1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PROFESSIONAL INFORMATION HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

IMMAVOR powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

Each IMMAVOR vial contains 200 mg voriconazole. When reconstituted as directed, each ml contains 10 mg voriconazole.

Sugar free

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

IMMAVOR is a White lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of invasive aspergillosis.

Treatment of serious invasive infections caused by *Candida* spp (including *C. krusei*).

Voriconazole has been used in the treatment of serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp.

Prevention of breakthrough of fungal infections in febrile high-risk patients (allogeneic bone marrow transplants, relapsed leukaemia patients) where liposomal amphotericin B cannot be used.

4.2 Posology and method of administration

Posology

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

IMMAVOR requires reconstitution and dilution prior to administration as an intravenous infusion.

Not for bolus injection.

Treatment

Adults

Therapy must be initiated with the specified loading dose of IMMAVOR to achieve plasma concentrations on Day 1 that are close to steady state.

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

	Intravenous
Loading Dose Regimen for all Indications (first 24 hours)	6 mg/kg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours) Prevention of breakthrough infections	3 mg/kg every 12 hours
Invasive aspergillosis, serious *Candida* infections, *Scedosporium/ Fusarium* infections	4 mg/kg every 12 hours

Dosage adjustment (Adults)

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

If patient is unable to tolerate intravenous treatment at 4 mg/kg twice daily, reduce the dose to 3 mg/kg twice daily.

Phenytoin may be co-administered with IMMAVOR if the maintenance dose of IMMAVOR is increased to 5 mg/kg intravenously every 12 hours (see section 4.4and 4.5)

Treatment duration depends upon patients' clinical and mycological response.

Use in the elderly

No dose adjustment is necessary for elderly patients.

Use in patients with renal impairment

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 IMMAVOR therapy.

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

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

IMMAVOR has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice. Patients with hepatic impairment must be carefully monitored for medicine toxicity (see also ‘Side effects’).

Use in children

Safety and effectiveness in paediatric subjects below the age of 2 years has not been established. Therefore, IMMAVOR 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 (2 to <12 years)

	Intravenous
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.

4.3 Contraindications

IMMAVOR is contraindicated in patients with known hypersensitivity to voriconazole or to any of the excipients.

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

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

Co-administration of standard doses of IMMAVOR with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma IMMAVOR concentrations in healthy subjects at these doses. IMMAVOR also significantly increases efavirenz plasma concentrations.

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

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

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

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

Co-administration of IMMAVOR with St John's Wort is contraindicated (see section 4.5).

Co-administration with venetoclax at initiation and during the venetoclax dose titration phase is contraindicated since IMMAVOR is likely to significantly increase plasma concentrations of venetoclax and increase risk of tumour lysis syndrome.

Patients with prolonged QT syndrome.

Pregnancy and lactation.

Severe impairment of hepatic function (Child-Pugh Class C).

4.4 Special warnings and precautions for use

Women of child-bearing potential

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

Hypersensitivity

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

Infusion-related reaction

During infusion of the intravenous formulation of IMMAVOR **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 rare cases of torsades de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concomitant medicinal products that may have been contributory. Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as:

• Congenital or acquired QTc-prolongation.

• Cardiomyopathy, in particular when heart failure is present.

• Sinus bradycardia.

• Existing symptomatic arrhythmias.

• Concomitant medicinal product that is known to prolong QTc interval. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2). A study has been conducted in healthy volunteers which examined the effect on QTc interval of single doses of voriconazole up to 4 times the usual daily dose. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec (see section 5.1).

Hepatic toxicity

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 IMMAVOR 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 IMMAVOR and at least weekly for the first month of treatment. Treatment duration should be as short as possible; however, if based on the benefit-risk assessment the treatment is continued (see section 4.2), monitoring frequency can be reduced to monthly if there are no changes in the liver function tests.

If the liver function tests become markedly elevated, IMMAVOR should be discontinued.

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

Serious dermatological adverse reactions

• Phototoxicity

In addition, IMMAVOR has been associated with phototoxicity including reactions such as ephelides, lentigo, actinic keratosis and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during IMMAVOR treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

• Squamous cell carcinoma of the skin (SCC)

Squamous cell carcinoma of the skin has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur multidisciplinary advice should be sought, IMMAVOR discontinuation and use of alternative antifungal medicines should be considered and the patient should be referred to a dermatologist. If IMMAVOR is continued, however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions. IMMAVOR 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) including 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 IMMAVOR discontinued if lesions progress.

Long-term treatment

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

Squamous cell carcinoma of the skin (SCC) has been reported in relation with long-term IMMAVOR treatment.

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

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

Visual adverse reactions

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

Renal adverse reactions

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

Monitoring of renal function

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

Monitoring of pancreatic function

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

Paediatric population

Safety and effectiveness in paediatric subjects below the age of two years has not been established (see sections 4.8 and 5.1). Voriconazole 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.

Prophylaxis

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

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

Careful monitoring of phenytoin levels is recommended when phenytoin is co-administered with voriconazole.

Concomitant use of voriconazole and phenytoin should be avoided (see section 4.5).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

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

Rifabutin (potent CYP450 inducer)

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

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Coadministration of voriconazole and low-dose ritonavir (100 mg twice daily) should be avoided (see sections 4.3 and 4.5).

Everolimus (CYP3A4 substrate, P-gp substrate)

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

Methadone (CYP3A4 substrate)

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

Short-acting opiates (CYP3A4 substrate)

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

Long-acting opiates (CYP3A4 substrate)

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

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

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

Ciclosporin and tacrolimus (CYP3A4 substrates)

316 Clinically significant medicine interactions with IMMAVOR may occur in patients who are receiving treatment with ciclosporin or tacrolimus (see section 4.5). Naloxegol (CYP3A4 substrate)

Co-administration of IMMAVOR and naloxegol 319 is not recommended because IMMAVOR is expected to significantly increase naloxegol concentrations. Currently there are insufficient data to allow doing recommendations of naloxegol in this situation (see section 4.5).

4.5 Interaction with other medicines and other forms of interaction

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

Voriconazole 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 and ivabradine), coadministration is contraindicated. (see section 4.3)

Effects of other medicinal products on voriconazole

Concomitant use of the following medicines with IMMAVOR *is contraindicated:*

St John's Wort (CYP450 inducer; P-gp inducer): In an independent published study in healthy volunteers, St John's Wort exhibited a short initial inhibitory effect followed by induction of IMMAVOR metabolism. Therefore, concomitant use of IMMAVOR with St John's Wort is contraindicated (see section 4.3).

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

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

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate): The effect of the co-administration of oral IMMAVOR (200 mg twice daily) and high dose (400 mg) and low dose (100 mg) oral ritonavir was investigated in two separate studies in healthy volunteers. High doses of ritonavir (400 mg twice daily) decreased the steady state C_{max} and AUC_t of oral IMMAVOR by an average of 66 % and 82 %, whereas low doses of ritonavir (100 mg twice daily) decreased the C_{max} and AUC_t of IMMAVOR by an average of 24 % and 39 % respectively. Administration of IMMAVOR did not have a significant effect on mean C_{max} and AUC_t of ritonavir in the high dose study, although a minor decrease in steady state C_{max} and AUC_t of ritonavir with an average of 25 % and 13 % respectively was observed in the low dose ritonavir interaction study. One outlier subject with raised IMMAVOR levels was identified in each of the ritonavir interaction studies. Co-administration of IMMAVOR and high doses of ritonavir (400 mg and above twice daily) is contraindicated. Co-administration of IMMAVOR and low dose ritonavir (100 mg twice daily) should be avoided (see section 4.3 & see section 4.4).

Carbamazepine and phenobarbital (potent CYP450 inducers): Although not studied, carbamazepine or phenobarbital are likely to significantly decrease plasma IMMAVOR concentrations.

Co-administration of IMMAVOR with carbamazepine and phenobarbital is contraindicated (see section 4.3).

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

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

Ranitidine (increases gastric pH): Ranitidine (150 mg twice daily) had no significant effect on IMMAVOR C_{max} and AUC_t.

Macrolide antibiotics: Erythromycin (CYP3A4 inhibitor; 1 g twice daily) and azithromycin (500 mg once daily) had no significant effect on IMMAVOR C_{max} and AUC_t.

Effects of IMMAVOR **on other medicinal products**

Concomitant use of the following medicines with IMMAVOR *is contraindicated:*

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

Sirolimus (CYP3A4 substrate): IMMAVOR increased sirolimus (2 mg single dose) C_{max} and AUC by 6 fold and 11 fold respectively. Co-administration of IMMAVOR and sirolimus is contraindicated (see section 4.3).

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

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

Ciclosporin (CYP3A4 substrate): In stable, renal transplant recipients, IMMAVOR increased cyclosporin C_{max} and AUC_t by at least 13 % and 70 % respectively. When initiating IMMAVOR in

patients already receiving ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. When IMMAVOR is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary (see section 4.4).

Tacrolimus (CYP3A4 substrate): IMMAVOR increased tacrolimus (0,1 mg/kg single dose) C_{max} and AUC_t (area under the plasma concentration time curve to the last quantifiable measurement) by 117 % and 221 %, respectively. When initiating IMMAVOR in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. When IMMAVOR is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary (see section 4.4).

Methadone (CYP3A4 substrate): Repeat dose administration of oral IMMAVOR (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 4 days) increased the C_{max} and AUC_t of pharmacologically active R-methadone by 31 % (90 % CI: 22 %, 40 %) and 47 % (90 % CI: 38 %, 57 %), respectively, in subjects receiving a methadone maintenance dose (30 - 100 mg daily) (see section 4.4).

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

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

Oxycodone (CYP3A4 substrate**):** In an independent published study, co-administration of multiple doses of oral IMMAVOR (400 mg every 12 hours, on Day 1 followed by five doses of 200 mg every 12

hours on Days 2 to 4) with a single 10 mg oral dose of oxycodone on Day 3 resulted in an increase in the mean C_{max} and AUC0–∞ of oxycodone by 1,7-fold (range 1,4- to 2,2-fold) and 3,6-fold (range 2,7- to 5,6-fold), respectively. The mean elimination half-life of oxycodone was also increased by 2,0-fold (range 1,4- to 2,5-fold). A reduction in oxycodone dosage may be needed during IMMAVOR treatment to avoid opioid related adverse effects. Extended and frequent monitoring for adverse effects associated with oxycodone and other long-acting opiates metabolised by CYP3A4 is recommended.

Oral anticoagulants:

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

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

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

Benzodiazepines (CYP3A4 substrates): Although not studied clinically, IMMAVOR has been shown to inhibit midazolam metabolism *in vitro* (human liver microsomes). Therefore, IMMAVOR is likely to increase the plasma levels of benzodiazepines that are metabolised by CYP3A4 (e.g. midazolam, triazolam and alprazolam) and lead to a prolonged sedative effect. It is recommended that dose adjustment of the benzodiazepine be considered during co-administration.

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

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

No significant pharmacokinetic interactions were observed when IMMAVOR *was co-administered with the following medicines. Therefore, no dosage adjustment for these medicines is necessary.*

Prednisolone (CYP3A4 substrate): IMMAVOR increased C_{max} and AUC_t of prednisolone (60 mg single dose) by 11 % and 34 %, respectively. No dosage adjustment is recommended.

Digoxin (P-glycoprotein mediated transport): IMMAVOR had no significant effect on C_{max} and AUC_t of digoxin (0,25 mg once daily).

Mycophenolic acid (UDP-glucuronyl transferase substrate): IMMAVOR had no effect on the C_{max} and AUC_t of mycophenolic acid (1 g single dose).

Two-way interactions

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

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

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

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

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Concomitant use of IMMAVOR and phenytoin should be avoided.

Phenytoin (300 mg once daily) decreased the C_{max} and AUC_t of IMMAVOR by 49 % and 69 %, respectively. IMMAVOR (400 mg twice daily, see section 4.2) increased C_{max} and AUC_t of phenytoin (300 mg once daily) by 67 % and 81 %, respectively. Careful monitoring of plasma phenytoin levels is recommended when phenytoin is co-administered with IMMAVOR.

Phenytoin may be co-administered with IMMAVOR if the maintenance dose of IMMAVOR is increased from 3 mg/kg to 5 mg /kg intravenously twice daily or from 200 mg to 400 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg), see section 4.2.

Rifabutin (CYP450 inducer): Concomitant use of IMMAVOR and rifabutin is contraindicated. (see section 4.3).

Rifabutin (300 mg once daily) decreased the C_{max} and AUC_t of IMMAVOR at 200 mg twice daily by 69 % and 78 %, respectively. During co-administration with rifabutin, the C_{max} and AUC_t of IMMAVOR at 350 mg twice daily were 96 % and 68 % of the levels when administered alone at 200 mg twice daily. At a IMMAVOR dose of 400 mg twice daily, C_{max} and AUC_t were 104 % and 87 % higher, respectively, compared with IMMAVOR alone at 200 mg twice daily, IMMAVOR at 400 mg twice daily increased C_{max} and AUC_t of rifabutin by 195 % and 331 %, respectively.

Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate): Omeprazole (40 mg once daily) increased IMMAVOR C_{max} and AUC_t

by 15 % and 41 %, respectively. No dosage adjustment of IMMAVOR is recommended. IMMAVOR increased omeprazole C_{max} and AUC_t by 116 % and 280 %, respectively. When initiating IMMAVOR in patients already receiving omeprazole, it is recommended that the omeprazole dose be halved. The metabolism of other proton pump inhibitors, which are CYP2C19 substrates, may also be inhibited by IMMAVOR.

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

Indinavir (CYP3A4 inhibitor and substrate): Indinavir (800 mg three times daily) had no significant effect on IMMAVOR C_{max} and AUC_t. IMMAVOR did not have a significant effect on C_{max} and AUC_t of indinavir (800 mg three times daily).

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

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

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

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

Pregnancy

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

Studies in animals have shown reproductive toxicity and teratogenicity (see section 5.3). The potential risk to humans is unknown.

Breast-feeding

The excretion of voriconazole into breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with IMMAVOR.

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

IMMAVOR 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

Summary of the safety profile

The safety profile of IMMAVOR is based on an integrated safety database of patients who participated in clinical 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. Duration of treatment ranged from 12 weeks to more than 6 months.

In the table below, since the majority of the studies were of an open nature, all causality adverse events, by system organ class and frequency.

The most commonly reported adverse events were visual disturbances, fever, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema and abdominal pain. The severity of the adverse events was

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

Tabulated list of adverse reactions

MedDRA System Organ Class	**Side effects**
Infections and infestations	
Frequent	Sinusitis, Pseudomembranous colitis
Blood and lymphatic system disorders	
Frequent	Thrombocytopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic), leukopenia, pancytopenia, agranulocytosis
Less Frequent	Lymphadenopathy, eosinophilia, disseminated intravascular coagulation, bone marrow depression
Immune system disorders	
Less frequent	Allergic reaction, anaphylactoid reaction
Endocrine disorders	
Less frequent	Adrenal cortex insufficiency, hypothyroidism
Frequency unknown	Hyperthyroidism
Metabolism and nutrition disorders	
Frequent	Peripheral oedema
Psychiatric disorders	

Frequent	Hallucinations, confusion, depression, anxiety, agitation, insomnia
Nervous system disorders	
Frequent	Headache Dizziness, tremor, paraesthesia, syncope, hypertonia, somnolence.
Less Frequent	Ataxia, brain oedema, hypertonia, hypoaesthesia, nystagmus
Frequency unknown	Guillain-Barre syndrome, oculogyric crisis, extrapyramidal syndrome, hepatic coma, insomnia, encephalopathy, somnolence during infusion
Eye disorders	
Frequent	Visual disturbances (including altered/enhanced visual perception, blurred vision, colour vision change, photophobia)
Less frequent	Blepharitis, optic nerve disorder, papilloedema, oculogyric crisis, scleritis, diplopia
Frequency unknown	Corneal opacity, optic atrophy
Ear and labyrinth disorders	
Less frequent	Vertigo, hypoacusis, tinnitus
Cardiac disorders	
Frequent	Supraventricular dysrhythmia, atrial dysrhythmia, tachycardia, bradycardia
Less frequent	Ventricular dysrhythmia, ventricular fibrillation, supraventricular tachycardia, prolonged QT interval

Frequency unknown	Atrioventricular (AV) complete block, bundle branch block, nodal dysrhythmia, ventricular tachycardia (including *Torsades de Pointes*)
Vascular disorders	
Frequent	Hypotension, thrombophlebitis, phlebitis
Frequency unknown	Lymphangitis
Respiratory, thoracic and mediastinal disorders	
Frequent	Acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal disorders	
Frequent	Nausea, vomiting, diarrhoea, abdominal pain, cheilitis, gastroenteritis, dyspepsia, constipation, gingivitis
Less frequent	Duodenitis, glossitis, pancreatitis, tongue oedema, peritonitis
Frequency unknown	Pseudomembranous colitis
Hepatobiliary disorders	
Frequent	Elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, LDH, bilirubin), jaundice, cholestatic jaundice, hepatitis
Less frequent	Cholecystitis, cholelithiasis, enlarged liver, hepatic failure
Skin and subcutaneous tissue disorders	
Frequent	Rash
Frequent	Pruritus, maculopapular rash, photosensitivity, skin reaction, alopecia, exfoliative dermatitis, purpura
Less frequent	Fixed drug eruption, eczema, psoriasis, Stevens-Johnson syndrome, urticaria

Frequency unknown	Angioedema, discoid lupus erythematosus, erythema multiforme, toxic epidermal necrolysis, pseudoporphyria
Musculoskeletal, connective tissue and bone disorders	
Frequent	Back pain
Less frequent	Arthritis
Renal and urinary disorders	
Frequent	Acute kidney/renal failure, haematuria
Less frequent	Nephritis, renal/kidney tubular necrosis, proteinuria
General disorders and administration site conditions	
Frequent	Pyrexia, peripheral oedema Chills, asthenia, chest pain, injection site reaction/inflammation, flu syndrome, facial oedema
Investigations	
Frequent	Increased creatinine
Less frequent	Hypercholesterolemia, increased blood urea

Reporting of suspected adverse reactions

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

4.9 Overdose

There is no known antidote to IMMAVOR.

Voriconazole is haemodialysed with a clearance of 121 ml/min. The intravenous vehicle, SBECD, is haemodialysed 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

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02A C03

Pharmacological classification: A 20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics

Mechanism of action:

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

Microbiology

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

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.

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

5.2 Pharmacokinetic properties

General Pharmacokinetic Characteristics

The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 200 mg or 300 mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or haematopoietic tissue), the observed pharmacokinetic characteristics of rapid and consistent absorption, accumulation and non-linear pharmacokinetics were in agreement with those observed in healthy subjects.

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

Absorption

Voriconazole is absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96%. When multiple doses of voriconazole are administered with high fat meals C_{max} and AUC_{t} are reduced by 34% and 24%, respectively, The absorption of voriconazole is not affected by changes in gastric pH.

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4,6 l/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58 %.

Detectable voriconazole concentrations are present in the cerebrospinal fluid of patients treated with voriconazole.

Biotransformation

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

The inter-individual variability of voriconazole pharmacokinetics is high.

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

average 2-fold higher voriconazole exposure than their homozygous extensive metaboliser counterparts.

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

Elimination

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

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

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

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_{τ} 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_{τ} were observed between healthy elderly males and healthy elderly females (≥ 65 years).

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

Elderly

In an oral multiple dose study C_{max} and AUC_{τ} 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_{τ} 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.

Renal impairment

In patients with moderate to severe renal dysfunction (serum creatinine levels > 2.5 mg/dl), accumulation of the intravenous vehicle, SBECD, occurs (see sections 4.2 and 4.4).

Paediatrics

IMMAVOR *IV 200 mg powder for solution for infusion*

A population pharmacokinetic analysis was conducted on data from 35 immuno-compromised subjects aged 2 to < 12 years old who were included in the intravenous single or multiple dose pharmacokinetic studies. Twenty four of these subjects received multiple doses of voriconazole. 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, with medians of 1186 ng/ml in children and 1155 ng/ml in adults. Therefore a maintenance dose of 4 mg/kg every 12 hours is recommended for children aged between 2 to < 12 years of age.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex Sulfobutyl Ether Sodium

6.2 Incompatibilities

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

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

Total parenteral nutrition: Total parenteral nutrition (TPN) need not be discontinued when prescribed with IMMAVOR but does need to be infused through a separate line. If infused through a multiple-lumen catheter, TPN needs to be administered using a different port from the one used for IMMAVOR. IMMAVOR must not be diluted with 4.2% Sodium Bicarbonate Infusion. Compatibility with other concentrations is unknown.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light

KEEP OUT OF REACH OF CHILDREN.

<u>After dilution</u>

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions

6.5 Nature and contents of container

One 25 ml clear Type I glass vial with 20 mm grey bromobutyl slotted rubber stopper and sealed with 20 mm red colour grain finish aluminium flip-off seal in unit carton. Packs of 1, 5 or 10

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicine and other handling

The product should be used immediately after opening.

The powder is reconstituted with either 19 ml of water for injections or 19 ml of 9 mg/ml (0.9%) Sodium Chloride for Infusion to obtain an extractable volume of 20 ml of clear concentrate containing 10 mg/ml of voriconazole. Discard the IMMAVOR vial if vacuum does not pull the diluent into the vial. It is recommended that a standard 20 ml (non-automated) syringe be used to ensure that the exact amount (19.0 ml) of water for injections or (9 mg/ml [0.9%]) Sodium Chloride for Infusion is dispensed. This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used.

For administration, the required volume of the reconstituted concentrate is added to a recommended compatible infusion solution (detailed below) to obtain a final voriconazole solution containing 0.5-5 mg/ml.

Required Volumes of 10 mg/ml IMMAVOR **Concentrate**

Body Weight (kg)	**Volume of** IMMAVOR **Concentrate (10 mg/ml) required for:**				
	3 mg/kg dose (number of vials)	**4 mg/kg dose (number of vials)**	**6 mg/kg dose (number of vials)**	**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)	12.0 ml (1)	18.0 ml (1)	24.0 ml (2)	27.0 ml (2)
35	10.5 ml (1)	14.0 ml (1)	21.0 ml (2)	28.0 ml (2)	31.5 ml (2)
40	12.0 ml (1)	16.0 ml (1)	24.0 ml (2)	32.0 ml (2)	36.0 ml (2)
45	13.5 ml (1)	18.0 ml (1)	27.0 ml (2)	36.0 ml (2)	40.5 ml (3)
50	15.0 ml (1)	20.0 ml (1)	30.0 ml (2)	40.0 ml (2)	45.0 ml (3)
55	16.5 ml (1)	22.0 ml (2)	33.0 ml (2)	44.0 ml (3)	49.5 ml (3)
60	18.0 ml (1)	24.0 ml (2)	36.0 ml (2)	48.0 ml (3)	54.0 ml (3)
65	19.5 ml (1)	26.0 ml (2)	39.0 ml (2)	52.0 ml (3)	58.5 ml (3)
70	21.0 ml (2)	28.0 ml (2)	42.0 ml (3)	-	-
75	22.5 ml (2)	30.0 ml (2)	45.0 ml (3)	-	-
80	24.0 ml (2)	32.0 ml (2)	48.0 ml (3)	-	-
85	25.5 ml (2)	34.0 ml (2)	51.0 ml (3)	-	-
90	27.0 ml (2)	36.0 ml (2)	54.0 ml (3)	-	-
95	28.5 ml (2)	38.0 ml (2)	57.0 ml (3)	-	-
100	30.0 ml (2)	40.0 ml (2)	60.0 ml (3)	-	-

IMMAVOR **does not contain an antimicrobial preservative. If the reconstituted solution is not used immediately, the reconstituted solution will remain suitable for its intended use for up to 24 hours, stored at 2 – 8^0 C, if reconstitution has taken place in controlled and validated aseptic conditions.**

The reconstituted solution can be diluted with:

Sodium Chloride 9 mg/ml (0.9%) Solution for Injection

Compound Sodium Lactate Intravenous Infusion

5% Glucose and Lactated Ringer's Intravenous Infusion

5% Glucose and 0.45% Sodium Chloride Intravenous Infusion

5% Glucose Intravenous Infusion

5 % Glucose in 20 mEq Potassium Chloride Intravenous Infusion

0.45% Sodium Chloride Intravenous Infusion

5% Glucose and 0.9% Sodium Chloride Intravenous Infusion

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

Blood products and concentrated electrolytes

IMMAVOR 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 IMMAVOR therapy.

Intravenous solutions containing (non-concentrated) electrolytes

IMMAVOR 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)

IMMAVOR 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 IMMAVOR.

Discard after single use.

Discard any unused portion.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

Unit 1, 96 Hartley Road

Durban. 4091

8 REGISTRATION NUMBER(S)

55/20.1.7/0782

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT