrations (see section 4.5 for lower doses)
- if VONDIP IV 200 mg is co-administered with the CYP3A4 substrates ergot alkaloids (dihydroergotamine, ergotamine), increased plasma concentrations of these medicines can lead to ergotism (see section 4.5)
- VONDIP IV 200 mg is likely to significantly increase plasma concentrations of sirolimus if taken concurrently (see section 4.5)
- VONDIP IV 200 mg is likely to significantly increase plasma concentrations of rifabutin

if taken concurrently (see section 4.5)

- the co-administration of VONDIP IV 200 mg with St John's Wort is contraindicated (see section 4.5)
- co-administration of standard doses of VONDIP IV 200 mg 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. VONDIP IV 200 mg also significantly increases efavirenz plasma concentrations (see section 4.5, for lower doses see section 4.4)
- co-administration of VONDIP IV 200 mg with naloxegol, a CYP3A4 substrate, is contraindicated since increased plasma concentrations of naloxegol can precipitate opioid withdrawal symptoms (see section 4.5)
- co-administration of VONDIP IV 200 mg with tolvaptan is contraindicated since strong CYP3A4 inhibitors such as VONDIP IV 200 mg significantly increase plasma concentrations of tolvaptan (see section 4.5)
- co-administration of VONDIP IV 200 mg with lurasidone is contraindicated since significant increases in lurasidone exposure have the potential for serious adverse reactions (see section 4.5)
- co-administration with venetoclax at initiation and during the venetoclax dose titration phase is contraindicated since VONDIP IV 200 mg is likely to significantly increase plasma concentrations of venetoclax and increase risk of tumour lysis syndrome (see section 4.5)
- patients with prolonged QT syndrome
- severe impairment of hepatic function (Child-Pugh Class C)

- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Prescribers are advised to ensure that the principles of antimicrobial stewardship are adhered to.

Women of child-bearing potential

During treatment with VONDIP IV 200 mg, women of child-bearing potential must always use effective contraception.

Hypersensitivity

When prescribing VONDIP IV 200 mg to patients with hypersensitivity to azoles, caution should be exercised (see section 4.8).

Infusion-related reaction

The following anaphylactoid-type reactions can occur during infusion with VONDIP IV 200 mg: chest tightness, dyspnoea, faintness, fever, flushing, nausea, pruritus, rash, sweating and tachycardia.

Symptoms appear immediately on infusion initiation. Consideration should be given to terminating treatment if symptoms are severe.

Liver function tests

Abnormalities in liver function tests may be associated with higher plasma concentrations and/or doses. Most abnormalities are resolved during therapy without dose adjustment or

following dose adjustment, including discontinuation of treatment.

VONDIP IV 200 mg has frequently been 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.

Hepatic toxicity

Uncommon cases of hepatic reactions have been reported during clinical trials with voriconazole, as contained in VONDIP IV 200 mg. Reactions include clinical hepatitis, cholestasis and fulminant hepatic failure (including fatalities). These reactions appear mainly in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient hepatic reactions, including hepatitis and jaundice have occurred in patients with no other identifiable risk factors. Liver dysfunction is normally reversible if treatment is stopped.

Hepatic function monitoring

Patients starting treatment with VONDIP IV 200 mg, and those who develop abnormal liver function tests during VONDIP IV 200 mg therapy, must be monitored routinely for the development of severe hepatic injury.
Patient management should include the laboratory evaluation of hepatic function (especially bilirubin and liver function tests) at the initiation of treatment with VONDIP IV 200 mg 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 clinical signs and symptoms are consistent with liver disease development, termination of treatment with VONDIP IV 200 mg should be considered. Monitoring of hepatic function should be carried out in both children and adults.

Visual adverse events

Irreversible visual side-effects, including optic neuritis, blurred vision, and papilloedema have been reported in patients taking voriconazole, as contained in VONDIP IV 200 mg. These side effects are experienced primarily in severely ill patients who have underlying conditions and/or concomitant medicines which may cause or contribute to these adverse events. Clinical studies indicate that visual related disturbances are frequent. Side effects include altered/enhanced visual perception, blurred vision, colour vision change or photophobia. These side effects are transient, fully reversible and resolve spontaneously within 60 minutes.

With repeat dosing of voriconazole, as contained in VONDIP IV 200 mg, there is evidence of attenuation.
Visual disturbances are generally mild, will rarely require the need for discontinuation of therapy, and are not associated with long-term sequelae. Visual disturbances may be linked with higher plasma concentrations and/or doses.

The site of action is likely to be within the retina, although the mechanism of action is unknown. Voriconazole, as contained in VONDIP IV 200 mg, may cause a decrease in the electroretinogram (ERG) waveform amplitude.

The ERG measures electrical currents in the retina. These ERG changes should not progress more than 29 days into VONDIP IV 200 mg therapy and are fully reversible on withdrawal of treatment.

The long-term effect of voriconazole, as contained in VONDIP IV 200 mg, has no clinically relevant effect on visual function as assessed by testing of visual acuity, visual fields, colour vision and contrast sensitivity. No signs of retinal toxicity has been reported.

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

Renal adverse events

Severely ill patients undergoing treatment with voriconazole, as contained in VONDIP IV 200 mg, may experience acute renal failure. Patients on VONDIP IV 200 mg therapy are likely to be treated concomitantly with nephrotoxic medicines and have concurrent conditions that could result in decreased renal function (see section 4.8).

Renal function monitoring

The development of abnormal renal function should be monitored in patients. This should include laboratory evaluation, especially of serum

creatinine.

Pancreatic function monitoring

During VONDIP IV 200 mg therapy, patients with risk factors for acute pancreatitis (e.g. haematopoietic stem cell transplantation [HSCT], recent chemotherapy) should be monitored for the development of pancreatitis.

Dermatological adverse events

Dermatological reactions are frequent during therapy with voriconazole,
as contained in VONDIP IV 200 mg. However, these patients usually have serious underlying diseases and are receiving multiple concomitant medicines. Most rashes are mild to moderately severe.

Serious cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema multiforme have rarely developed in patients during treatment with voriconazole, as contained in VONDIP IV 200 mg. DRESS (drug reaction with eosinophilia and systemic symptoms), which can be life-threatening or fatal, have been reported with the use of voriconazole, as contained in VONDIP IV 200 mg. Patients who develop a rash should be closely monitored and VONDIP IV 200 mg therapy should be stopped if lesions progress.

Phototoxicity reactions have been reported, such as ephelides, lentigo, actinic keratosis and pseudoporphyria, especially during long-term therapy. It is recommended that patients avoid

prolonged and intense exposure to direct sunlight during VONDIP IV 200 mg therapy.

Squamous cell carcinoma of the skin (SCC)

Melanoma and squamous cell carcinoma of the skin have been reported during long-term therapy, in patients with photosensitivity skin reactions and additional risk factors.

If phototoxic reactions occur multidisciplinary advice should be sought, VONDIP IV 200 mg discontinuation and use of alternative antifungal medicines should be considered and the patient should be referred to a dermatologist. If VONDIP IV 200 mg is continued, however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions.
Discontinuation of VONDIP IV 200 mg treatment should be considered if a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma.

Prophylaxis

Discontinuation of VONDIP IV 200 mg should be considered in cases of treatment-related adverse events such as hepatotoxicity, severe skin reactions including phototoxicity and squamous cell carcinoma of the skin (SCC), severe or prolonged visual disorders and periostitis.

Cardiovascular

Voriconazole, as contained in VONDIP IV 200 mg, may prolong the QT interval without a clear relationship to plasma concentration. VONDIP IV 200 mg should not be co-

administered with other medicines which prolong the QT interval (see section 4.3).

Rare cases of Torsade's de pointes has been reported in patients taking voriconazole, as contained in VONDIP IV 200 mg, who had high risk factors such as a history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concurrent use of medicines which may have been contributory (see section 4.3).

VONDIP IV 200 mg should be administered with caution to patients who have the following potentially pro-dysrhythmic conditions:

- Congenital or acquired QTc-prolongation
- Cardiomyopathy, especially in the presence of heart failure
- Sinus bradycardia
- Symptomatic dysrhythmias (existing)
- Concomitant medicine known to prolong QTc- interval.

Electrolyte disturbances such as hypocalcaemia, hypokalaemia and hypomagnesaemia should be monitored and corrected, if necessary, before and during treatment with VONDIP IV 200 mg.

Adrenal events

Reversible cases of adrenal insufficiency have been reported in patients receiving azoles, including VONDIP IV 200 mg. Adrenal insufficiency has been reported in patients receiving azoles with or without concomitant corticosteroids. In patients receiving azoles without corticosteroids, adrenal insufficiency is related to direct inhibition of steroidogenesis by azoles. In patients taking corticosteroids, VONDIP IV 200 mg associated CYP3A4 inhibition

of their metabolism may lead to corticosteroid excess and adrenal suppression (see section 4.5). Cushing's syndrome with and without subsequent adrenal insufficiency has also been reported in patients receiving VONDIP IV 200 mg concomitantly with corticosteroids.

Patients on long-term treatment with VONDIP IV 200 mg and corticosteroids (including inhaled corticosteroids e.g. budesonide and intranasal corticosteroids) should be carefully monitored for adrenal cortex dysfunction both during treatment and when VONDIP IV 200 mg is discontinued (see section 4.5). Patients should be instructed to seek immediate medical care if they develop signs and symptoms of Cushing's syndrome or adrenal insufficiency.

Non-infectious periostitis

Periostitis has been reported in transplant patients during long-term VONDIP IV 200 mg therapy. If a patient develops skeletal pain and radiologic findings compatible with periostitis, VONDIP IV 200 mg should be discontinued (see section 4.8).

Methadone (CYP3A4 substrate)

Toxicity, including QT prolongation, have been associated with increased plasma concentrations of methadone. It is recommended to frequently monitor for adverse events and toxicity related to methadone during co- administration with VONDIP IV 200 mg. A reduction in the dose of methadone may be required (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) is recommended when taken concurrently with VONDIP IV 200 mg (see section 4.5). The half-life of alfentanil is prolonged in a 4-fold manner when co-administered with voriconazole, as contained in VONDIP IV 200 mg, therefore frequent monitoring for opiate- associated side effects (including a longer respiratory monitoring period) may be required.

Oxycodone (CYP3A4 substrate)

A reduction in the dose of oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g. hydrocodone) should be considered when taken concomitantly with VONDIP IV 200 mg. Frequent monitoring for opiate-associated side effects may be required (see section 4.5).

Ciclosporin and tacrolimus (CYP3A4 substrates)

Patients receiving VONDIP IV 200 mg concomitantly with ciclosporin or tacrolimus may experience clinically significant interactions (see section 4.5).

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

It is recommended to closely monitor phenytoin levels when co-administered with VONDIP IV 200 mg. Unless the benefit outweighs the risk, concomitant use of VONDIP IV 200 mg and phenytoin should be avoided (see section 4.5).

Ritonavir

The use of VONDIP IV 200 mg concomitantly with a low dose of ritonavir (100 mg twice daily) should be avoided (see section 4.5 and for higher doses see section 4.3).

Efavirenz (CYP450 inducer, CYP3A4 inhibitor and substrate)

When efavirenz is taken concurrently with VONDIP IV 200 mg the dose of efavirenz should be decreased to 300 mg once daily and that of VONDIP IV 200 mg should be increased to 400 mg twice daily (see section 4.5).

Everolimus (CYP3A4 substrate, P-gp substrate)

It is not recommended to co-administer everolismus with VONDIP IV 200 mg, since voriconazole is expected to significantly increase everolismus concentrations.

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

A significant increase in C_{max} and AUC_t of voriconazole, as contained in VONDIP IV 200 mg, results from the co-administration of oral voriconazole and oral fluconazole. The reduced dose and/or frequency of fluconazole and voriconazole, that would eliminate this increase, has not yet been established. Monitoring for voriconazole – associated adverse reactions of voriconazole is used sequentially after fluconazole (see section 4.5).

Glasdegib (CYP3A4 substrate)

Co-administration of VONDIP IV 200 mg is expected to increase glasdegib plasma concentrations and increase the risk of QTc prolongation (see section 4.5). If concomitant

use cannot be avoided, frequent ECG monitoring is recommended.

Tyrosine kinase inhibitors (CYP3A4 substrate)

Co-administration of VONDIP IV 200 mg with tyrosine kinase inhibitors metabolised by CYP3A4 is expected to increase tyrosine kinase inhibitor plasma concentrations and the risk of adverse reactions. If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring is recommended (see section 4.5).

Long-term treatment

Long-term therapy or prophylaxis greater than 180 days (6 months) with voriconazole, as contained in VONDIP IV 200 mg is not indicated. Therefore, medical practitioners should limit the exposure of VONDIP IV 200 mg (see section 4.2 and 5.1).

Paediatric population

The safety and efficacy of voriconazole, as contained in VONDIP IV 200 mg, has not been established in children below 2 years of age (see section 4.8 and 5.1).

The adverse event profile of children aged 2 to < 12 years is similar to adults, but with children exhibiting a high occurrence of skin reactions compared to adults.

Serious dermatological adverse reactions (including Squamous cell carcinoma (SCC)

The frequency of phototoxicity reactions is higher in paediatric patients. As an evolution towards SCC has been reported, stringent measures for the photoprotection are warranted in this patient group. Children experiencing photoaging injuries (such as lentigines or ephelides), sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation.

A higher frequency of liver enzyme elevations in children compared to adults.

Pancreatitis has been reported in paediatric patients.

Sodium

Each vial of VONDIP IV 200 mg powder for solution for infusion contains 88,74 mg of sodium. Consideration is therefore advised in patients on a controlled sodium diet.

Cyclodextrin

In patients with moderate to severe renal dysfunction accumulation of cyclodextrins may occur (see section 5.2).

4.5 Interaction with other medicines and other forms of interaction

Voriconazole, as contained in VONDIP IV 200 mg, is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes CYP2C19, CYP2C9 and CYP3A4. Inducers or inhibitors of

these isoenzymes may decrease or increase voriconazole plasma concentrations, respectively. There is potential for VONDIP IV 200 mg to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.

VONDIP IV 200 mg should be administered with caution in patients receiving concomitant treatment with medicines known to prolong QT interval.

Voriconazole may prolong the QT interval without a clear relationship to plasma concentration. VONDIP IV 200 mg should not be used concomitantly with other medicines which prolong the QT interval.
When there is also a potential for VONDIP IV 200 mg to increase the plasma level of medicines metabolised by CYP3A4 isoenzymes (e.g. certain antihistamines, quinidine, cisapride, pimozide and ivabradine) co-administration is contraindicated (see below and section 4.3).

Co-administration of the following medicines with VONDIP IV 200 mg is Contraindicated (see section 4.3)

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

A study showed that St John's Wort exhibits a short initial inhibitory effect followed by induction of voriconazole metabolism.

Rifampicin (CYP450 inducer):

Rifampicin (600 mg daily) has been shown to significantly decrease the plasma concentration of voriconazole, as contained in VONDIP IV 200 mg.

Ritonavir (CYP450 inducer, CYP3A4 inhibitor and substrate):

VONDIP IV 200 mg, with high doses of ritonavir (400 mg and above, twice daily) is contraindicated (see section 4.3). The co-administration of VONDIP IV 200 mg with lower doses of ritonavir (100 mg twice daily) is not recommended unless a benefit/risk assessment justifies the use of this medicine (see section 4.4).

Carbamazepine and long-acting barbiturates e.g. phenobarbitone, mephobarbitone (potent CYP450 inducers):

Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma concentrations of voriconazole, as contained in VONDIP IV 200 mg (see section 4.3).

Ergot alkaloids e.g. ergotamine and dihydroergotamine (CYP3A4 substrates):

Voriconazole, as contained in VONDIP IV 200 mg, may increase plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. The co-administration of VONDIP IV 200 mg with ergot alkaloids is contraindicated (see section 4.3).

Efavirenz, a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer, CYP3A4 inhibitor and substrate):

The co-administration of standard doses of VONDIP IV 200 mg with 400 mg daily or higher doses of efavirenz is should not be used (see section 4.4).

VONDIP IV 200 mg may be taken concomitantly with efavirenz if the VONDIP IV 200 mg maintenance dose is increased to 400 mg twice daily, and the efavirenz dose is decreased to 300 mg once daily (see section 4.2). The initial dose of efavirenz should be re-introduced when

VONDIP IV 200 mg therapy is stopped.

Rifabutin (CYP450 inducer):

VONDIP IV 200 mg is likely to significantly increase plasma concentrations of rifabutin if taken concurrently (see section 4.3).

Cisapride, pimozide, astemizole and quinidine (CYP3A4 substrates):

Although not studied, caution is advised if administering VONDIP IV 200 mg to patients who are also taking medicines that prolong QT interval.

Co-administration with the CYPA34 substrates cisapride, pimozide, astemizole or quinidine is contraindicated since increased plasma concentrations of these medicines can lead to QTc prolongation, and rarely Torsade's de Pointes (see section 4.3).

Sirolimus (CYP3A4 substrate):

VONDIP IV 200 mg is likely to significantly increase plasma concentrations of sirolimus if taken concurrently (see section 4.3).

Lurasidone (CYP3A4 substrate):

Although not studied, VONDIP IV 200 mg is likely to significantly increase the plasma concentrations of lurasidone (see section 4.3).

Naloxegol (CYP3A4 substrate):

Although not studied, VONDIP IV 200 mg is likely to significantly increase the plasma concentrations of naloxegol (see section 4.3).

Tolvaptan (CYP3A substrate):

Although not studied, VONDIP IV 200 mg is likely to significantly increase the plasma concentrations of tolvaptan (see section 4.3).

Venetoclax (CYP3A substrate):

Although not studied, VONDIP IV 200 mg is likely to significantly increase the plasma concentrations of venetoclax (see section 4.3).

Co-administration with the following medicine is not recommended

Everolismus (CYP3A4 substrate, P-gp substrate):

It is not recommended to co-administer everolismus with VONDIP IV 200 mg, since voriconazole is expected to significantly increase everolismus concentration.

Ritonavir:

Ritonavir at lower doses (100 mg twice a day) should be avoided unless an assessment of the benefit/risk to the patient justifies the use of VONDIP IV 200 mg.

If VONDIP IV 200 mg is co-administered with the following medicines, precautions including dosage adjustment should be considered

Ciclosporin (CYP3A4 substrate):

When commencing therapy with VONDIP IV 200 mg in patients already receiving ciclosporin, it is recommended that the dose of ciclosporin be halved and ciclosporin levels closely monitored. Increased levels of ciclosporin have been associated with nephrotoxicity. On discontinuation of VONDIP IV 200 mg treatment, ciclosporin levels must be monitored and the dose increased as necessary (see section 4.4).

Tacrolimus (CYP3A4 substrate):

When commencing therapy with VONDIP IV 200 mg in patients already receiving tacrolimus, it is recommended that the dose of tacrolimus be reduced to a third of the original dose and

tacrolimus levels closely monitored. Increased levels of tacrolimus has been associated with nephrotoxicity. On discontinuation of VONDIP IV 200 mg treatment, tacrolimus levels must be monitored and the dose increased as necessary (see section 4.4).

Methadone (CYP3A4 substrate):

Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended if co-administered with VONDIP IV 200 mg. A dose reduction of methadone may be required (see section 4.4).

Short-acting opiates e.g. alfentanil, fentanyl (CYP3A4 substrates):

Dose reduction of alfentanil, fentanyl and other short-acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g. sufentanil) should be considered if co-administered with VONDIP IV 200 mg. Frequent and extended monitoring for respiratory depression and other fentanyl-associated adverse reactions is recommended, and a reduction in the dosage of fentanyl may be warranted.

Long-acting opiates e.g. oxycodone (CYP3A4 substrates):

A dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g. hydrocodone) should be considered. It may be necessary to frequently monitor for opiate-associated adverse reactions.

Oral anticoagulant e.g. warfarin (CYP2C9 substrate):

Co-administration of voriconazole, as contained in VONDIP IV 200 mg, with warfarin increases the maximum prothrombin time/international normalised ratio (INR) by 93 %. It is recommended to monitor prothrombin time/INR if these medications are administered together.

Other oral coumarins (including but not limited to: phen-procoumon, acenocoumarol) (CYP2C9 and CYP3A4 substrates):

Although not studied, VONDIP IV 200 mg may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time. Close monitoring of prothrombin time or other suitable anticoagulation tests are recommended, and the dose of anticoagulants should be adjusted accordingly.

Sulphonylureas e.g. tolbutamide, glipizide, glyburide (CYP2C9 substrates):

Voriconazole, as contained in VONDIP IV 200 mg, is likely to increase the plasma concentrations of sulphonylureas and cause hypoglycaemia. If these medicines are administered together, careful monitoring of blood glucose is recommended. Dose reduction of sulphonylureas should be considered.

Statins e.g. lovastatin (CYP3A4 substrates):

Although not clinically studied, voriconazole, as contained in VONDIP IV 200 mg, has been shown to inhibit lovastatin metabolism in-vitro (human liver microsomes). VONDIP IV 200 mg therefore, may increase plasma concentrations of statins that are metabolised by CYP3A4, if administered concurrently with these medicines. Rhabdomyolysis has been associated with increased levels of statin. Dose adjustment of the statin should be considered.

Benzodiazepines e.g. midazolam, triazolam, alprazolam (CYP3A4 substrates):

Although not clinically studied, voriconazole, as contained in VONDIP IV 200 mg, has been shown to inhibit midazolam metabolism in-vitro (human liver microsomes). VONDIP IV 200

mg therefore, may increase plasma levels of benzodiazepines that are metabolised by CYP3A4 and

cause a prolonged sedative effect. Dose adjustment of the benzodiazepine should be considered.

Vinca alkaloids e.g. vincristine, vinblastine (CYP3A4 substrates):

Although not clinically studied, voriconazole, as contained in VONDIP IV 200 mg, has been shown to increase the plasma concentrations of vinca alkaloids and lead to neurotoxicity. Dose reduction of vinca alkaloids should be considered.

Non-steroidal anti-inflammatory drugs (NSAIDs) e.g. ibuprofen, diclofenac (CYP2C9 substrates):

Frequent monitoring for toxicity and adverse events related to NSAID's is recommended, due to increased plasma concentrations observed in studies. Dose reduction of NSAIDs may be needed.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer):

VONDIP IV 200 mg should not be prescribed with phenytoin. Careful monitoring of phenytoin plasma levels is recommended due to increased plasma concentrations observed in studies. Therefore, phenytoin may only be administered together with VONDIP IV 200 mg, if the maintenance dose of the latter is increased from 3 mg/kg to 5 mg/kg intravenously twice daily (see section 4.2).

Oral contraceptives e.g. norethisterone and ethinylestradiol (CYP3A4 substrates):

Studies conducted with the co-administration of 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 AUC_t of ethinylestradiol (36 % and 61 % respectively) and norethisterone (15 %

and 53 % respectively). Voriconazole IV C_{max} and AUC_t increased by 14 % and 46 % respectively. Oral contraceptives containing doses
other than 1 mg norethistrone and 0,035 mg ethinylestradiol have not been studied. The ratio between norethisterone and ethinylestradiol remains similar during interaction with voriconazole, as contained in VONDIP IV 200 mg; their contraceptive activity is likely not to be
affected. It is recommended to monitor for adverse reactions related to both oral contraceptives and voriconazole when these medicines are co-administered.

Other HIV protease inhibitors e.g. amprenavir, nelfinavir, saquinavir (CYP3A4 INHIBITORS):

In-vitro studies suggest that voriconazole, as contained in VONDIP IV 200 mg, may inhibit the metabolism of HIV protease inhibitors, and that the metabolism of voriconazole may be inhibited by HIV protease inhibitors. It is recommended to closely monitor for any occurrence of drug toxicity and/or lack of efficacy during co-administration of these medicines.

Other non-nucleoside reverse transcriptase inhibitors (NNRTIs) e.g. delavirdine and nevirapine (CYP3A4 substrates, inhibitors or CYP450 inducers):

The metabolism of voriconazole, as contained in VONDIP IV 200 mg, may be any inhibited by delavirdine and induced by nevirapine. Although not studied, the metabolism of VONDIP IV 200 mg may be induced by nevirapine. Voriconazole may also inhibit the metabolism of NNRTIs. It is recommended to closely monitor for occurrence of drug toxicity and/or lack of efficacy during co-administration of these medicines.

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

A significant increase in C_{max} and AUC_t of voriconazole, as contained in VONDIP IV 200 mg,

results from the co-administration of oral voriconazole and oral fluconazole. The reduced dose and/or frequency of fluconazole and voriconazole, that would eliminate this increase, has not yet been established.

Letermovir (CYP2C9 and CYP2C19 inducer):

If concomitant administration of VONDIP IV 200 mg with letermovir cannot be avoided, monitor for loss of voriconazole effectiveness.

Flucloxacillin (CYP450 inducer):

Significantly decreased plasma voriconazole concentrations have been reported.

If concomitant administration of VONDIP IV 200 mg with flucloxacillin cannot be avoided, monitor for potential loss of voriconazole effectiveness (e.g., by therapeutic drug monitoring); increasing the dose of VONDIP IV 200 mg may be needed.

Glasdegib (CYP3A4 substrate):

Although not studied, voriconazole is likely to increase the plasma concentrations of glasdegib and increase risk of QTc prolongation.

If concomitant use cannot be avoided, frequent ECG monitoring is recommended (see section 4.4).

Tyrosine kinase inhibitors (including but not limited to: axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) (CYP3A4 substrates):

Although not studied, voriconazole may increase plasma concentrations of tyrosine kinase inhibitors metabolised by CYP3A4.

If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and

close clinical monitoring is recommended

(see section 4.4).

Ivacaftor (CYP3A4 substrate):

Although not studied, VONDIP IV 200 mg is likely to increase the plasma concentrations of ivacaftor with risk of increased adverse reactions. Dose reduction of ivacaftor is recommended.

Tretinoin (CYP3A4 substrate):

Although not studied, VONDIP IV 200 mg may increase tretinoin concentrations and increase risk of adverse reactions (pseudo-tumour cerebri, hypercalcaemia). Dose adjustment of tretinoin is recommended during treatment with VONDIP IV 200 mg and after its discontinuation.

If VONDIP IV 200 mg is co-administered with the following medicines, no dose adjustment is necessary

- cimetidine (non-specific CYP450 inhibitor and increases gastric pH)
- ranitidine (increases gastric pH)
- macrolide antibiotics: erythromycin (CYP3A4 inhibitor)
- azithromycin
- prednisolone (CYP3A4 substrate)
- digoxin (P-glycoprotein mediated transport)
- mycophenolic acid (UDP-glucuronyl transferase substrate).

Omeprazole (CYP2C19 inhibitor, CYP2C19 and CYP3A4 substrate):

If VONDIP IV 200 mg is co-administered with omeprazole, no dose adjustment is necessary. When commencing VONDIP IV 200 mg therapy in patients already taking omeprazole, it is recommended to halve the dose of omeprazole.

Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole, as contained in VONDIP IV 200 mg, and may lead to increased plasma concentrations of these medicines.

Indinavir (CYP3A4 inhibitor and substrate):

No dose adjustment is required when VONDIP IV 200 mg is administered with indinavir.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of child bearing age should use effective contraception during treatment with VONDIP IV 200 mg.

Pregnancy

VONDIP IV 200 mg must not be administered to pregnant or lactating women (see section 4.3).

Safety in pregnancy and lactation has not been established.

Breastfeeding

The excretion of VONDIP IV 200 mg into breastmilk has not been established. Breastfeeding must be stopped on initiation of treatment with VONDIP IV 200 mg (see section 4.3).

Fertility

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

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

Voriconazole has moderate influence on the ability to drive and use machines.

VONDIP IV 200 mg may lead to transient and reversible changes in vision, including blurred vision, altered/enhanced visual perception, and/or photophobia. Patients should avoid potentially hazardous tasks

such as operating machinery or driving.

In addition, any patient taking VONDIP IV 200 mg, whether experiencing visual disturbances or not, should not drive at night (see section 4.8)

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, abnormal liver function test, 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.

Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Infections and Infestations	Frequent Less frequent	Influenza-like illness, sinusitis Pseudomembranous colitis
Neoplasms benign and malignant (including cysts and polyps)	Frequency unknown	Squamous cell carcinoma*
Blood and lymphatic system disorders	Frequent Less frequent	Anaemia (including macrocytic, microcytic, normocytic, aplastic megaloblastic), leucocytosis, leukopenia, pancytopenia, thrombocytopenia Bone marrow depression, disseminated intravascular coagulation, eosinophilia, lymphadenopathy, agranulocytosis (including febrile neutropenia and neutropenia)
Immune system disorders	Frequent Less frequent	Sepsis Hypersensitivity, anaphylactoid reaction
Endocrine disorders	Less frequent	Adrenal cortex insufficiency, hyperthyroidism, hypothyroidism
Metabolism and nutrition disorders	Frequent Less frequent	Hypoglycaemia, hypokalaemia, hyponatraemia*, oedema peripheral Hypercholesterolaemia
Psychiatric disorders	Frequent	Agitation, anxiety, confusion, depression, hallucinations, insomnia

Nervous system disorders	Frequent Less frequent	Convulsions, dizziness, headache, hypertonia, paraesthesia, tremor Somnolence during infusion, insomnia, ataxia, altered taste perception, brain oedema, encephalopathy, extrapyramidal syndrome, Guillain-Barre syndrome, hepatic coma, hypoaesthesia, neuropathy, nystagmus, oculogyric crisis, peripheral neuropathy, dysgeusia, syncope
Eye disorders	Frequent Less frequent	Visual disturbances (including visual blurred vision, colour vision change, photophobia, altered/enhanced perception), retinal haemorrhage Blepharitis, corneal opacity, diplopia, optic atrophy, optic neuritis (optic nerve damage), papilloedema, scleritis, oculogyric crisis
Ear and labyrinth disorders	Less frequent	Vertigo, hypoacusis, tinnitus

Cardiac disorders	Frequent	Lung oedema, dysrhythmia supraventricular, tachycardia, bradycardia
	Less frequent	Atrial dysrhythmia, ventricular dysrhythmia, ventricular fibrillation, supraventricular tachycardia, prolonged QT interval
	Frequency unknown	Atrioventricular (AV) complete block, bundle branch block, nodal dysrhythmia, ventricular tachycardia (including Torsade's de Pointes), nodal rhythm
Vascular disorders	Frequent	Hypotension, phlebitis, thrombophlebitis
	Less frequent	Lymphangitis
Respiratory, thoracic and mediastinal disorders	Frequent	Acute respiratory distress syndrome, pulmonary oedema, respiratory distress (included dyspnoea and external dyspnoea)
Gastrointestinal disorders	Frequent	Abdominal pain, cheilitis, diarrhoea, nausea, vomiting, gastroenteritis, constipation, dyspepsia, gingivitis
	Less frequent	Peritonitis, pancreatitis, swollen tongue, duodenitis, glossitis

Hepatobiliary disorders	Frequent	Cholestatic jaundice, elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, LDH, bilirubin), jaundice
	Less frequent	Cholecystitis, cholelithiasis, enlarged liver, hepatic coma, hepatic failure hepatomegaly, hepatitis (includes drug-induced liver injury, toxic hepatitis, hepatocellular injury and hepatotoxicity)
Skin and subcutaneous tissue disorders	Frequent	Alopecia, exfoliative dermatitis, facial oedema, maculopapular rash, photosensitivity, pruritus, purpura, rash, skin reaction, erythema
	Less frequent	Angioedema, discoid lupus erythema erythematosis, eczema, ephelides, erythema multiforme, lentigo, psoriasis, urticaria, toxic epidermal necrolysis, DRESS (a drug reaction with eosinophilia and systemic symptoms), pseudoporphyria, Stevens-Johnson Syndrome, phototoxicity, allergic dermatitis, fixed drug eruption
	Frequency unknown	Cutaneous lupus erythematosus*, ephelides and lentigo
Musculoskeletal, connective tissue and bone disorders	Frequent	Back pain
	Less frequent	Arthritis
	Frequency unknown	Periostitis*

Renal and urinary disorders	Frequent Less frequent	Increased creatinine, haematuria, acute kidney failure Albuminuria, increased blood urea, kidney tubular necrosis, nephritis, proteinuria
General disorders and administrative site conditions	Frequent	Asthenia, chest pain, chills, fever, flu like syndrome, injection site reaction/inflammation, peripheral oedema
Investigations	Frequent Less frequent	Increased blood creatinine Increased blood urea, blood cholesterol increased

*Post marketing experience

a. Description of selected adverse reactions

Visual impairments

In clinical trials, visual impairments (including blurred vision, photophobia, chloropsia, and chromatopsia, colour blindness, cyanopsia, eye disorder, halo vision, night blindness, oscillopsia, photopsia, scintillating scotoma, reduced visual acuity, visual brightness, visual field defect, vitreous floaters, and xanthopsia) with voriconazole are very common, however, are transient fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects expected. There is evidence of attenuation with repeated doses of voriconazole. The

visual impairments are generally mild, rarely result in discontinuation and are not associated with long-term sequelae. Visual impairments may be associated with higher plasma concentrations and/or doses.

There have, however, been post-marketing reports of prolonged visual

adverse events (see section 4.4).

Dermatological reactions

Studies indicate that the frequent occurrence of dermatological reactions in patients treated with voriconazole, were in those patients who had serious underlying diseases and were receiving multiple concomitant medicines. The majority of rashes were of mild to moderate severity. Patients have developed severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) (uncommon), toxic epidermal necrolysis (TEN) (rare), drug reaction with eosinophilia and systemic symptoms (DRESS) (rare) and erythema multiforme (rare) during treatment with voriconazole (see section 4.4).

If a patient develops a rash, they should be monitored closely and VONDIP IV 200 mg discontinued if lesions progress.

Photosensitivity reactions such as ephelides, lentigo and actinic keratosis have been reported, especially during long-term therapy (see section 4.4).

Sun avoidance and photo-protection are recommended for all patients. There is a potential increased risk of skin reactions/toxicity with concomitant use of photosensitising agents (e.g. methotrexate). If phototoxicity occurs, VONDIP IV 200 mg discontinuation and dermatological evaluation should be considered (see section 4.4).

There have been reports of squamous cell carcinoma of the skin in patients treated with VONDIP IV 200 mg for long periods of time; the mechanism has not been established (see section 4.4).

Liver function tests:

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

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

Infusion-related reactions:

During infusion of the intravenous formulation of voriconazole 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 (see section 4.4).

b. Paediatric population

The safety of voriconazole was investigated in clinical trials in paediatric patients aged 2 to <12 years and 12 to <18 years who received voriconazole for prophylaxis and therapeutic use.

The safety of voriconazole was also investigated in 158 additional paediatric patients aged 2 to <12 years in compassionate use programs.

Overall, the safety profile of voriconazole in paediatric population was similar to that in adults. However, a trend towards a higher frequency of

liver enzyme elevations, reported as adverse events was observed in paediatric patients as compared to adults. Post-marketing data suggest there might be a higher occurrence of skin reactions (especially erythema) in the paediatric population compared to adults. In patients less than 2 years old who received voriconazole in a compassionate use programme, the following adverse reactions (for which a relationship to voriconazole could not be excluded) were reported:

photosensitivity reaction (1), arrhythmia (1), pancreatitis (1), blood bilirubin increased (1), hepatic enzymes increased (1), rash (1) and papilloedema (1). There have been post-marketing reports

of pancreatitis in paediatric patients.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

In overdose, side effects can be precipitated and/or be of increased severity (see section

4.8).

Photophobia has been reported as an adverse event to overdosage with voriconazole, as contained in VONDIP IV 200 mg.

Management of overdose:

There is no known antidote to VONDIP IV 200 mg.

The intravenous vehicle, sulfobutylether beta cyclodextrin sodium (SBECD), is haemodialysed with a clearance of 55 mL/min.

Voriconazole is haemodialysed with a clearance of 121 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

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives

ATC code: J02A C03

Pharmacological classification: A 20.1.7 Antimicrobial (chemotherapeutic) medicines: Antifungal antibiotics.

Mechanism of action

Voriconazole is a broad spectrum triazole antifungal medicine.

The primary mode of action of voriconazole is the inhibition of fungal cytochrome P450-mediated 14 alpha-lanosterol demethylation, an

essential step in fungal ergosterol biosynthesis.

Microbiology:

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

Prior to therapy, specimens for fungal culture and other relevant to isolate laboratory studies (histopathology, serology) should be obtained, in order and identify the causative organisms. Treatment can commence before these results are obtained, however once results are available, anti-infective therapy should be adjusted accordingly.

Clinical isolates with decreased susceptibility to voriconazole have been identified, however correlation of clinical outcome with in-vitro activity is difficult due to the complexity of the patients studied.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

Voriconazole exhibits non-linear pharmacokinetics due to saturation of its metabolism. A greater than proportional increase in exposure is observed with increasing dose. When the

recommended dosage of intravenous voriconazole is administered, plasma concentrations close to steady-state are observed with the first 24 hours. Without the loading dose regimens, accumulation occurs during twice daily multiple dosing. Steady-state plasma voriconazole concentrations are achieved by day 6 in most patients.

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 of voriconazole, at steady state, is estimated at 4,6 L/kg. This suggests extensive distribution of voriconazole in the liver. Plasma protein binding is estimated at 58 %.

Voriconazole is detected in the cerebrospinal fluid of patients treated with voriconazole.

Biotransformation:

Voriconazole is metabolised by the hepatic cytochrome P450 isoenzymes CYP2C9, CYP2C19 and CYP3A4.

The inter-individual variability of voriconazole pharmacokinetics is high.

CYP2C19 is significantly involved in voriconazole metabolism; the enzyme exhibits genetic polymorphism. 15 - 20 % of Asian populations are likely to be poor metabolisers; for Caucasians and Blacks the prevalence is 3 - 5 %. Poor metabolisers have, on average, 4 times higher voriconazole exposure (AUC_t) than homozygous extensive metabolisers. Heterozygous metabolisers have on average 2 times higher voriconazole exposure than homozygous extensive metabolisers.

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

Elimination:

Voriconazole is eliminated via hepatic metabolism, with less than 2 % of the dose excreted unchanged in the urine. The plasma elimination half-life voriconazole is 6 hours.

After multiple intravenous dosing of radiolabelled voriconazole,
approximately 80 % of the radioactivity is recovered in the urine. The majority (> 94 %) of the total radioactivity is excreted in the first 96 hours after dosing. 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 has not been observed between mean, maximum or minimum plasma voriconazole concentration and efficacy.

Pharmacokinetic-Pharmacodynamic analyses identified a positive association between plasma voriconazole concentrations and both visual disturbances and liver function abnormalities.

Pharmacokinetics in special patient groups

Elderly

A relationship between plasma concentrations and age has been patients observed. However, the safety profile of voriconazole in young and elderly is similar, therefore no dosage adjustment is necessary for the elderly.

Patients with renal impairment

IV-administrated cyclodextrins disappear rapidly from systemic circulation and are renally excreted intact. Systemically absorbed cyclodextrins distribute mainly in the extracellular compartments, and no compartments or storage pools are involved. The total plasma clearance for HP-β-CD in all species tested is similar to the glomerular filtration rate. The $t_{1/2}$ varies from 20 to 100 minutes. Only RM-β-CD has a longer $t_{1/2}$ compared to other cyclodextrins derivates (7h), probably related to its ability to interact with cellular membranes. In patients with moderate to severe renal dysfunction (serum creatinine levels > 2,5 mg/dL),

accumulation of the intravenous vehicle, sulfobutylether beta cyclodextrin sodium (SBECD), occurs (see sections 4.2 and 4.4).

Patients with hepatic impairment

Studies after single dose (200 mg) indicated that the AUC of voriconazole is higher in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared to patients with normal hepatic function. Protein binding of voriconazole is not affected by impaired hepatic function.

In patients with moderate liver function, AUC_t is similar to that of subjects with moderate hepatic cirrhosis (Child Pugh Class B) as reported in an oral multidose study, no pharmacokinetic information is available for patients with severe hepatic cirrhosis (Child-Pugh C) (see sections 4.2 and 4.4).

Gender

In an oral multiple-dose study, C_{max} and AUC 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 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.

Paediatric population

Average steady-state plasma concentrations in children receiving a maintenance intravenous dose of 4 mg/kg every 12 hours are similar to those in adults receiving 3 mg/kg every 12 hours. A maintenance dose of 4 mg/kg every 12 hours is therefore recommended in children aged 2 to < 12 years of age. (see section 4.2).

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl beta cyclodextrine

Sodium chloride

Hydrochloric acid concentrated (for pH adjustment)

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Powder: Store at or below 25 °C.

After reconstitution with 19 mL of Water for Injections:

Store at 2 - 8 °C (in a refrigerator) for not longer than 72 hours

(see section 4.2). Do not freeze.

Protect from light. Keep the vial in the carton until required for use.

6.5 Nature and contents of container

Clear Type I glass vial (25 mL) sealed with a grey rubber stopper and red aluminium cap with a red plastic sub-cap seal. Each vial is placed in an outer carton.

Each vial contains 200mg Powder for solution for infusion.

6.6 Special precautions for disposal and other handling

Discard partially used vials.

The vial contents are reconstituted with 19 mL of Water for Injections to obtain a clear solution containing 10 mg/mL of VONDIP IV 200 mg to obtain an extractable volume of 20 mL.

For administration, the required volume of the reconstituted solution is

added to a recommended compatible infusion solution (detailed below) to obtain, where appropriate, a final VONDIP IV 200 mg solution concentrate containing 0,5 - 5 mg/mL.

It is recommended that a standard 20 mL (non-automated) syringe to be used to ensure that the exact amount (19,0 mL) of water for injections or (9 mg/mL) [0,9 %])

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

Required volumes of 10 mg/mL VONDIP IV 200 mg concentrate

Body Weight (kg)	**3 mg/kg dose (number of vials)**	**4 mg/kg dose (number of vials)**	**6 mg/kg dose (number of vials)**	**8 mg/kg dose (number of vials)**	**9 mg/kg dose (number of vials)**
10	-	4,0 ml (1)	-	8,0 ml (1)	9,0 ml (1)
15	-	6,0 ml (1)	-	12,0 ml (1)	13,5 ml (1)
20	-	8,0 ml (1)	-	16,0 ml (1)	18,0 ml (1)
25	-	10,0 ml (1)	-	20,0 ml (1)	22,5 ml (2)
30	9,0 ml (1)	12 ml (1)	18 ml (1)	24 ml (2)	27 ml (2)
35	10,5 ml (1)	14 ml (1)	21 ml (2)	28 ml (2)	31,5 ml (2)
40	12,0 ml (1)	16 ml (1)	24 ml (2)	32 ml (2)	36 ml (2)
45	13,5 ml (1)	18 ml (1)	27 ml (2)	36 ml (2)	40,5 ml (3)
50	15,0 ml (1)	20 ml (2)	30 ml (2)	40 ml (2)	45 ml (3)
55	16,5 ml (1)	22 ml (2)	33 ml (2)	44 ml (3)	49,5 ml (3)
60	18,0 ml (1)	24 ml (2)	36 ml (2)	48 ml (3)	54 ml (3)
65	19,5 ml (1)	26 ml (2)	39 ml (2)	52 ml (3)	58,5 ml (3)
70	21,0 ml (2)	28 ml (2)	42 ml (3)	-	-
75	22,5 ml (2)	30 ml (2)	45 ml (3)	-	-
80	24,0 ml (2)	32 ml (2)	48 ml (3)	-	-
85	25,5 ml (2)	34 ml (2)	51 ml (3)	-	-
90	27,0 ml (2)	36 ml (2)	54 ml (3)	-	-

95	28,5 ml (2)	38 ml (20	57 ml (3)	-	-
100	30,0 ml (2)	40 ml (2)	60 ml (3)	-	-

VONDIP IV 200 mg 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 72 hours, stored at 2 - 8 ºC, if reconstitution has taken place in controlled and validated aseptic conditions.

The reconstituted solution can be diluted with

0,9 % Sodium Chloride Intravenous Infusion

Compound Sodium Lactate Intravenous Infusion

5 % Glucose and Compound Sodium Lactate Intravenous Infusion

5 % Glucose and 0,45 % Sodium Chloride Intravenous Infusion

5 % Glucose Intravenous Infusion

5 % Glucose in 20 mmol Potassium Chloride Intravenous Infusion

0,45 % Sodium Chloride Intravenous Infusion

5 % Glucose and 0,9 % Sodium Chloride Intravenous Infusion

The compatibility of VONDIP IV 200 mg with diluents other than those described above is unknown (see incompatibilities below).

VONDIP IV 200 mg must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition.

4,2 % Sodium Bicarbonate Intravenous Infusion is not compatible with VONDIP IV 200 mg and must not be used as a diluent. Compatibility with other

concentrations is unknown.

Blood products and concentrated electrolytes

VONDIP IV 200 mg must not be infused concomitantly with any blood product or any short-term infusion of concentrated electrolytes, even if the two infusions are running in separate intravenous lines (or cannulas).

Electrolyte disturbance such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of VONDIP IV 200 mg therapy.

Intravenous solutions containing (non-concentrated) electrolytes

VONDIP IV 200 mg can be infused at the same time as other intravenous solutions containing (non-concentrated) electrolytes, but must be infused through a separate line.

Total parenteral nutrition (TPN)

VONDIP IV 200 mg can be used at the same time as total parenteral nutrition, 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 VONDIP IV 200 mg.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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