1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

VICOMYL 200 mg IV (Powder for Solution for Infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VICOMYL 200 mg IV vial contains 200 mg voriconazole.

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

VICOMYL 200 MG IV contains sodium. This should be particularly taken into account for those on a low salt diet.

- Sodium 222 mg

VICOMYL 200 MG IV also contains cyclodextrin, which may accumulate in patients with moderate to severe renal dysfunction.

- Cyclodextrin 2978 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

VICOMYL 200 MG IV powder for solution for infusion is a white lyophilised powder or cake filled in flint vial with rubber stopper and aluminium seal.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VICOMYL 200 MG IV is indicated for:

- Treatment of invasive aspergillosis.
- Treatment of serious invasive infections caused by *Candida* spp (including *C*. *krusei*).
- Voriconazole has been used in the treatment of serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp.
- Prevention of breakthrough of fungal infections in febrile high-risk patients (allogeneic bone marrow transplants, relapsed leukaemia patients) where liposomal amphotericin B cannot be used.

4.2 Posology and method of administration

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)*.

Posology:

It is recommended that VICOMYL 200 MG IV is administered at a maximum rate of 3 mg/kg per hour over 1 to 2 hours. Not for bolus injection.

(*See 'Method of administration' below and 'Instructions for reconstitution', section 6.6*)

Special populations:

Use in the elderly

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, SBECD, occurs. Serum creatinine levels should be closely monitored in these patients and, if increases occur, consideration should be given to changing to oral voriconazole therapy.

VICOMYL 200 MG IV is haemodialysed with a clearance of 121 ml/min. A four-hour haemodialysis session does not remove a sufficient amount of VICOMYL 200 MG IV to warrant dose adjustment. The intravenous vehicle, SBECD, is haemodialysed with a clearance of 55 ml/min.

Use in patients with hepatic impairment

No dose adjustment is necessary in patients with acute hepatic injury, manifested by elevated liver function tests (ALT, AST), but continued monitoring of liver function tests for future elevations is recommended. It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving VICOMYL 200 MG IV. VICOMYL 200 MG IV has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C). VICOMYL 200 MG 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 medicine toxicity (*also see section 4.8*).

Method of administration:

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

VICOMYL 200 MG 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

VICOMYL 200 MG IV is contraindicated in:

- Patients with known hypersensitivity to voriconazole or to any of the excipients (see section 6.1).
- Co-administration with CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine since increased plasma concentrations of these medicines can lead to QTc prolongation and rare occurrences of torsades de pointes (*see section 4.5*).
- Co-administration with rifampicin, carbamazepine and phenobarbital since these medicines are likely to decrease plasma voriconazole concentrations significantly *(see section 4.5*).
- Co-administration with high-dose ritonavir (400 mg and above twice daily) because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose (*see section 4.5, for lower doses see section 4.4*).
- Co-administration with ergot alkaloids (ergotamine, dihydroergotamine),

which are CYP3A4 substrates, since increased plasma concentrations of these medicines can lead to ergotism (*see section 4.5)*.

- Co-administration with sirolimus since voriconazole is likely to increase plasma concentrations of sirolimus significantly (*see section 4.5)*.
- Co-administration with St. John's Wort (*see section 4.5*).
- Co-administration with rifabutin since VICOMYL 200 MG IV is likely to increase plasma concentrations of rifabutin significantly *(see section 4.5)*.
- Patients with prolonged QT syndrome.
- Pregnancy and lactation.
- Severe impairment of hepatic function (Child-Pugh Class C).
- Co-administration of standard doses of VICOMYL 200 MG IV with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations. Voriconazole also significantly increases efavirenz plasma concentrations (*see section 4.5, for lower doses see section 4.4)*.
- Co-administration of VICOMYL 200 MG IV 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 VICOMYL 200 MG IV with tolvaptan is contraindicated since strong CYP3A4 inhibitors such as VICOMYL 200 MG IV significantly increase plasma concentrations of tolvaptan (*see section 4.5*).
- Co-administration of VICOMYL 200 MG IV 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 VICOMYL 200 MG IV is likely to significantly increase plasma concentrations of venetoclax and increase risk of tumour lysis syndrome (*see section 4.5*).

4.4 Special warnings and precautions for use

Women of child-bearing potential

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

Hypersensitivity

Caution should be used in prescribing VICOMYL 200 MG IV to patients with hypersensitivity to other azoles (*see also section 4.8)*.

Infusion-related reaction

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. Depending on the severity of the symptoms, consideration should be given to stopping treatment.

Cardiovascular

Voriconazole 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 a history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concomitant medicines that may have been contributory. VICOMYL 200 MG IV should be administered with caution to patients with potentially proarrhythmic conditions, such as:

- Congenital or acquired QTc-prolongation (*see section 4.3*). Voriconazole may prolong the QT interval without a clear relationship to plasma concentration. VICOMYL 200 MG IV should not be used concomitantly with other medicines which prolong the QT interval.
- Cardiomyopathy, in particular when heart failure is present.
- Sinus bradycardia.
- Existing symptomatic arrhythmias.

Hepatic toxicity

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

Monitoring of hepatic function

Patients receiving VICOMYL 200 MG IV must be carefully monitored for hepatic toxicity. Clinical management should include laboratory evaluation of hepatic function (specifically AST and ALT) at the initiation of treatment with VICOMYL 200 MG IV and at least weekly for the first month of treatment. Treatment duration should be as short as possible. Monitoring frequency can be reduced to monthly if there are no changes in the liver function tests.

If the liver function tests become markedly elevated, VICOMYL 200 MG IV should be discontinued. Monitoring of hepatic function should be carried out in both children and adults.

Serious dermatological adverse reactions

- Phototoxicity

In addition, VICOMYL 200 MG IV has been associated with phototoxicity including reactions such as ephelides, lentigo, actinic keratosis and pseudo porphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during VICOMYL 200 MG IV treatment and use measures such as protective clothing and sunscreen with a 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, VICOMYL 200 MG IV discontinuation and use of alternative antifungal agents should be considered and the patient should be referred to a dermatologist. If VICOMYL 200 MG IV is continued,

however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions. VICOMYL 200 MG 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 should be monitored closely and VICOMYL 200 MG IV discontinued if lesions progress.

Visual adverse reactions

There have been reports of prolonged visual adverse reactions, including blurred vision, optic neuritis and papilloedema (*see section 4.8*). These visual disturbances may be transient and fully reversible, with the majority spontaneously resolving within 60 minutes *(see section 4.8)*.

Renal adverse reactions

Acute renal failure has been observed in severely ill patients undergoing treatment with VICOMYL 200 MG IV. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medicines and have concurrent conditions that may result in decreased renal function (*see section 4.8*).

Monitoring of renal function

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

Monitoring of pancreatic function

Patients, especially children, with risk factors for acute pancreatitis (e.g. recent chemotherapy or haematopoietic stem cell transplantation [HSCT]), should be monitored closely during VICOMYL 200 MG IV treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

Careful monitoring of phenytoin levels is recommended when phenytoin is co-administered with VICOMYL 200 MG IV. Concomitant use of VICOMYL 200 MG IV and phenytoin should be avoided (*see section 4.5*).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

When VICOMYL 200 MG IV is co-administered with efavirenz the dose of VICOMYL 200 MG IV should be increased to 400 mg every 12 hours and the dose of efavirenz should be decreased to 300 mg every 24 hours *(see sections 4.3 and 4.5*).

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Co-administration of VICOMYL 200 MG IV and low-dose ritonavir (100 mg twice daily) should be avoided (*see section 4.3 for higher doses and section 4.5*).

Everolimus (CYP3A4 substrate, P-gp substrate)

Co-administration of VICOMYL 200 MG IV with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations. Currently there are insufficient data to allow dosing recommendations in this situation *(see section 4.5*).

Methadone (CYP3A4 substrate)

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

Short-acting opiates (CYP3A4 substrate)

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

Long-acting opiates (CYP3A4 substrate)

Reduction in the dose of oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g. hydrocodone) should be considered when co-administered with VICOMYL 200 MG IV. Frequent monitoring for opiate-associated adverse reactions may be necessary (*see section 4.5)*.

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Co-administration of oral voriconazole and oral fluconazole resulted in a significant increase in C_{max} and AUC of voriconazole in healthy subjects. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for VICOMYL 200 MG IV-associated adverse reactions is recommended if VICOMYL 200 MG IV is used sequentially after fluconazole (*see section 4.5*).

Ciclosporin and tacrolimus (CYP3A4 substrates)

Clinically significant medicine interactions with VICOMYL 200 MG IV may occur in patients who are receiving treatment with ciclosporin or tacrolimus (*see section 4.5*).

Glasdegib (CYP3A4 substrate)

Co-administration of VICOMYL 200 MG IV 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 VICOMYL 200 MG IV 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 monitoring is recommended *(see section 4.5)*.

Adrenal events

Adrenal insufficiency has been reported in patients receiving azoles, as contained in VICOMYL 200 MG IV. Adrenal insufficiency has been reported in patients receiving VICOMYL 200 MG IV 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, VICOMYL 200 MG IV-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 VICOMYL 200 MG IV concomitantly with corticosteroids.

Patients on long-term treatment with VICOMYL 200 MG IV and corticosteroids (including inhaled corticosteroids e.g. budesonide and intranasal corticosteroids) should be carefully monitored for adrenal cortex dysfunction both during treatment and when VICOMYL 200 MG IV 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

Long-term treatment

Squamous cell carcinoma of the skin (SCC)

In patients with photosensitivity skin reactions and additional risk factors, squamous cell carcinoma of the skin and melanoma have been reported during long-term therapy. If phototoxic reactions occur, contact your doctor and discontinue using VICOMYL 200 MG IV. If VICOMYL 200 MG IV is continued, however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions.
If a patient develops a skin lesion consistent with premalignant skin lesions, squamous cell carcinoma or melanoma, VICOMYL 200 MG IV discontinuation should be considered.

Non-infectious periostitis

Periostitis has been reported in transplant patients during long-term VICOMYL 200 MG IV therapy. If a patient develops skeletal pain and radiologic findings compatible with periostitis, VICOMYL 200 MG IV should be discontinued.

Paediatric population

Safety and effectiveness in paediatric subjects below the age of two years has not been established (*see sections 4.8 and 5.1*). VICOMYL 200 MG IV is indicated for paediatric patients aged two years or older. A higher frequency of

liver enzyme elevations was observed in the paediatric population (*see section 4.8)*. Hepatic function should be monitored in both children and adults. Oral bioavailability may be limited in paediatric patients aged 2 to < 12 years with malabsorption and very low body weight for age. In that case, intravenous voriconazole administration is recommended.

- *Serious dermatological adverse reactions (including SCC)*

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

Excipients

Sodium:

VICOMYL 200 MG IV contains sodium (222 mg/vial). This should be particularly taken into account for those on a low salt diet.

Cyclodextrin:

VICOMYL 200 MG IV also contains cyclodextrin (2978 mg/vial), which may accumulate in patients with moderate to severe renal dysfunction.

4.5 Interaction with other medicines and other forms of interaction

Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these

isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.

Unless otherwise specified, interaction studies have been performed in healthy adult male subjects using multiple dosing to steady state with oral voriconazole at 200 mg twice daily (BID). These results are relevant to other populations and routes of administration.

VICOMYL 200 MG 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 voriconazole 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*).

Interaction table

Interactions between voriconazole and other medicines are listed in the table below (once daily as “QD”, twice daily as “BID”, three times daily as “TID” and not determined as “ND”). The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), below (↓) or above (↑) the 80-125% range. The asterisk (*) indicates a two-way interaction. AUC, AUC_t and AUC0-∞ represent area under the curve over a dosing interval, from time zero to the time with detectable measurement and from time zero to infinity, respectively.

The interactions in the table are presented in the following order: contraindications, those requiring dose adjustment and careful clinical and/or biological monitoring,

and finally those that have no significant pharmacokinetic interaction but may be of clinical interest in this therapeutic field.

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
Astemizole, cisapride, pimozide, quinidine and terfenadine *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of these medicines can lead to QTc prolongation and rare occurrences of torsades de pointes.	**Contraindicated** *(see section 4.3*)
Carbamazepine and long-acting barbiturates (e.g. phenobarbital, mephobarbital) *[potent CYP450 inducers]*	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	**Contraindicated** *(see section 4.3*)
Ergot alkaloids (e.g. ergotamine and dihydroergotamine) [CYP3A4 substrates]	Although not studied, voriconazole is likely to increase the plasma concentrations of ergot	**Contraindicated** (*see section 4.3*)

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
	alkaloids and lead to ergotism.	
Lurasidone [CYP3A4 substrate	Although not studied, VICOMYL 200 MG IV is likely to significantly increase the plasma concentrations of lurasidone.	**Contraindicated** *(see section 4.3*)
Naloxegol [CYP3A4 substrate]	Although not studied, VICOMYL 200 MG IV is likely to significantly increase the plasma concentrations of naloxegol.	**Contraindicated** *(see section 4.3*)
Rifabutin *[potent CYP450 inducer]* 300 mg QD	Voriconazole C_{max} ↓ 69 %	

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
300 mg QD (co-administered with voriconazole 350 mg BID)*	Voriconazole AUCτ ↓ 78 % Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ 4 % Voriconazole AUCτ ↓ 32 %	
300 mg QD (co-administered with voriconazole 400 mg BID)*	Rifabutin C_{max} ↑ 195 % Rifabutin AUCτ ↑ 331 % Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104 % Voriconazole AUCτ ↑ 87 %	Concomitant use of voriconazole and rifabutin should be avoided. The maintenance dose of voriconazole may be increased to 5 mg/kg intravenously BID or from 200 mg to 350 mg orally BID (100 mg to 200 mg orally BID in patients less

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
		than 40 kg) (see section 4.2). Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g. uveitis) is recommended when rifabutin is co-administered with voriconazole.
Rifampicin (600 mg QD) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓ 93 % Voriconazole AUC_{τ} ↓ 96 %	**Contraindicated** *(see section 4.3)*
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4*		

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
inhibitor and substrate]		
High dose (400 mg BID)	Ritonavir C_{max} and AUCτ ↔ Voriconazole C_{max} ↓ 66 % Voriconazole AUCτ ↓ 82 %	Co-administration of voriconazole and high doses of ritonavir (400 mg and above BID) is **contraindicated** *(see section 4.3*).
Low dose (100 mg BID)*	Ritonavir C_{max} ↓ 25 % Ritonavir AUCτ ↓13 % Voriconazole C_{max} ↓ 24 % Voriconazole AUCτ ↓ 39 %	Co-administration of voriconazole and low dose ritonavir (100 mg BID) should be avoided.
St John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg TID (co-administered with	In an independent published study, Voriconazole AUC_{∞} ↓ 59 %	**Contraindicated** *(see section 4.3*)

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
voriconazole 400 mg single dose)		
Tolvaptan [CYP3A substrate]	Although not studied clinically, VICOMYL 200 MG IV is likely to significantly increase the plasma concentrations of tolvaptan.	**Contraindicated** *(see section 4.3)*
Venetoclax [CYP3A substrate]	Although not studied, VICOMYL 200 MG IV is likely to significantly increase the plasma concentrations of venetoclax.	Concomitant administration of VICOMYL 200 MG IV is contraindicated at initiation and during venetoclax dose titration phase *(see section 4.3*). Dose reduction of venetoclax is required as instructed in venetoclax prescribing

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
		information during steady daily dosing; close monitoring for signs of toxicity is recommended.
Everolimus *[CYP3A4 substrate, P-gP substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	Co-administration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (*see section 4.4*).
Fluconazole (200 mg QD)	Voriconazole C_{max} ↑ 57 % Voriconazole AUC_T ↑ 79 % Fluconazole C_{max} ND Fluconazole AUC_T ND	The reduced dose and/or frequency of voriconazole and fluconazole that would

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
[CYP2C9, CYP2C19 and CYP3A4 inhibitor]		eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.
Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]* 300 mg QD	Voriconazole C_{max} ↓ 49 % Voriconazole AUC_{τ} ↓ 69 %	Concomitant use of voriconazole and phenytoin should be avoided. Careful monitoring of phenytoin plasma levels is recommended.

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
300 mg QD (co-administered with VICOMYL 200 mg IV	Phenytoin Cmax ↑ 67 % Phenytoin AUCτ ↑ 81 % Compared to VICOMYL 200 mg IV 200 mg BID, VICOMYL 200 mg IV Cmax ↑ 34 % VICOMYL 200 mg IV AUCτ ↑ 39 %	Phenytoin may be co-administered with VICOMYL 200 mg IV if the maintenance dose of VICOMYL 200 mg IV is increased to 5 mg/kg IV BID (*see section 6.6*).
Letermovir [CYP2C9 and CYP2C19 inducer]	VICOMYL 200 MG IV Cmax ↓ 39 % VICOMYL 200 MG IV AUC0-12 ↓ 44 % VICOMYL 200 MG IV C12 ↓ 51 %	If concomitant administration of VICOMYL 200 MG IV with letermovir cannot be avoided, monitor for loss of VICOMYL 200 MG IV effectiveness.
Glasdegib [CYP3A4 substrate]	Although not studied, VICOMYL 200 MG IV is likely to increase the plasma concentrations of	If concomitant use cannot be avoided, frequent ECG monitoring is

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
	glasdegib and increase risk of QTc prolongation.	recommended *(see section 4.4*).
Tyrosine kinase inhibitors (e.g. axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) [CYP3A4 substrates]	Although not studied, VICOMYL 200 MG IV may increase plasma concentrations of tyrosine kinase inhibitors metabolised by CYP3A4.	If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor is recommended *(see section 4.4*).
Anticoagulants Warfarin (30 mg single dose, co-administered with 300 mg BID voriconazole) *[CYP2C9 substrate]*	Maximum increase in prothrombin time was approximately 2-fold	Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
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.	accordingly.
Ivacaftor [CYP3A4 substrate]	Although not studied, VICOMYL 200 MG IV is likely to increase the plasma concentrations of ivacaftor with risk of increased adverse effects.	Dose reduction of ivacaftor is recommended.
Benzodiazepines (e.g. midazolam, triazolam, alprazolam) *[CYP3A4 substrates]*	Although not studied clinically, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	Dose reduction of benzodiazepines should be considered.

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
Immunosuppressants *[CYP3A4 substrates]*	In an independent published study:	
Sirolimus (2 mg single dose)	Sirolimus C_{max} ↑ 6.6-fold Sirolimus AUC_{∞} ↑ 11-fold	Co-administration of voriconazole and sirolimus is **contraindicated** (*see section 4.3*).
Ciclosporin (In stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin C_{max} ↑ 13 % Ciclosporin AUC_{T} ↑ 70 %	When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. When voriconazole is

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
		discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.
Tacrolimus (0.1 mg/kg single dose)	Tacrolimus C_{max} ↑ 117 % Tacrolimus AUC_t ↑ 221 %	When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. When

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
		voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.
Long-Acting Opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose)	In an independent published study, Oxycodone C_{max} ↑ 1,7-fold Oxycodone AUC_{∞} ↑ 3,6-fold	Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g. hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse reactions may be necessary.
Methadone (32-100 mg QD)	R-methadone (active) C_{max} ↑ 31 %	Frequent monitoring for adverse reactions

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
[CYP3A4 substrate]	R-methadone (active) AUCτ ↑ 47 % S-methadone C_{max} ↑ 65 % S-methadone AUCτ ↑ 103 %	and toxicity related to methadone, including QT prolongation, is recommended. Dose reduction of methadone may be needed.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) *[CYP2C9 substrates]* Ibuprofen (400 mg single dose) Diclofenac (50 mg single dose)	 S-Ibuprofen C_{max} ↑ 20 % S-Ibuprofen AUC_{∞} ↑ 100 % Diclofenac C_{max} ↑ 114 % Diclofenac AUC_{∞} ↑ 78 %	 Frequent monitoring for adverse reactions and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.
Omeprazole (40 mg QD)*	Omeprazole C_{max} ↑ 116 % Omeprazole AUCτ ↑ 280 % Voriconazole C_{max} ↑ 15 %	No dose adjustment of voriconazole is recommended.

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]	Voriconazole AUCτ ↑ 41 % Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicines.	When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose be halved.
Oral Contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ethinylestradiol (1 mg/0.035 mg QD)	Ethinylestradiol C_{max} ↑ 36 % Ethinylestradiol AUCτ ↑ 61 % Norethisterone C_{max} ↑ 15 % Norethisterone AUCτ ↑ 53 % Voriconazole C_{max} ↑ 14 % Voriconazole AUCτ ↑ 46 %	Monitoring for adverse reactions related to oral contraceptives, in addition to those for voriconazole, is recommended.
Short Acting Opiates *[CYP3A4 substrates]*		Dose reduction of alfentanil, fentanyl and

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
Alfentanil (20 µg/kg single dose, with concomitant naloxone)	In an independent published study, Alfentanil AUC_{∞} ↑ 6-fold	other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g. sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse reactions is recommended.
Fentanyl (5 µg/kg single dose)	In an independent published study, Fentanyl AUC_{∞} ↑ 1,34-fold	
Statins (e.g. lovastatin) *[CYP3A4 substrates]*	Although not studied clinically, voriconazole is likely to increase the plasma concentrations of statins that are metabolised	Dose reduction of statins should be considered.

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

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
[CYP3A4 substrates and inhibitors]	metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	and dose adjustment may be needed.
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (e.g. delavirdine, nevirapine)* *[CYP3A4 substrates, inhibitors or CYP450 inducers]*	Not studied clinically. *In vitro* studies show that the metabolism of voriconazole may be inhibited by NNRTIs and voriconazole may inhibit the metabolism of NNRTIs. The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by a NNRTI.	Careful monitoring for any occurrence of medicine toxicity and/or lack of efficacy, and dose adjustment may be needed.
Tretinoin [CYP3A4 substrate]	Although not studied, VICOMYL 200 mg IV may increase tretinoin concentrations and	Dose adjustment of tretinoin is recommended during treatment with

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
	increase risk of adversereactions (pseudotumour cerebri, hypercalcaemia).	VICOMYL 200 mg IV and after its discontinuation.
Cimetidine (400 mg BID) *[non-specific CYP450 inhibitor and increases gastric pH]*	Voriconazole C_{max} ↑ 18 % Voriconazole AUCτ ↑ 23 %	No dose adjustment
Digoxin (0.25 mg QD) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUCτ ↔	No dose adjustment
Indinavir (800 mg TID) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUCτ ↔ Voriconazole C_{max} ↔ Voriconazole AUCτ ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) *[CYP3A4 inhibitor]*	Voriconazole C_{max} and AUCτ ↔	No dose adjustment

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
Azithromycin (500 mg QD)	Voriconazole C_{max} and AUCτ ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	
Mycophenolic acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_t ↔	No dose adjustment
Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	Prednisolone C_{max} ↑ 11 % Prednisolone AUC_∞ ↑ 34 %	No dose adjustment Patients on long-term treatment with VICOMYL 200 MG IV and corticosteroids (including inhaled corticosteroids e.g. budesonide and intranasal corticosteroids) should be carefully monitored

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
		for adrenal cortex dysfunction both during treatment and when voriconazole is discontinued (*see secti on 4.4*).
Ranitidine (150 mg BID) *[increases gastric pH]*	Voriconazole C_{max} and AUCτ ↔	No dose adjustment
Flucloxacillin *[CYP450 inducer]*	Significantly decreased plasma voriconazole concentrations have been reported.	If concomitant administration of voriconazole with flucloxacillin cannot be avoided, monitor for potential loss of voriconazole effectiveness (e.g. by therapeutic medicine monitoring); increasing the dose of

Medicine [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
		voriconazole may be needed.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

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

Pregnancy

There are no adequate data on the use of VICOMYL 200 MG IV in pregnant women available. Studies in animals have shown reproductive toxicity (*see section 5.3*). The potential risk for humans is unknown. VICOMYL 200 MG IV must not be used during pregnancy.

Breastfeeding

The excretion of voriconazole into breast milk has not been investigated.

Breastfeeding must be stopped on initiation of treatment with VICOMYL 200 MG IV.

Fertility

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

4.7 Effects on ability to drive and use machines

VICOMYL 200 MG IV has moderate influence on the ability to drive and use machines. It may cause transient and reversible changes to vision, including blurring, altered/enhanced visual perception and/or photophobia. Patients must avoid potentially hazardous tasks, such as driving or operating machinery while experiencing these symptoms.

4.8 Undesirable effects

a) Summary of adverse effects

The safety profile of voriconazole in adults is based on an integrated safety database of more than 2,000 subjects (including 1,603 adult patients in therapeutic trials) and an additional 270 adults in prophylaxis trials. This represents a heterogeneous population, containing patients with haematological malignancy, HIV-infected patients with oesophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidaemia or aspergillosis and healthy volunteers.

The most frequently reported adverse reactions were visual impairment, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema, liver function test abnormal, respiratory distress and abdominal pain.

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

b) Tabulated list of adverse reactions

In the table below, since the majority of the studies were of an open nature, all causality adverse reactions and their frequency categories in 1 873 adults from pooled therapeutic (1 603) and prophylaxis (270) studies, by system organ class, are listed.

Frequency categories are expressed as: Frequent, Less frequent and Frequency unknown (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Undesirable effects reported in subjects receiving voriconazole:

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

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MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Frequent	Agranulocytosis[a], pancytopenia, thrombocytopenia[b], leukopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic)
	Less frequent	Bone marrow failure, lymphadenopathy, eosinophilia, disseminated intravascular coagulation
Immune system disorders	Less frequent	Hypersensitivity, anaphylactoid reaction
Endocrine disorders	Less frequent	Adrenal insufficiency, hypothyroidism, hyperthyroidism
Metabolism and nutrition disorders	Frequent	Peripheral oedema, hypoglycaemia, hypokalaemia, hyponatraemia
Psychiatric disorders	Frequent	Depression, hallucination, anxiety, insomnia, agitation, confusional state
Nervous system disorders	Frequent	Headache, convulsion, syncope, tremor, hypertonia[e], paraesthesia, somnolence, dizziness
	Less frequent	Brain oedema, encephalopathy[c], extrapyramidal disorder[d], neuropathy peripheral, ataxia,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		hypoaesthesia, dysgeusia, hepatic encephalopathy, Guillain-Barre syndrome, nystagmus
Eye disorders	Frequent	Visual impairment[h] (including altered/enhanced visual perception, blurred vision, colour vision, change, photophobia), retinal haemorrhage
	Less frequent	Optic nerve disorder[f], papilloedema[g], oculogyric crisis, diplopia, scleritis, blepharitis, optic atrophy, corneal opacity
Ear and labyrinth disorders	Less frequent	Hypoacusis, vertigo, tinnitus
Cardiac disorders	Frequent	Supraventricular dysrhythmia, atrial dysrhythmia, tachycardia, bradycardia
	Less frequent	Ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia, *Torsades de Pointes*, atrioventricular block complete, bundle branch block, nodal rhythm
Vascular disorders	Frequent	Hypotension, phlebitis
	Less frequent	Thrombophlebitis, lymphangitis

1.3.1.1 Professional Information for medicines for human use

MedDRA system organ class	**Frequency**	**Adverse reactions**
Respiratory, thoracic and mediastinal disorders	Frequent	Respiratory distress, acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting, abdominal pain, nausea, cheilitis, dyspepsia, constipation, gingivitis
	Less frequent	Peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis
Hepato-biliary disorders	Frequent	Abnormal liver function test (including AST, ALT, alkaline phosphatase, GGT, LDH, bilirubin), jaundice, jaundice cholestatic, hepatitis[i]
	Less frequent	Hepatic failure, hepatomegaly, cholecystitis, cholelithiasis
Skin and subcutaneous tissue disorders	Frequent	Rash, exfoliative dermatitis, alopecia, maculopapular rash, pruritus, erythema, purpura, phototoxicity
	Less frequent	Stevens-Johnson syndrome, urticaria, dermatitis allergic, eczema, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), angioedema, actinic keratosis, pseudo

MedDRA system organ class	**Frequency**	**Adverse reactions**
		porphyria erythema multiforme, psoriasis, drug eruption, discoid lupus erythematosus
	Frequency unknown	Cutaneous lupus erythematosus, ephelides, lentigo
Musculoskeletal and connective tissue disorders	Frequent	Back pain
	Less frequent	Arthritis
	Frequency unknown	Periostitis
Renal and urinary disorders	Frequent	Acute renal failure, haematuria
	Less frequent	Renal tubular necrosis, proteinuria, nephritis
General disorders and administration site conditions	Frequent	Pyrexia, chest pain, facial oedema[j], asthenia, chills
	Less frequent	Infusion site reaction, influenza like illness
Investigations	Frequent	Increased blood creatinine
	Less frequent	Increased blood urea, increased blood cholesterol

a Includes febrile neutropenia and neutropenia.

b Includes immune thrombocytopenic purpura.

c Includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy.

d Includes akathisia and parkinsonism.

e Includes nuchal rigidity and tetany.

f Prolonged optic neuritis has been reported post-marketing (*see section 4.4*).

g See section 4.4.

h See “Visual impairments” paragraph in section 4.8.

i Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.

j Includes periorbital oedema, lip oedema, and mouth oedema.

Post-marketing experience

System Organ Class	**Adverse reaction**
Metabolism and nutrition disorders	Hyponatraemia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Squamous cell carcinoma
Skin and subcutaneous tissue disorders	Cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms

Description of selected adverse reactions

Visual impairments:

Visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, colour blindness, cyanopsia, eye disorder, halo vision, night blindness, oscillopsia, photopsia, scintillating scotoma, reduction in visual acuity,

visual brightness, visual field defect, vitreous floaters, and xanthopsia) with VICOMYL 200 MG IV were reported. These visual impairments were transient and fully reversible (*see section 4.4)*. There have been post-marketing reports of prolonged visual adverse events (*see section 4.4)*.

Dermatological reactions:

Patients have less frequently 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) which was reported post-marketing and erythema multiforme (rare) during treatment with VICOMYL 200 MG IV (*see section 4.4*).

Photosensitivity reactions have been reported, especially during long-term therapy (*see section 4.4*).

Dermatological adverse reactions potentially related to phototoxicity (pseudo porphyria, cheilitis, and cutaneous lupus erythematosus) are also reported with VICOMYL 200 MG IV. Sun avoidance and photoprotection are recommended for all patients. If phototoxicity occurs, VICOMYL 200 MG IV discontinuation and dermatological evaluation should be considered (*see section 4.4)*.

Liver function tests:

Cases of serious hepatic toxicity in patients with other serious underlying conditions such as jaundice, hepatitis and hepatic failure leading to death (*see section 4.4*) have been reported.

Infusion-related reactions:

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During infusion of VICOMYL 200 MG IV anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnoea, faintness, nausea, pruritus and rash have occurred.

Paediatric population:

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

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

4.9 Overdose

In clinical trials there were 3 cases of accidental overdose. All occurred in paediatric patients, who received up to five times the recommended intravenous dose of voriconazole. A single adverse reaction of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is haemodialysed with a clearance of 121 ml/min. The intravenous vehicle, SBECD, is haemodialyzed with a clearance of 55 ml/min. In an overdose,

haemodialysis may assist in the removal of voriconazole and SBECD from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Mode 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. 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.

Clinical efficacy and safety

In vitro, voriconazole displays broad-spectrum antifungal activity with antifungal potency against *Candida* species (including fluconazole- resistant *C. krusei* and resistant strains of *C. glabrata* and *C. albicans*) and fungicidal activity against all

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

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

5.2 Pharmacokinetic properties

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

Absorption:

When multiple doses of voriconazole are administered with high fat meals C_{max} and AUC_T are reduced by 34 % and 24 %, respectively.

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

Distribution:

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

Metabolism:

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

The inter-individual variability of voriconazole pharmacokinetics is high.

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

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

Excretion:

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

After administration of a radiolabeled dose of voriconazole, approximately 80 % of the radioactivity is recovered in the urine after multiple intravenous dosing and 83 % in the urine after multiple oral dosing. The majority (> 94 %) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing. The terminal half-life of voriconazole depends on dose and is approximately 6 hours following 200 mg (orally). Because of non-linear pharmacokinetics, the terminal half-life is not useful in the prediction of the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic Relationships

A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy in therapeutic studies was not found. Pharmacokinetic–Pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances.

Pharmacokinetics in Special Patient Groups:

Gender:

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

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

Elderly:

In an oral multiple dose study C_{max} and AUC_T in healthy elderly males (≥ 65 years) were 61 % and 86 % higher, respectively, than in healthy young males (18 - 45 years). No significant differences in C_{max} and AUC_T were observed between healthy elderly females (≥ 65 years) and healthy young females (18 - 45 years).
In the therapeutic studies no dosage adjustment was made on the basis of age. A relationship between plasma concentrations and age was observed. However, the safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly (see section 4.2).

Paediatric population:

The recommended doses in children and adolescent patients are based on a population pharmacokinetic analysis, which 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 an oral single dose (200 mg) study in subjects with normal renal function and mild (creatinine clearance 41 – 60 ml/min) to severe (creatinine clearance < 20 ml/min) renal impairment, the pharmacokinetics of voriconazole were not significantly affected by renal impairment. The plasma protein binding of voriconazole was similar in subjects with different degrees of renal impairment (see sections 4.3 and 4.4).

Hepatic Impairment:

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

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

5.3 Preclinical safety data

In reproduction studies, voriconazole was shown to be teratogenic in rats and embryotoxic in rabbits at systemic exposures equal to those obtained in humans with therapeutic doses. Voriconazole administration induced no impairment of male or female fertility in rats at exposures similar to those obtained in humans at therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulphobutylether beta cyclodextrin sodium (SBECD), which contains:

- Sodium 222 mg
- Cyclodextrin 2978 mg

6.2 Incompatibilities

VICOMYL 200 MG IV must not be infused into the same line or cannula concomitantly with other medicine infusions, including parenteral nutrition. 4,2 % Sodium Bicarbonate Intravenous Infusion is not compatible with VICOMYL 200 MG IV and must not be used as a diluent. Compatibility with other concentrations is unknown.

Blood products and concentrated electrolytes

VICOMYL 200 MG IV 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 disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of VICOMYL 200 MG IV therapy.

Intravenous solutions containing (non-concentrated) electrolytes

VICOMYL 200 MG IV 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)

VICOMYL 200 MG IV can be infused 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 VICOMYL 200 MG IV.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Powder for solution for infusion: Store at or below 25 °C.

Reconstituted concentrate: Store at 2 °C - 8 °C for up to 24 hours (in a refrigerator).

6.5 Nature and contents of container

VICOMYL 200 MG IV powder for solution for infusion is available as a single use 30 ml Type I tubular flint glass vial with 20 mm dark grey bromobutyl lyo stopper, 20 mm flip-off aluminium seal.

6.6 Special precautions for disposal and other handling

1.3.1.1 Professional Information for medicines for human use

VICOMYL 200 MG IV requires reconstitution and dilution prior to administration as an intravenous infusion. Not for bolus injection.

Use in Adults:

Detailed information on dosage recommendations is provided in the following table: (1)

	Inravenous
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

Therapy must be initiated with the specified loading dose regimen of VICOMYL 200 MG IV to achieve plasma concentrations on Day 1 that are close to steady state.

The vial contents are reconstituted with 19 ml of water for injections to obtain a clear solution containing 10 mg/ml of VICOMYL 200 MG IV and an extractable volume of 20 ml.

For administration, the required volume of the reconstituted solution is added to a recommended compatible infusion solution (tabulated below) to obtain, where appropriate, a final VICOMYL 200 MG IV solution containing 0,5 - 5 mg/ml.

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, VICOMYL 200 MG 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 aged 2 to < 12 years:

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 VICOMYL 200 MG 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 VICOMYL 200 MG IV if the maintenance dose of VICOMYL 200 MG IV is increased to 5 mg/kg intravenously every 12 hours (*see sections 4.4 and 4.5*).

When VICOMYL 200 MG IV is co-administered with adjusted doses of efavirenz, VICOMYL 200 MG IV maintenance dose should be increased to 400 mg every 12 hours (*see sections 4.4 and 4.5*).

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris South Africa

4 Brewery Street,

Isando

Johannesburg, 1609

Republic of South Africa

8 REGISTRATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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