℞VORICA

(Voriconazole Powder For Solution For Infusion 200 mg/vial)

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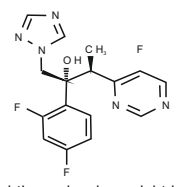
Each vial contains Voriconazole Ph. Eur. 200 mg.

DRUG DESCRIPTION

Voriconazole is chemically described as (2R, 3S)-2-(2, 4-difluorophen yl)-3-(5-fluoro-4-pyrimidinyl)- I -(I H 1 ,2,4-triazol-I -yl)-2-butanol. Voriconazole is a white or almost white powder with a molecular weight of 349.3. It is freely soluble in acetone and in methylene chloride.

The physicochemical characteristics of Voriconazole drug substance, as reported in the literature, are outlined in the table below.



The empirical formula for Voriconazole $C_{16}H_{14}F_3N_5O$ and the molecular weight is 349.3. Voriconazole is a white or almost white powder. Freely soluble in acetone and in methylene chloride, very slightly soluble in water.

THERAPEUTIC INDICATIONS

Voriconazole is indicated for use in treatment of the following conditions:

- Treatment of invasive Aspergillosis
- Treatment of fluconazole-resistant serious invasive candida infection (including *C.krusei*)
- Serious fungal infection caused by *Scedosporium spp.* (Asexual form of Pseudallescheria body) and *Fusarium spp.,*

CONTRAINDICATIONS

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

Co-administration of CY3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine since increased plasma concentration of these drugs can lead to QTc prolongation and rare occurrences of torsades de points.

Coadministration of Voriconazole with sirolimus is contraindicated because voriconazole significantly increases plasma concentrations of sirolimus.

Co-administration of Voriconazole with rifampicin, rifampin, carbamazepine and long acting barbiturates (e.g. phenobarbital, mephobarbital) is contraindicated since these drugs are likely to decrease Plasma Voriconazole concentrations significantly.

Co-administration of Voriconazole with ritonavir (400 mg twice daily) is contraindicated because ritonavir significantly decreases plasma voriconazole.

Co-administration of Voriconazole with rifabutin is contraindicated since Voriconazole significantly increases rifabutin plasma concentration and nlabulin also significantly decreases voriconazole plasma concentrations.

Co-administration of Voriconazole with ergot alkaloids (ergotamine and dihydroergotamine) is contraindicated because voriconazole may increase the plasma concentration of ergot alkaloids which may lead to ergotism.

Co-administration of voriconazole with St. John's Wort is contraindicated.

Co-administration of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is contraindicated because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations (see drug interactions).

Co-administration of voriconazole with naloxegol is contraindicated because voriconazole may significantly increase plasma concentrations of naloxegol which may precipitate opioid withdrawal symptoms (see drug interactions).
Co-administration of voriconazole with tolvaptan is contraindicated because voriconazole may significantly increase plasma concentrations of tolvaptan (see drug interactions).
Co-administration of voriconazole with venetoclax is contraindicated at initiation and during the venetoclax dose titration phase since voriconazole is likely to significantly increase plasma concentrations of venetoclax and increase risk of tumour lysis syndrome (see drug interactions).
Co-administration of voriconazole with lurasidone is contraindicated since it may result in significant increases in lurasidone exposure and the potential for serious adverse reactions (see drug interactions).

DRUG INTERACTIONS

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, in particular for substances metabolised by CYP3A4 since voriconazole is a strong CYP3A4 inhibitor though the increase in AUC is substrate dependent (see Interaction table below).

Unless otherwise specified, drug 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.

Voriconazole should be administered with caution in patients with concomitant medication that is known to prolong QT 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 Contraindications).

Interaction table

Interactions between voriconazole and other medicinal products 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_τ, AUC_t and $AUC_{0-\infty}$ 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.

Medicinal product [Mechanism of Interaction]	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
Astemizole, cisapride, pimozide, quinidine, terfenadine and ivabradine [CYP3A4 substrates]	Although not studied, increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of torsades de pointes.	Contraindicated (see Section Contraindications).
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 Contraindications).
Efavirenz (a non- nucleoside reverse transcriptase inhibitor) *[CYP450 inducer; CYP3A4 inhibitor and substrate]* Efavirenz 400 mg QD, co-administered with voriconazole 200 mg BID Efavirenz 300 mg QD, co- administered with voriconazole 400 mg BID*	Efavirenz C_{max} ↑38% Efavirenz AUC_τ↑44% Voriconazole ↓C_{max} 61% Voriconazole AUC_τ ↓77% Compared to efavirenz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUC_t↑17% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 23% Voriconazole AUCτ ↓ 7%	Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is contraindicated (see Section Contraindications). Voriconazole may be co-administered with efavirenz if the voriconazole maintenance dose is increased to 400 mg BID and the efavirenz dose is decreased to 300 mg QD. When voriconazole treatment is stopped, the initial dose of efavirenz should be restored.
Ergot alkaloids (e.g., ergotamine and dihydroergotamine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.	Contraindicated (see Section Contraindications).
Rifabutin *[potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with voriconazole 350 mg BID)* 300 mg QD (co-administered with voriconazole 400 mg BID)*	 Voriconazole C_{max} ↓69% Voriconazole AUC_τ ↓78% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓4% Voriconazole AUCt ↓32% Rifabutin C_{max} ↑195% Rifabutin AUC_τ ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑104% Voriconazole AUC_t ↑87%	Contraindicated (see Section Contraindications).
Lurasidone [CYP3A4 substrate]	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of lurasidone.	Contraindicated (see Section Contraindications).
Rifampicin (600 mg QD) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓93% Voriconazole AUC_t ↓96%	Contraindicated (see Section Contraindications).
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]* High dose (400 mg BID) Low dose (100 mg BID)*	 Ritonavir C_{max} and AUC_t ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUC_t ↓82% Ritonavir C_{max} ↓25% Ritonavir AUC_t ↓13% Voriconazole C_{max} ↓24% Voriconazole AUC_t ↓39%	Co-administration of voriconazole and high doses of ritonavir (400 mg and higher BID) is contraindicated. Co-administration of voriconazole and low dose ritonavir (100 mg BID) should be avoided, unless an assessment of the benefit/ risk to the patient justifies the use of voriconazole.
St. John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg TID (co-administered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole $AUC_{0-\infty}$ ↓59%	Contraindicated
Naloxegol *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of naloxegol.	Contraindicated (see Section Contraindications).
Fluconazole (200 mg QD) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	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 eliminate this effect have not been established. Monitoring for voriconazole-associated adverse events is recommended if voriconazole is used sequentially after fluconazole.
Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with voriconazole 400 mg BID)*	 Voriconazole C_{max} ↓49% Voriconazole AUC_t ↓69% Phenytoin C_{max} ↑67% Phenytoin AUC_t ↑81% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑34% Voriconazole AUC_t ↑39%	Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended. Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID (100 mg to 200 mg oral BID in patients less than 40 kg)
Letermovir *[CYP2C9 and CYP2C19 inducer]*	Voriconazole C_{max} ↓ 39% Voriconazole AUC_{0-12} ↓ 44% Voriconazole C_{12} ↓ 51%	If concomitant administration of voriconazole with letermovir cannot be avoided, monitor for loss of voriconazole effectiveness.
Glasdegib [CYP3A4 substrate]	Although not studied, voriconazole is likely to increase the plasma concentrations of glasdegib and increase risk of QTc prolongation.	If concomitant use cannot be avoided, frequent ECG monitoring is recommended.
Tyrosine kinase inhibitors (e.g., axitinib, bosutinib, cabozantinib ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) [CYP3A4 substrates]	Although not studied, voriconazole may increase plasma concentrations of tyrosine kinase inhibitors metabolised by CYP3A4.	If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor is recommended.
Anticoagulants Warfarin (30 mg single dose, co-administered with 300 mg BID voriconazole) *[CYP2C9 substrate]* Other oral coumarins (e.g., phenprocoumon, acenocoumarol) *[CYP2C9 and CYP3A4 substrates]*	 Maximum increase in prothrombin time was approximately 2-fold. Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.	Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.
Ivacaftor *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of ivacaftor with risk of increased adverse effects.	Dose reduction of ivacaftor is recommended.
Eszopiclone [CYP3A4 substrate	Although not studied, voriconazole is likely to increase the plasma concentrations and sedative effect of eszopiclone.	Dose reduction of eszopiclone is recommended.
Benzodiazepines [CYP3A4 substrates] Midazolam (0.05 mg/kg IV single dose) Midazolam (7.5 mg oral single dose) Other benzodiazepines (e.g., triazolam, alprazolam)	 In an independent published study, Midazolam $AUC_{0-\infty}$ ↑ 3.6-fold In an independent published study, Midazolam C_{max} ↑ 3.8-fold Midazolam $AUC_{0-\infty}$↑ 10.3-fold Although not studied, voriconazole is likely to increase the plasma concentrations of other benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	Dose reduction of benzodiazepines should be considered.
Tolvaptan *[CYP3A substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of tolvaptan.	Contraindicated (see Section Contraindications).
Venetoclax [CYP3A substrate]	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of venetoclax.	Concomitant administration of voriconazole is contraindicated at initiation and during venetoclax dose titration phase (see Section Contraindications). Dose reduction of venetoclax is required as instructed in venetoclax prescribing information during steady daily dosing; close monitoring for signs of toxicity is recommended.
Immunosuppressants *[CYP3A4 substrates]* Everolimus [also P-gp substrate] Sirolimus (2 mg single dose) Ciclosporin (In stable renal transplant recipients receiving chronic ciclosporin therapy)	 Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus. In an independent published study Sirolimus Cmax 6.6-fold Sirolimus $AUC_{0-\infty}$ ↑11-fold Ciclosporin C_{max} ↑13% Ciclosporin AUC_t ↑70%	Co-administration of voriconazole and everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see Section warnings and precautions for use). Co-administration of voriconazole and sirolimus is **contraindicated** 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 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 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 $AUC_{0-\infty}$ ↑3.6-fold	Dose reduction in oxycodone and other long-acting opiates metabolized by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse events may be necessary.
Methadone (32-100 mg QD) *[CYP3A4 substrate]*	R-methadone (active) C_{max} ↑31% R-methadone (active) AUC_τ ↑47% S-methadone C_{max} ↑65% S-methadone AUC_τ ↑103%	Frequent monitoring for adverse events 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 $AUC_{0-\infty}$ ↑100% Diclofenac C_{max} ↑114% Diclofenac $AUC_{0-\infty}$ ↑78%	Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.
Omeprazole (40 mg QD)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	Omeprazole C_{max} 116% Omeprazole AUC^t 280% Voriconazole C_{max} 15% Voriconazole AUC_t 41% Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicinal products.	No dose adjustment of voriconazole is recommended. 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 AUC_τ ↑61% Norethisterone C_{max} ↑15% Norethisterone AUC_τ ↑53% Voriconazole C_{max} ↑14% Voriconazole AUC_τ ↑46%	Monitoring for adverse events related to oral contraceptives, in addition to those for voriconazole, is recommended.
Short Acting Opiates *[CYP3A4 substrates]* Alfentanil (20 µg/kg single dose, with concomitant naloxone) Fentanyl (5 mg/kg single dose)	 In an independent published study, Alfentanil $AUC_{0-\infty}$ ↑6-fold In an independent published study, Fentanyl $AUC_{0-\infty}$ ↑1.34-fold	Dose reduction of alfentanil, fentanyl and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse events is recommended.
Statins (e.g., lovastatin) *[CYP3A4 substrates]*	Although not studied voriconazole is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis.	If concomitant administration of voriconazole with statins metabolised by CYP3A4 cannot be avoided, dose reduction of the statin should be considered.
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)* *[CYP3A4 substrates and inhibitors]*	Not studied clinically. *In vitro* studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	Careful monitoring for any occurrence of drug toxicity and/ or lack of efficacy, 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 drug toxicity and/ or lack of efficacy, and dose adjustment may be needed.
Tretinoin [CYP3A4 substrate]	Although not studied, voriconazole may increase tretinoin concentrations and increase risk of adverse reactions (pseudotumor cerebri, hypercalcaemia).	Dose adjustment of tretinoin is recommended during treatment with voriconazole and after its discontinuation.
Cimetidine (400 mg BID) *[non-specific CYP450 inhibitor and increases gastric pH]*	Voriconazole C_{max} ↑18% Voriconazole AUC_τ ↑23%	No dose adjustment.
Digoxin (0.25 mg QD) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUC_τ ↔	No dose adjustment.
Indinavir (800 mg TID) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUC_τ ↔ Voriconazole C_{max} ↔ Voriconazole AUC_τ ↔	No dose adjustment.
Macrolide antibiotics Erythromycin (1 g BID) *[CYP3A4 inhibitor]* Azithromycin (500 mg QD)	Voriconazole C_{max} and AUC_τ ↔ Voriconazole C_{max} and AUC_τ ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment.
Mycophenolic Acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_τ ↔	No dose adjustment.
Corticosteroids Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	Prednisolone C_{max} ↑11% Prednisolone $AUC_{0-\infty}$ 34%	No dose adjustment. Patients on long-term treatment with voriconazole and corticosteroids (including inhaled corticosteroids e.g., budesonide) should be carefully monitored for adrenal cortex dysfunction both during treatment and when voriconazole is discontinued (see Section 4.4).
Ranitidine (150 mg BID) *[increases gastric pH]*	Voriconazole C_{max} and AUC_τ ↔	No dose adjustment.

Calcium channel blockers (CYP3A4 substrates): Although not studied clinically, voriconazole has been shown to inhibit felodipine metabolism in vitro. Therefore, voriconazole is likely to increase the plasma concentrations of calcium channel blockers that are metabolised by CYP3A4. Frequent monitoring of adverse events and toxicity related to calcium channel blockers are recommended during co-administration. Dose adjustment of the calcium channel blocker may be needed.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Caution should be used in prescribing voriconazole to patients with hypersensitivity to other azoles.

Infusion-related reactions: Infusion-related reactions, predominantly flushing and nausea have been observed during administration of the intravenous formulation of voriconazole. Depending on the severity of symptoms, consideration should be given to stopping treatment.

Cardiac adverse events: Some azoles, including voriconazole, have been associated with QT interval prolongation on the electrocardiogram. During clinical development and post-marketing surveillance, 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 medications that may have been contributory. Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as:

- Congenital or acquired QT-prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant medication that is known to prolong QT interval (see Drug Interactions)

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation of and during voriconazole therapy. A study has been conducted in healthy volunteers which examined the effect on QT 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.

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 hematological 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.

Monitoring of hepatic function: Patients receiving voriconazole must be carefully monitored for hepatic toxicity. Clinical management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin) at the initiation of treatment with voriconazole and at least weekly for the first month of treatment. If treatment is continued, monitoring frequency can be reduced to monthly if there are no changes in the liver function tests.

If the liver function tests become markedly elevated, voriconazole should be discontinued, unless the medical judgment of the risk-benefit of the treatment for the patient justifies continued use.

Visual adverse events: There have been post-marketing reports of prolonged visual adverse events, including optic neuritis and papilledema. These events occurred primarily in severely ill patients who had underlying conditions and/or concomitant medications which may have caused or contributed to these events.

Renal adverse events: Acute renal failure has been observed in severely ill patients undergoing treatment with voriconazole. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function.

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

Monitoring of pancreatic function: Adults and children with risk factors for acute pancreatitis (e.g., recent chemotherapy, hematopoietic stem cell transplantation [HSCT]), should be monitored closely for development of pancreatitis during voriconazole treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.

Dermatological adverse events: During treatment with voriconazole, patients have developed 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 (see Side Effects). If a patient develops a severe cutaneous adverse reaction voriconazole should be discontinued.

In addition voriconazole has been associated with photosensitivity skin reaction. An increased risk of skin toxicity with concomitant use of methotrexate, a drug associated with ultraviolet (UV) reactivation has been observed. There is a potential for this risk to be observed with other drugs associated with UV reactivation. It is recommended that patients, including children avoid exposure to direct sunlight during voriconazole treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

Adrenal events: Reversible cases of adrenal insufficiency have been reported in patients receiving azoles, including voriconazole. Adrenal insufficiency has been reported in patients receiving azoles with or without concomitant corticosteroids. In patients receiving azoles without corticosteroids, adrenal insufficiency is related to direct inhibition of steroidogenesis by azoles. In patients taking corticosteroids, voriconazole associated CYP3A4 inhibition of their metabolism may lead to corticosteroid excess and adrenal suppression (see drug interactions). Cushing's syndrome with and without subsequent adrenal insufficiency has also been reported in patients receiving voriconazole concomitantly with corticosteroids.

Patients on long-term treatment with voriconazole and corticosteroids (including inhaled corticosteroids e.g., budesonide) should be carefully monitored for adrenal cortex dysfunction both during treatment and when voriconazole is discontinued. 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
The following severe adverse events have been reported in relation with long-term voriconazole 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, multidisciplinary advice should be sought and the patient should be referred to a dermatologist.

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and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, 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, voriconazole discontinuation should be considered.

Non-infectious periostitis: Periostitis has been reported in transplant patients during long-term voriconazole therapy. If a patient develops skeletal pain and radiologic findings compatible with periostitis, voriconazole should be discontinued.

Pediatric use: Safety and effectiveness in pediatric subjects below the age of 2 years has not been established. Voriconazole is indicated for pediatric patients aged two years or older. A higher frequency of liver enzyme elevations was observed in the pediatric population. Hepatic function should be monitored in both children and adults. Oral bioavailability may be limited in pediatric patients 2 to 12 years with malabsorption and very low body weight for age. In that case, intravenous voriconazole administration is recommended.

The frequency of phototoxicity reactions is higher in the pediatric 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.

Everolimus (CYP3A4 substrate, P-gp substrate): Co-administration 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.

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Co-administration of oral voriconazole and oral fluconazole resulted in a significant increase in C_{max} and AUC, of voriconazole in healthy subjects. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

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 that of efavirenz should be decreased to 300 mg every 24 hours.

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 unless the benefit outweighs the risk.

Ritonavir (potent CYP450 inducer, CYP3A4 inhibitor and substrate): Co-administration of voriconazole and low dose ritonavir (100 mg twice daily) should be avoided unless an assessment of the benefit/risk justifies the use of voriconazole.

Methadone (CYP3A4 substrate): Frequent monitoring for adverse events and toxicity related to methadone, including QT prolongation, is recommended when co-administered with voriconazole since methadone levels increased following co-administration of voriconazole. Dose reduction of methadone may be needed.

Short-acting opiates (CYP3A4 substrate): Reduction in the dose of alfentanil, fentanyl and other short-acting opiates similar in structure to alfentanil and metabolized by CYP3A4 (e.g., sufentanil) should be considered when co-administered with voriconazole (see Drug Interactions). 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 by 1.4-fold, frequent monitoring for opiate-associated adverse events (including a longer respiratory monitoring period) may be necessary.

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

Visual disturbances: The effect of voriconazole on visual function is not known if treatment continues beyond 28 days. If treatment continues beyond 28 days, visual function including visual acuity, visual field and colour perception should be monitored.

Cyclosporine and tacrolimus (CYP3A4 substrates): Clinically significant drug interactions with voriconazole may occur in patients who are receiving treatment with cyclosporine or tacrolimus.

Glasdegib (CYP3A4 substrate): Co-administration of voriconazole is expected to increase glasdegib plasma concentrations and increase the risk of QTc prolongation (see drug interactions). If concomitant use cannot be avoided, frequent ECG monitoring is recommended.

PREGNANCY AND LACTATION

voriconazole can cause foetal harm when administered to pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus. voriconazole must not be used during pregnancy unless the benefits to the mother clearly out weight the potential risk to the foetus. Women of child bearing potential should use effective contraception during treatment.

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

Effects on ability to drive and use machines

Voriconazole 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. Patients should not drive at night while taking voriconazole.

SIDE EFFECTS

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

In addition, the safety of voriconazole was investigated in 279 patients (including 270 adults) who were treated with voriconazole in prophylaxis studies. The adverse event profile in these prophylaxis studies was similar to the established safety profile from 2,000 subjects in voriconazole clinical trials.

The table below includes all causality adverse reactions in 1,873 adults from pooled therapeutic (1,603) and prophylaxis (270) studies. The most commonly reported adverse events were visual impairment, liver function test abnormal, pyrexia, rash, vomiting, nausea, diarrhea, headache, peripheral edema 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 analyzed by age, race, or gender.

Adults in combined therapeutic and prophylaxis studies: ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1\,000	Frequency Not Known (Cannot be Estimated from the Available Data)
Infections and infestations		sinusitis	pseudomembranous colitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)					squamous cell carcinoma*,g
Blood and lymphatic system disorders		agranulocytosis[a], pancytopenia, thrombocytopenia[b], leukopenia, anaemia	bone marrow failure, lymphadenopathy, eosinophilia	disseminated intravascular coagulation	
Immune system disorders			hypersensitivity	anaphylactoid reaction	
Endocrine disorders			adrenal insufficiency, hypothyroidism	hyperthyroidism	
Metabolism and nutrition disorders	oedema peripheral	hypoglycaemia, hypokalaemia, hyponatraemia*			
Psychiatric disorders		depression, hallucination, anxiety, insomnia, agitation, confusional state			
Nervous system disorders	headache	syncope, tremor, hypertonia[e], paraesthesia, somnolence, dizziness	brain oedema, encephalopathy[c], extrapyramidal disorder[d], neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia	Convulsion, hepatic encephalopathy, Guillain-Barré syndrome, nystagmus	
Eye disorders	visual impairment[h]	retinal haemorrhage	optic nerve disorder[f], papilloedema[g], oculogyric crisis, diplopia, scleritis, blepharitis	optic atrophy, corneal opacity	
Ear and labyrinth disorders			hypoacusis, vertigo, tinnitus		
Cardiac disorders		arrhythmia supraventricular, tachycardia, bradycardia	ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged,	*torsades de pointes*, atrioventricular block complete, bundle branch block, nodal rhythm supraventricular tachycardia	
Vascular disorders		hypotension, phlebitis	thrombophlebitis, lymphangitis		
Respiratory, thoracic and mediastinal disorders		acute respiratory distress syndrome, pulmonary oedema			
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea	cheilitis, dyspepsia, constipation, gingivitis	peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis		
Hepatobiliary disorders	liver function test abnormal	jaundice, jaundice cholestatic, hepatitisi	hepatic failure, hepatomegaly, cholecystitis, cholelithiasis		
Skin and subcutaneous tissue disorders	rash	dermatitis exfoliative, alopecia, rash maculo-papular, pruritus	Stevens-Johnson syndromeg, photosensitivity reaction, purpura, urticaria, eczema	toxic epidermal necrolysisg, angioedema, pseudoporphyria, erythema multiforme, psoriasis, drug eruption	cutaneous lupus erythematosus*, drug reaction with eosinophilia and systemic symptoms*,g
Musculoskeletal and connective tissue disorders		back pain	arthritis		periostitis
Renal and urinary disorders		renal failure acute, haematuria	renal tubular necrosis, proteinuria, nephritis		
General disorders and administration site conditions	pyrexia	chest pain, face oedemaj, asthenia, chills	infusion site reaction, influenza like illness		
Investigations		blood creatinine increased	blood urea increased, blood cholesterol increased		

* ADR identified post-marketing
[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.
[g] See Section Special warnings and precautions for use.
[h] See "Visual impairments"
[i] Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.
[j] Includes periorbital oedema, lip oedema, and oedema mouth.

Visual Impairments
In clinical trials, visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, color blindness, cyanopsia, eye disorder, halo vision, night blindness, oscillopsia, photopsia, scintillating scotoma, visual acuity reduced, visual brightness, visual field defect, vitreous floaters, and xanthopsia) with voriconazole were very common.

These visual impairments were transient and fully reversible, with the majority spontaneously resolving within 60 minutes. There was evidence of attenuation with repeated doses of voriconazole. The visual impairments were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairments may be associated with higher plasma levels and/or doses.

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

The mechanism of action is unknown, although the site of action is most likely to be within the retina.

In a study in healthy volunteers investigating the impact of voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude. The ERG measures electrical currents in the retina. The ERG changes did not progress over 29 days of administration and were fully reversible on withdrawal of voriconazole.

The long-term effect of voriconazole (median 169 days; range 5-353 days) on visual function was evaluated in subjects with paracoccidioidomycosis. Voriconazole had no clinically relevant effect on visual function as assessed by testing of visual acuity, visual fields, color vision and contrast sensitivity. There were no signs of retinal toxicity. 17/35 voriconazole subjects experienced visual adverse events. These events did not lead to discontinuation, were generally mild, occurred during the first week of therapy and resolved during continued voriconazole therapy.

Dermatological Reactions
Dermatological reactions were very common in patients treated with voriconazole in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medications. The majority of rashes were of mild to moderate severity. Patients have developed severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (uncommon), toxic epidermal necrolysis (rare), drug reaction with eosinophilia and systemic symptoms (DRESS) which was reported post-marketing (not known), and erythema multiforme (rare) during treatment with voriconazole.

If patients develop a rash they should be monitored closely and voriconazole discontinued if lesions progress. Patients receiving long-term voriconazole therapy have developed photosensitive skin reactions.

Dermatological adverse reactions potentially related to phototoxicity (pseudoporphyria, cheilitis, and cutaneous lupus erythematosus) are also reported with voriconazole. Sun avoidance and photoprotection are recommended for all patients. If phototoxicity occurs, voriconazole discontinuation and dermatological evaluation should be considered.

Liver Function Tests
The overall incidence of transaminase increases >3 x ULN (not necessarily comprising an adverse event) in the voriconazole clinical program was 18.0% (319/1,768) in adults and 25.8% (73/283) in pediatric subjects who received voriconazole for pooled therapeutic and prophylaxis use. Liver function test abnormalities may be associated with higher plasma levels and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

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

Pediatric Use
The safety of voriconazole was investigated in 288 pediatric patients aged 2 to <12 years (169) and 12 to <18 years (119) who received voriconazole for prophylaxis (183) and therapeutic use (105). The adverse event profile in these 288 pediatric patients was similar to that in adults. A higher frequency of liver enzyme elevations reported as adverse events (14.2% transaminases increased in pediatrics compared to 5.3% in adults) was observed in pediatric patients as compared to adults. The safety of voriconazole was investigated in additional pediatric patients aged 2 to <12 years who were observed in compassionate use programs (158 pediatric patients). The adverse event profile in these pediatric patients was similar to that observed in adults.

Post-marketing data suggest there might be a higher occurrence of skin reactions in the pediatric population compared to adults. In the 22 patients less than 2 years old who received voriconazole in a compassionate use programme, the following adverse events (for which a relationship to voriconazole could not be excluded) were reported: photosensitivity reaction (1), arrhythmia (1), pancreatitis (1), blood bilirubin increased (1), hepatic enzymes increased (1), rash (1) and papilloedema (1).

There have been post-marketing reports of pancreatitis in pediatric patients.

Altered Taste Perception
In the combined data from three bioequivalence studies using the powder for oral suspension formulation, treatment related taste perversion was recorded in 12 (14%) of subjects.

Infusion-related Reactions
During infusion of the intravenous formulation of voriconazole in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnea, faintness, nausea, pruritus and rash have occurred. Symptoms appeared immediately upon initiating the infusion.

OVERDOSE
In clinical trials there were three cases of accidental overdose

All occurred in pediatric patients who received up to five times recommended intravenous dose the voriconazole.. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is hemodialysed with clearance of 121 mL/Kg. The intravenous vehicle, SBECD, is hemodialysed with clearance of 55 mL/ min. In an overdose, hemodialysis may assist in the removal of voriconazole and SBECD from the body.

DOSAGE AND ADMINISTRATION
Voriconazole requires reconstitution of 10 mg/mL and subsequent dilution to 0.5 - 5mg/mL prior to administration as an infusion at a maximum rate of 3 mg/kg per hour over 1-3 hours.
Not for IV bolus injection
Electrolyte disturbance such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of Voriconazole therapy.

Dose for adults: Therapy must be initiated with specified loading dose regimen of intravenous Voriconazole to achieve to plasma concentrations on Day 1 that are close to steady state.

Voriconazole 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).

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

Voriconazole 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 voriconazole.

Voriconazole must not be infused into the same line or cannula concomitantly with other intravenous products.

	Intravenous
Loading dose (first 24hrs)	6 mg/kg every 12hrs (for the first 24hrs)
Maintenance dose (after first 24hrs)	4 mg/kg twice daily

Dose adjustments:
If patients are unable to tolerate treatment, reduce the intravenous maintenance dose to 3 mg/kg every 12 hours.

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

Duration of therapy should be based on the Severity of the patient's underlying

Disease recovery from immunosuppression, and clinical response.

Elderly: No dose adjustment is necessary for elderly for patients.

Children: Safely and effectiveness is pediatric patients below the age of 2 years has not been established therefore Voriconazole is not recommended for children less than 2 years of age.

The recommended maintenance dosing regimen in pediatric patients 2 to <12 years is as follows.

Children aged 2 to <12 years:

	Intravenous
Maintenance dose	7 mg/kg twice daily

The pharmacokinetics and tolerability of higher doses have not been characterized in pediatric populations.

If pediatric patients are unable to tolerate an intravenous dose of 7 mg/kg twice daily, a dose reduction from 7 mg/kg to 4 mg/kg twice daily may be considered based on the population pharmacokinetic analysis and previous clinical experience. This provides equivalent exposure to 3 mg/kg twice daily in adults

Use in pediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied.

Adolescents 12to 16 years age: should be given the same dose as adults.

Hepatic impairment: No dose adjustment is necessary in patients with acute hepatic injury manifested by elevated liver function tests (ALAT, ASAT) but continued monitoring of liver function tests for further 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 class A and B).

Voriconazole has not been studied in patients with severe hepatic cirrhosis (Child-Pugh class C) or in patients with chronic hepatitis B or chronic hepatitis C disease. Voriconazole has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and should only be used in patients with severe hepatic insufficiency if the benefit outweighs the potential risk. Patients with hepatic insufficiency must be carefully monitored for drug toxicity.

Renal Impairment:
In patients with moderate or severe renal insufficiency (creatinine clearance <50 mL/min), Accumulation of the intravenous vehicle, SBECD occurs. Oral Voriconazole should not be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of intravenous Voriconazole. Serum creatinine levels should be closely monitored in these patients and if increases occur, consideration should be given to changing to oral Voriconazole therapy.

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD is hemodialyzed with clearance of 55 mL/min A 4 hour hemodialysis session does not remove a sufficient amount of Voriconazole to warrant dose adjustment.

Intravenous administration
Reconstitution: The powder is reconstituted with 19 mL of Water for Injection to obtain an extractable volume of 20 mL of clear concentrate containing 10 mg/mL of Voriconazole. It is recommended that a standard 20 mL (none automated) syringe be used to ensure that the exact amount (19.0 mL) of water for injection is dispensed, Discard the vial if a vacuum does not pull the diluent into the vial. Shake the vial until all the powder is dissolved.

Dilution: The required volume of the 10 mg/mL Voriconazole concentrate should be further diluted as follows:

1) Calculate the volume of 10 mg/mL Voriconazole concentrate required based on the patient's weight (as per the table given below.)
2) In order to allow the required volume of Voriconazole to be added, withdraw and discard at least an equal volume of diluent from the infusion bag or bottle to be used. The volume of diluent remaining in the bag or bottle should be such that when the 10 mg/mL Voriconazole concentrate is added the final concentration is not less then 0.5 mg/mL or greater than 5 mg/mL.
3) Using a suitable size syringe and aseptic technique, withdraw the required volume of Voriconazole concentrate from the appropriate number of vials and add to the infusion bag or bottle. Discard partially used vials.

The final Voriconazole solution must be infused over 1-3 hours at a maximum rate of 3 mg/kg per hour.

Required volumes of 10 mg/mL Voriconazole concentrate:

Body weight (kg)	Volume for Voriconazole 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)	7 mg/kg dose (number of vials)
10	-	4 mL (1)	-	7 mL (1)
15	-	6 mL(1)	-	10.5 mL (1)
20	-	8 mL (1)	-	14.0 mL (1)
25	-	10 mL (1)	-	17.5 mL (1)
30	9.0 mL (1)	12mL (1)	18 mL (1)	21.0 mL (2)
35	10.5 mL (1)	14 mL(1)	21 mL (2)	24.5 mL (2)
40	12.0mL (1)	16 mL (1)	24 mL (2)	28.0 mL (2)
45	13.5 mL (1)	18 mL (1)	27 mL (2)	31.5 mL (2)
50	15.0 mL (1)	20 mL (1)	30 mL (2)	35.0 mL (2)
55	16.0 mL (1)	22 mL (2)	33 mL (2)	-
60	18.0 mL (1)	24 mL (2)	36 mL (2)	-
65	19.5 mL (1)	26 mL (2)	39 mL (2)	-
70	21.0 mL (2)	28 mL (2)	42 mL (3)	-
75	22.5 mL (2)	30 mL (2)	45 mL (3)	-
80	24.0 mL (2)	32 mL (2)	48 mL (3)	-
85	25.5 mL (2)	34 mL (2)	51 mL (3)	-
90	27.0 mL (2)	36 mL (2)	54 mL (3)	-
95	28.5 mL (2)	38 mL (2)	57 mL (3)	-
100	30 mL (2)	40 mL (2)	60 mL (3)	-

Voriconazole is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, once reconstituted, 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 should not be longer than 24 hours at 2° to 8° C (36° to 46° F).

This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used.

The reconstituted solution can be diluted with 0.9% Sodium Chloride USP, Lactated Ringers USP, 5% Dextrose and Lactated Ringers USP, 5% Dextrose and 0.45% Sodium Chloride USP, 5% Dextrose USP, 5% Dextrose and 20mEq Potassium Chloride USP, 0.45% Sodium Chloride USP, 5% Dextrose and 0.9% Sodium Chloride USP.

The compatibility of Voriconazole with diluents other than those described above is unknown.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Incompatibilities Voriconazole must not be infused into the same line or cannula concomitantly with other drug infusions including parenteral nutrition, e.g. Aminofusin 10% Plus. Aminofusin 10% Plus is physically incompatible with an increase in sub visible particulate matter after 24 hours storage at 4° C.

Infusion of blood products must not occur simultaneously with Voriconazole even if the two infusions are running in separate intravenous lines (or cannulas).

Infusion of total parenteral nutrition can occur simultaneously with Voriconazole, but must be infused through a separate line.

Voriconazole must not be diluted with 4.2% Sodium Bicarbonate Infusion. The mildly alkaline nature of this diluent caused slight degradation of Voriconazole after 24 hours storage at room temperature. Although refrigerated storage is recommended following reconstitution, use of this diluent is not recommended as a precautionary measure. Compatibility with other concentration is unknown.

CLINICAL PHARMACOLOGY:
Voriconazole is a broad spectrum, triazole antifungal agent.

Mechanism of Action
The primary mode of action of Voriconazole is inhibition of fungal cytochrome P450- mediated 14 alpha-lansoterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 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. It is shown to be more selective for fungal cytochrome P 450 enzymes than for various mammalian cytochrome P 450 enzymes systems.

In vitro, Voriconazole displays broad spectrum antifungal activity with antifungal potency against candida species (including fluconazole resistant *C.Krusei* and resistant strains of *C. galbrata* 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 agents.

Clinical efficacy (with partial or complete response, see below under Clinical Experience) has been demonstrated for Aspergillus spp. including *A. flavus, A. fumigatus, A. terreus, A. niger, A. nidulans*, *Candida spp., including C. albicans, C. glabrata, C. krusei, C. parapsilosis and C. tropicalis and limited numbers of C. dubliniensis, C. inconspicua, and C. guilliermondii, Scedosporium spp., including S. apiospermum, S. prolificans and Fusarium spp.*

Other treated fungal infections (with often partial or complete response) included isolated cases of *Alternaria spp., Blastomyces dermatitidis, Blastoschizomyces capitatus, Cladosporium spp. Coccidioides immitis, Conidiobouls coronatus, Cryptococcus neoformans, Exserohilum rostratum, Exophiala spinifera, Fonsecaea pedrosoi, Madurella mycetomatis, Paecilomyces lilacinus, Penicillium spp.* including *P.Marneffei, Phialophora richardsiae, Scopulariopsis brevicaulis, Trichosporon spp.* inculding *T.beigelii* infections.

In vitro activity against clinical isolates have be observed for *Acremonium spp., Alternaria spp., Bipolaris spp., Cladophialophora spp., Histoplasma capsulatum*, with most strains being inhibited by interactions of Voriconazole in the range of 0.05 to 2 µg/mL.

In vitro activity against the following pathogens has been shown, but the clinical significance is unknown: Curvularia spp. and Sporothrix app.

PHARMACOKINETICS:
The pharmacokinetics of Voriconazole is non linear due to saturation of its metabolism. The inter individual variability of Voriconazole pharmacokinetics is high. Greater than proportion increase in exposure is observed with increasing dose.

When the recommended intravenous or oral loading dose regimens are administered to healthy subjects, peak plasma concentration close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice daily multiple dosing with steady state through plasma concentration with Voriconazole being achieved by Day 6 in the majority of subjects. Steady state through plasma concentrations with Voriconazole are achieved after approximately 5days of oral or intravenous dosing without a loading dose regimen. However, when an intravenous loading dose regimen is used, steady state through plasma concentrations are achieved within one day.

The volume of distribution of steady state of Voriconazole is estimated to be 4.6 L/kg suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58%.

In vitro studies showed that Voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 AND CYP3A4. In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of Voriconazole. This enzyme exhibits polymorphism. For example 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and blacks the prevalence of poor metabolizers are 3-5%.

Studies conducted in Caucasian and Japanese healthy subject have shown that poor metabolizers have, on average, 4-fold higher Voriconazole exposure(AUC) than their homozygous extensive metabolizer counter parts. Subjects who are heterozygous extensive metabolizers have on average 2-fold higher voriconazole exposures than their homozygous extensive metabolizer counter parts.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma.

Since this metabolite has minimal antifungal activity it does not contribute to the overall efficacy of voriconazole.

Voriconazole is eliminated via hepatic metabolism with less 2% of the dose excreted unchanged in the urine. After administration of single radiolabelled dose of either oral or IV voriconazole preceded by multiple oral or IV dosing approximately 80% to 83% of the radioactivity is recovered in the urine. The majority (>94%) of the total radioactivity excreted in the first 96 hours after both oral and intravenous dosing. The terminal half life of voriconazole is approximately 6hours at 200 mg (orally).

As a result of nonlinear pharmacokinetics, the terminal half life of voriconazole is dose dependent and therefore not useful in the prediction of the accumulation or elimination of voriconazole.

In oral multiple dose study, the mean C_{max} and AUC in healthy elderly males (≥65years) were 61% and 86% higher, respectively than in young in males (18-45 years).

No significant differences in the mean C_{max} and AUC were observed between healthy elderly females (≥65years) and healthy young females (18-45) years. The safety profile of Voriconazole in young and elderly subjects was similar.

After a single oral dose (200 mg) of Voriconazole in patients with mild (Child-Pugh class A) and patients with moderate (Child–Pugh class b) hepatic insufficiency, the mean systemic exposure (AUC) was 3.2 fold higher than controls with normal hepatic function. There was no difference in mean peak plasma concentration (C_{max}) between the groups, in oral dose study ,AUC was similar in subjects with moderate hepatic impairment (Child-Pugh Class B) given a lower maintenance dose of 100mg twice daily compared to subject with normal hepatic function given the standard 200 mg twice daily maintenance dose.

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 Class A and B) receiving Voriconazole. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh class C).

In a single oral dose (200 mg) study subjects with normal renal function and mild to severe renal impairment, systemic exposure (AUC) and peak plasma concentration (C_{max}) of voriconazole were not significantly affected by renal impairment.

However, in patients with moderate renal dysfunction (creatinine clearance 30-50 mL/Min) accumulation of the intravenous vehicle, betadex sulfobutyl ether sodium (SBECD) occurs. The mean systemic exposure(AUC) and peak plasma concentration (C_{max}) of SBECD were increased by 4 fold and almost 50% respectively in the moderately impaired group compared to the normal control group.

A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with clearance of 121 mL/Min. The intravenous vehicle SBECD is haemodialysed with a clearance of 55 mL/Min.

HOW SUPPLIED

Each vial contains Voriconazole Ph. Eur. 200 mg.

A white to off-white lyophilized cake filled in 25 mL clear,Type I molded glass and sealed with grey bromo butyl lyophilisation rubber stopper and white colored flip off seal.

List of excipients
Betadex Sulfobutyl ether sodium, Water for injection, Nitrogen

PACKAGING INFORMATION:

Voriconazole is available in sterile single-use vials individually packed in a carton.

STORAGE: Store below 30°C and protect from light.

Product Owner:
HETERO LABS LIMITED
7-2-A 2, Hetero Corporate,
Industrial Estates, Sanath nagar,
Hyderabad - 500 018, INDIA.

Manufactured by:
ASPIRO PHARMA LIMITED
Sy. No. 321, Biotech Park, Phase-III,
Karkapatla Village, Markook Mandal,
Siddipet District - 502281, Telangana,
INDIA.

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