# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Voriconazole Hospira 200 mg powder for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg of voriconazole.

After reconstitution each ml contains 10 mg of voriconazole. Once reconstituted further dilution is required before administration.

Excipient with known effect: each vial contains 217.6 mg sodium

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for infusion (powder for infusion)

White to off-white lyophilised cake.

pH of the reconstituted solution is 4.0 to 7.0.

Osmolality: 500± 50 mOsm/kg

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Voriconazole is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

- Treatment of invasive aspergillosis.
- Treatment of candidaemia in non-neutropenic patients
- Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*).
- Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

Voriconazole should be administered primarily to patients with progressive, possibly life-threatening infections.

### 4.2 Posology and method of administration

Posology
Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.4).

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

Treatment
*Adults*
Voriconazole Hospira 200 mg powder for solution for infusion is for intravenous use only. Oral dosage forms of voriconazole are available from other manufacturers.

Therapy must be initiated with the specified loading dose regimen of either intravenous or oral voriconazole to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96 %; see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

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

| | **Intravenous** | **Oral*** | |
|---|---|---|---|
| | | *Patients 40 kg and above*** | *Patients less than 40 kg*** |
| **Loading dose regimen (first 24 hours)** | 6 mg/kg every 12 hours | 400 mg every 12 hours | 200 mg every 12 hours |
| **Maintenance dose (after first 24 hours)** | 4 mg/kg twice daily | 200 mg twice daily | 100 mg twice daily |

*Oral dosage forms of voriconazole are available from other manufacturers
**This also applies to patients aged 15 years and older.

*Duration of treatment*
Treatment duration should be as short as possible depending on the patient's clinical and mycological response. Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance (see sections 4.4 and 5.1).

*Dosage adjustment (Adults)*
If patient is unable to tolerate intravenous treatment at 4 mg/kg twice daily, reduce the dose to 3 mg/kg twice daily.

If patient response to treatment is inadequate, the maintenance dose may be increased to 300 mg twice daily for oral administration. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily.

If patient is unable to tolerate treatment at a higher dose reduce the oral dose by 50 mg steps to the 200 mg twice daily (or 100 mg twice daily for patients less than 40 kg) maintenance dose.

*Children (2 to <12 years) and young adolescents with low body weight (12 to 14 years and <50 kg)*
Voriconazole should be dosed as children as these young adolescents may metabolize voriconazole more similarly to children than to adults.

The recommended dosing regimen is as follows:

| | **Intravenous** | **Oral*** |
|---|---|---|
| **Loading Dose Regimen (first 24 hours)** | 9 mg/kg every 12 hours | Not recommended |
| **Maintenance Dose (after first 24 hours)** | 8 mg/kg twice daily | 9 mg/kg twice daily (a maximum dose of 350 mg twice daily) |

*Oral dosage forms of voriconazole are available from other manufacturers
Note: Based on a population pharmacokinetic analysis in 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescents aged 12 to <17 years.

It is recommended to initiate the therapy with intravenous regimen, and oral regimen should be considered only after there is a significant clinical improvement. It should be noted that an 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.

*All other adolescents (12 to 14 years and ≥50 kg; 15 to 17 years regardless of body weight)*
Voriconazole should be dosed as adults.

*Dosage adjustment (Children [2 to <12 years] and young adolescents with low body weight [12 to 14 years and <50 kg])*
If patient response to treatment is inadequate, the dose may be increased by 1 mg/kg steps. If patients are unable to tolerate treatment, reduce the dose by 1 mg/kg steps.

Use in paediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied (see sections 4.8 and 5.2).

*Dosage adjustment*
In the case of treatment-related adverse events, discontinuation of voriconazole and use of alternative antifungal agents must be considered (see section 4.4 and 4.8)

*Dosage adjustments in case of co-administration*
Rifabutin or phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg intravenously twice daily, see sections 4.4 and 4.5.

Efavirenz may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 400 mg every 12 hours and the efavirenz dose is reduced by 50%, i.e. to 300 mg once daily. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored (see sections 4.4 and 4.5).

*Elderly patients*
No dose adjustment is necessary for elderly patients (see section 5.2).

*Patients with renal impairment*
In patients with moderate to severe renal dysfunction (creatinine clearance < 50 ml/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the risk benefit 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 (see section 5.2).

Voriconazole is haemodialysed with a clearance of 121 ml/min. A 4 hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

The intravenous vehicle, SBECD, is haemodialysed with a clearance of 55 ml/min.

*Patients with hepatic impairment*
It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole (see section 5.2).

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

There is limited data on the safety of voriconazole in patients with abnormal liver function tests (aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP), or total bilirubin >5 times the upper limit of normal).

Voriconazole has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and must only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk. Patients with hepatic impairment must be carefully monitored for drug toxicity (see section 4.8).

*Paediatric population*

The safety and efficacy of voriconazole in children below 2 years has not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

Method of administration

Voriconazole Hospira requires reconstitution and dilution (see section 6.6) prior to administration as an intravenous infusion. Not for bolus injection.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine 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 with rifampicin, carbamazepine and phenobarbital since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see section 4.5).

Co-administration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at theses doses. Voriconazole also significantly increases efavirenz plasma concentrations (see section 4.5, for lower doses see section 4.4).

Co-administration with high dose ritonavir (400 mg and above twice daily) because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose. (see section 4.5, for lower doses see section 4.4).

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

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

Co-administration with St John's Wort (see section 4.5).

## 4.4 Special warnings and precautions for use

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

Duration of treatment
The duration of treatment with the intravenous formulation should be no longer than 6 months (see section 5.3).

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).

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 (see section 4.8).

Hepatic toxicity
In clinical trials, there have been uncommon 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 voriconazole 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 voriconazole and at least weekly for the first month of treatment. Treatment 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, Voriconazole Hospira should be discontinued, unless the medical judgment of the risk-benefit of the treatment for the patient justifies continued use.

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

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 voriconazole. 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 voriconazole treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.

Dermatological adverse reactions
Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with voriconazole. If patients develop a rash they should be monitored closely and Voriconazole Hospira discontinued if lesions progress.

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

Long-term treatment
Long term exposure greater than 180 days (6 months) requires careful assessment of the benefit-risk balance and physicians should therefore consider the need to limit exposure to voriconazole (see sections 4.2 and 5.1). The following severe adverse events have been reported in relation with long-term voriconazole treatment:

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 and the patient should be referred to a dermatologist. Voriconazole Hospira discontinuation and use of alternative antifungal agents should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever Voriconazole Hospira is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. Voriconazole Hospira should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified.

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 Voriconazole Hospira discontinuation should be considered after multidisciplinary advice.

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. 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.

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.

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 (see section 4.5).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)
When voriconazole is coadministered 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 (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 unless the benefit outweighs the risk (see section 4.5).

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 to the patient justifies the use of voriconazole (see sections 4.5 and 4.3).

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 (see section 4.5).

Methadone (CYP3A4 substrate)
Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended when co-administered with voriconazole since methadone levels increased following co-administration of voriconazole. Dose reduction of methadone may be needed (see section 4.5).

Short acting opiates (CYP3A4 substrate)
Reduction in the dose of alfentanil, fentanyl and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered when co-administered with voriconazole (see section 4.5). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is co-administered with voriconazole and in an independent published study, concomitant use of voriconazole with fentanyl resulted in an increase in the mean AUC $0\text{-}\infty$ 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 coadministered 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 $AUC\tau$ 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).

Sodium content
Each vial contains 217.6 mg of sodium. This should be taken into consideration for patients on a controlled sodium diet.

## 4.5 Interaction with other medicinal products and other forms of interaction

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

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

Interaction table
Interactions between voriconazole and other 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. $AUC_\tau$, $AUC_t$ and $AUC_{0\text{-}\infty}$ 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**<br>***[Mechanism of Interaction]*** | **Interaction**<br>**Geometric mean changes (%)** | **Recommendations concerning co-administration** |
|---|---|---|
| Astemizole, cisapride, pimozide, quinidine and terfenadine<br>*[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 4.3) |
| Carbamazepine and long-acting barbiturates (e.g., phenobarbital, mephobarbital)<br>*[potent CYP450 inducers]* | Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations. | **Contraindicated** (see section 4.3) |
| Efavirenz (a non-nucleoside reverse transcriptase inhibitor)<br>*[CYP450 inducer; CYP3A4 inhibitor and substrate]* | | |
| Efavirenz 400 mg QD, coadministered with voriconazole 200 mg BID* | Efavirenz $C_{max}$ ↑ 38%<br>Efavirenz AUCτ ↑ 44%<br>Voriconazole $C_{max}$ ↓ 61%<br>Voriconazole AUCτ ↓ 77% | Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is **contraindicated** (see section 4.3). |
| Efavirenz 300 mg QD, co-administered with voriconazole 400 mg BID)* | Compared to efavirenz 600 mg QD,<br>Efavirenz $C_{max}$ ↔<br>Efavirenz AUCτ ↑ 17%<br><br>Compared to voriconazole 200 mg BID,<br>Voriconazole $C_{max}$ ↑ 23%<br>Voriconazole AUCτ ↓ 7% | 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 (see section 4.2 and 4.4). |
| Ergot alkaloids (e.g., ergotamine and dihydroergotamine)<br>*[CYP3A4 substrates]* | Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism. | **Contraindicated** (see section 4.3) |
| Rifabutin<br>*[potent CYP450 inducer]* | | Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk. |
| 300 mg QD | Voriconazole $C_{max}$ ↓ 69%<br>Voriconazole AUCτ ↓ 78% | |
| 300 mg QD (co-administered with voriconazole 350 mg BID)* | Compared to voriconazole 200 mg BID,<br>Voriconazole $C_{max}$ ↓ 4%<br>Voriconazole AUCτ ↓ 32% | The maintenance dose of voriconazole may be increased to 5 mg/kg intravenously BID or from 200 mg to 350 mg orally BID (100 mg to 200 mg orally BID in patients less than 40 kg) (see section 4.2). |

| **Medicinal product**<br>***[Mechanism of Interaction]*** | **Interaction**<br>**Geometric mean changes (%)** | **Recommendations concerning co-administration** |
|---|---|---|
| 300 mg QD (co-administered with voriconazole 400 mg BID)* | Rifabutin $C_{max}$ ↑ 195%<br>Rifabutin AUCτ ↑ 331%<br>Compared to voriconazole 200 mg BID,<br>Voriconazole $C_{max}$ ↑ 104%<br>Voriconazole AUCτ ↑ 87% | Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) is recommended when rifabutin is coadministered with voriconazole. |
| Rifampicin (600 mg QD)<br>*[potent CYP450 inducer]* | Voriconazole $C_{max}$ ↓ 93%<br>Voriconazole AUCτ ↓ 96% | **Contraindicated** (see section 4.3) |
| Ritonavir (protease inhibitor)<br>*[potent CYP450 inducer; CYP3A4 inhibitor and substrate]*<br><br>High dose (400 mg BID) | Ritonavir $C_{max}$ and AUCτ ↔<br>Voriconazole $C_{max}$ ↓ 66%<br>Voriconazole AUCτ ↓ 82% | Co-administration of voriconazole and high doses of ritonavir (400 mg and above BID) is **contraindicated** (see section 4.3). |
| Low dose (100 mg BID)* | Ritonavir $C_{max}$ ↓ 25%<br>Ritonavir AUCτ ↓13%<br>Voriconazole $C_{max}$ ↓ 24%<br>Voriconazole AUCτ ↓ 39% | 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<br>*[CYP450 inducer; P-gp inducer]*<br>300 mg TID (co-administered with voriconazole 400 mg single dose) | In an independent published study,<br>Voriconazole $AUC_{0-\infty}$ ↓ 59% | **Contraindicated** (see section 4.3) |
| Everolimus<br>*[CYP3A4 substrate, P-gP substrate]* | Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus. | Co-administration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see section 4.4). |
| Fluconazole (200 mg QD)<br>*[CYP2C9, CYP2C19 and CYP3A4 inhibitor]* | Voriconazole $C_{max}$ ↑ 57%<br>Voriconazole AUCτ ↑ 79%<br>Fluconazole $C_{max}$ ND<br>Fluconazole AUCτ 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 reactions is recommended if voriconazole is used sequentially after fluconazole. |
| Phenytoin<br>*[CYP2C9 substrate and potent CYP450 inducer]*<br><br>300 mg QD | Voriconazole $C_{max}$ ↓ 49% | Concomitant use of voriconazole |

| **Medicinal product**<br>***[Mechanism of Interaction]*** | **Interaction**<br>**Geometric mean changes (%)** | **Recommendations concerning co-administration** |
|---|---|---|
| 300 mg QD (co-administered with voriconazole 400 mg BID)* | Voriconazole AUCτ ↓ 69%<br><br>Phenytoin $C_{max}$ ↑ 67%<br>Phenytoin AUCτ ↑ 81%<br>Compared to voriconazole 200 mg BID,<br>Voriconazole $C_{max}$ ↑ 34%<br>Voriconazole AUCτ ↑ 39% | and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended.<br><br>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) (see section 4.2). |
| Anticoagulants<br>Warfarin (30 mg single dose, co-administered with 300 mg BID voriconazole)<br>*[CYP2C9 substrate]*<br>Other oral coumarins (e.g., phenprocoumon, acenocoumarol)<br>*[CYP2C9 and CYP3A4 substrates]* | Maximum increase in prothrombin time was approximately 2-fold<br><br>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. |
| Benzodiazepines (e.g., midazolam, triazolam, alprazolam)<br>*[CYP3A4 substrates]* | Although not studied clinically, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect. | Dose reduction of benzodiazepines should be considered. |

| **Medicinal product**<br>***[Mechanism of Interaction]*** | **Interaction**<br>**Geometric mean changes (%)** | **Recommendations concerning co-administration** |
|---|---|---|
| Immunosuppressants<br>*[CYP3A4 substrates]*<br>Sirolimus (2 mg single dose) | In an independent published study,<br>Sirolimus $C_{max}$ ↑ 6.6-fold<br>Sirolimus $AUC_{0-\infty}$ ↑ 11-fold | Co-administration of voriconazole and sirolimus is **contraindicated** (see section 4.3). |
| Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy) | Ciclosporin $C_{max}$ ↑ 13%<br>Ciclosporin AUCτ ↑ 70% | When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary. |
| Tacrolimus (0.1 mg/kg single dose) | Tacrolimus $C_{max}$ ↑ 117%<br>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<br>*[CYP3A4 substrates]*<br>Oxycodone (10 mg single dose) | In an independent published study,<br>Oxycodone $C_{max}$ ↑ 1.7-fold<br>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 reactions may be necessary. |
| Methadone (32-100 mg QD)<br>*[CYP3A4 substrate]* | R-methadone (active) $C_{max}$ ↑ 31%<br>R-methadone (active) AUCτ ↑ 47%<br>S-methadone $C_{max}$ ↑ 65%<br>S-methadone AUCτ ↑ 103% | Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended. Dose reduction of methadone may be needed. |
| Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)<br>*[CYP2C9 substrates]*<br>Ibuprofen (400 mg single dose) | S-Ibuprofen $C_{max}$ ↑ 20%<br>S-Ibuprofen $AUC_{0-\infty}$ ↑ 100% | Frequent monitoring for adverse reactions and toxicity related to |

| **Medicinal product**<br>***[Mechanism of Interaction]*** | **Interaction**<br>**Geometric mean changes (%)** | **Recommendations concerning co-administration** |
|---|---|---|
| Diclofenac (50 mg single dose) | Diclofenac $C_{max}$ ↑ 114%<br>Diclofenac $AUC_{0-\infty}$ ↑ 78% | NSAIDs is recommended. Dose reduction of NSAIDs may be needed. |
| Omeprazole (40 mg QD)*<br>*[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]* | Omeprazole $C_{max}$ ↑ 116%<br>Omeprazole AUCτ ↑ 280%<br>Voriconazole $C_{max}$ ↑ 15%<br>Voriconazole AUCτ ↑ 41%<br>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*<br>*[CYP3A4 substrate; CYP2C19 inhibitor]*<br>Norethisterone/ethinylestradiol (1 mg/0.035 mg QD) | Ethinylestradiol $C_{max}$ ↑ 36%<br>Ethinylestradiol AUCτ ↑ 61%<br>Norethisterone $C_{max}$ ↑ 15%<br>Norethisterone AUCτ ↑ 53%<br>Voriconazole $C_{max}$ ↑ 14%<br>Voriconazole AUCτ ↑ 46% | Monitoring for adverse reactions related to oral contraceptives, in addition to those for voriconazole, is recommended. |
| Short -acting Opiates<br>*[CYP3A4 substrates]*<br><br>Alfentanil (20 µg/kg single dose, with concomitant naloxone)<br><br>Fentanyl (5 µg/kg single dose) | <br><br>In an independent published study, Alfentanil $AUC_{\infty}$ ↑ 6-fold<br><br>In an independent published study, Fentanyl $AUC_{\infty}$ ↑ 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 reactions is recommended. |
| Statins (e.g., lovastatin)<br>*[CYP3A4 substrates]* | Although not studied clinically, voriconazole is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis. | Dose reduction of statins should be considered. |
| Sulphonylureas (e.g., tolbutamide, glipizide, glyburide)<br>*[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)<br>*[CYP3A4 substrates]* | Although not studied, voriconazole is likely to increase the plasma concentrations of vinca alkaloids and lead to neurotoxicity. | Dose reduction of vinca alkaloids should be considered. |
| Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir)* | Not studied clinically. *In vitro* studies show that voriconazole may inhibit the metabolism of | Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose |

| **Medicinal product** ***[Mechanism of Interaction]*** | **Interaction** **Geometric mean changes (%)** | **Recommendations concerning co-administration** |
|---|---|---|
| *[CYP3A4 substrates and inhibitors]* | HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors. | 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.<br>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. |
| Cimetidine (400 mg BID) *[non-specific CYP450 inhibitor and increases gastric pH]* | Voriconazole $C_{max}$ ↑ 18%<br>Voriconazole AUCτ ↑ 23% | No dose adjustment |
| Digoxin (0.25 mg QD) *[P-gp substrate]* | Digoxin $C_{max}$ ↔<br>Digoxin AUCτ ↔ | No dose adjustment |
| Indinavir (800 mg TID) *[CYP3A4 inhibitor and substrate]* | Indinavir $C_{max}$ ↔<br>Indinavir AUCτ ↔<br>Voriconazole $C_{max}$ ↔<br>Voriconazole AUCτ ↔ | No dose adjustment |
| Macrolide antibiotics<br>Erythromycin (1 g BID) *[CYP3A4 inhibitor]*<br>Azithromycin (500 mg QD) | Voriconazole $C_{max}$ and AUCτ ↔<br><br>Voriconazole $C_{max}$ and AUCτ ↔<br>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 $C_{max}$ ↔<br>Mycophenolic acid $AUC_t$ ↔ | No dose adjustment |
| Prednisolone (60 mg single dose) *[CYP3A4 substrate]* | Prednisolone $C_{max}$ ↑ 11%<br>Prednisolone $AUC_{0-\infty}$ ↑ 34% | No dose adjustment |
| Ranitidine (150 mg BID) *[increases gastric pH]* | Voriconazole $C_{max}$ and AUCτ ↔ | No dose adjustment |

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of voriconazole in pregnant women available.

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

Voriconazole Hospira must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Women of child-bearing potential

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

Breast-feeding

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

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

Voriconazole Hospira has a 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 safety profile

The safety profile of voriconazole is based on an integrated safety database of more than 2,000 subjects (1,655 patients in therapeutic 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. Seven hundred and five (705) patients had a duration of voriconazole therapy of greater than 12 weeks, with 164 patients receiving voriconazole for over 6 months.

The most commonly reported adverse reactions were visual disturbances, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema and abdominal pain.

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

Tabulated list of adverse reactions

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

Frequency categories are expressed as: 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); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

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

**Undesirable effects reported in subjects receiving voriconazole**

| **System Organ Class** | **Adverse drug reactions** |
|---|---|
| **Infections and infestation** | |
| Common | Gastroenteritis, sinusitis, gingivitis |
| Uncommon | Pseudomembranous colitis , lymphangitis, peritonitis |

| | |
|---|---|
| **Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)** | |
| Not known | Squamous cell carcinoma* |
| **Blood and lymphatic system disorders** | |
| Common | Agranulocytosis, pancytopenia, thrombocytopenia, anaemia |
| Uncommon | Disseminated intravascular coagulation, bone marrow failure, leukopenia, lymphadenopathy, eosinophilia |
| **Immune system disorders** | |
| Common | Hypersensitivity |
| Uncommon | Anaphylactoid reaction |
| **Endocrine disorders** | |
| Uncommon | Adrenal insufficiency, hypothyroidism |
| Rare | Hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common | Oedema peripheral |
| Common | Hypoglycaemia, hypokalaemia, hyponatraemia |
| **Psychiatric disorders** | |
| Common | Depression, hallucination, anxiety, insomnia, agitation, confusional state |
| **Nervous system disorders** | |
| Very common | Headache |
| Common | Convulsion, tremor, paraesthesia, hypertonia, somnolence, syncope, dizziness |
| Uncommon | Brain oedema, encephalopathy, extrapyramidal disorder, neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia, nystagmus |
| Rare | Hepatic encephalopathy, Guillain-Barre syndrome |
| **Eye disorders** | |
| Very common | Visual disturbances (including blurred vision (see section 4.4), chromotopsia and photophobia) |
| Common | Retinal haemorrhage |
| Uncommon | Oculogyric crisis, optic nerve disorder (including optic neuritis, see section 4.4), papilloedema (see section 4.4), scleritis, blepharitis, diplopia |
| Rare | Optic atrophy, corneal opacity |
| **Ear and labyrinth disorders** | |
| Uncommon | Hypoacusis, vertigo, tinnitus |
| **Cardiac disorders** | |
| Common | Arrhythmia supraventricular, tachycardia, bradycardia |
| Uncommon | Ventricular fibrillation, ventricular extrasystoles, supraventricular tachycardia, ventricular tachycardia, |
| Rare | Torsades de pointes, atrioventricular block complete, bundle branch block, nodal |

| | |
|---|---|
| | rhythm |
| **Vascular disorders** | |
| Common | Hypotension, phlebitis |
| Uncommon | Thrombophlebitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common | Respiratory distress |
| Common | Acute respiratory distress syndrome, pulmonary oedema |
| **Gastrointestinal disorders** | |
| Very common | Abdominal pain, nausea, vomiting, diarrhoea |
| Common | Dyspepsia, constipation, cheilitis |
| Uncommon | Pancreatitis, duodenitis, glossitis, swollen tongue |
| | |
| **Hepato-biliary disorders** | |
| Very common | Liver function test abnormal (including AST, ALT, alkaline phosphatase, gamma-glutamyl transpeptidase [GGT], lactate dehydrogenase [LDH], bilirubin) |
| Common | Jaundice, jaundice cholestatic, hepatitis |
| Uncommon | Hepatic failure, hepatomegaly, cholecystitis, cholelithiasis |
| **Skin and subcutaneous tissue disorders** | |
| Very common | Rash |
| Common | Dermatitis exfoliative, rash maculo-papular, pruritus, alopecia, erythema |
| Uncommon | Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, angioedema, psoriasis, urticaria, dermatitis allergic, phototoxicity, rash macular, rash papular, purpura, eczema |
| Rare | Pseudoporphyria, fixed drug eruption |
| Not known | Cutaneous lupus erythematosus* |
| **Musculoskeletal and connective tissue disorders** | |
| Common | Back pain |
| Uncommon | Arthritis |
| Not known | Periostitis* |
| **Renal and urinary disorders** | |
| Common | Renal failure acute, haematuria |
| Uncommon | Renal tubular necrosis, proteinuria, nephritis |
| **General disorders and administration site conditions** | |
| Very common | Pyrexia |
| Common | Chest pain, face oedema, asthenia, influenza like illness, chills |
| Uncommon | Injection site reaction |

| **Investigations** | |
|---|---|
| Common | Blood creatinine increased |
| Uncommon | Electrocardiogram QTc interval prolonged, blood urea increased, blood cholesterol increased |

*Undesirable events identified during post-approval use

Description of selected adverse reactions

*Visual disturbances*
In clinical trials, visual impairments with voriconazole were very common. In therapeutic studies, voriconazole treatment-related visual disturbances were very common. In these studies, short-term as well as long-term treatment, approximately 21 % of subjects experienced altered/enhanced visual perception, blurred vision, colour vision change or photophobia. These visual disturbances were transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There was evidence of attenuation with repeated doses of voriconazole. The visual disturbances were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual disturbances may be associated with higher plasma concentrations and/or doses.

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 treatment and were fully reversible on withdrawal of voriconazole.

There have been post-marketing reports of prolonged visual adverse events (see section 4.4).

*Dermatological reactions*
Dermatological reactions were common in patients treated with voriconazole in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medicinal products. The majority of rashes were of mild to moderate severity. Patients have rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with voriconazole.

If patients develop a rash they should be monitored closely and Voriconazole Hospira discontinued if lesions progress. Photosensitivity reactions have been reported, especially during long-term therapy (see section 4.4).

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

*Liver function tests*
The overall incidence of clinically significant transaminase abnormalities in the voriconazole clinical programme was 13.5% (258/1918) of subjects treated with voriconazole. Liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

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

*Infusion-related reactions*
During infusion of the intravenous formulation of voriconazole in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnoea, faintness, nausea,

pruritus and rash have occurred. Symptoms appeared immediately upon initiating the infusion (see section 4.4).

*Paediatric population*
The safety of voriconazole was investigated in 285 paediatric patients aged 2 to <12 years who were treated with voriconazole in pharmacokinetic studies (127 paediatric patients) and in compassionate use programs (158 paediatric patients). The adverse reaction profile of these 285 paediatric patients was similar to that in adults. Post-marketing data suggest there might be a higher occurrence of skin reactions (especially erythema) in the paediatric population compared to adults. In the 22 patients less than 2 years old who received voriconazole in a compassionate use programme, the following adverse reactions (for which a relationship to voriconazole could not be excluded) were reported: photosensitivity reaction (1), arrhythmia (1), pancreatitis (1), blood bilirubin increased (1), hepatic enzymes increased (1), rash (1) and papilloedema (1). There have been post-marketing reports of pancreatitis in paediatric patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

## 4.9 Overdose

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

There is no known antidote to voriconazole.

Voriconazole is haemodialysed with a clearance of 121 ml/min. The intravenous vehicle, SBECD, is 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: J02AC03

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

Pharmacokinetic/pharmacodynamic relationship
In 10 therapeutic studies, the median for the average and maximum plasma concentrations in individual subjects across the studies was 2425 ng/ml (inter-quartile range 1193 to 4380 ng/ml) and 3742 ng/ml (inter-quartile range 2027 to 6302 ng/ml), respectively. 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.

Clinical efficacy and safety

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* which have limited susceptibility to existing antifungal agents.

Clinical efficacy defined as partial or complete response, 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 (often with partial or complete response) included isolated cases of *Alternaria* spp., *Blastomyces dermatitidis, Blastoschizomyces capitatus, Cladosporium* spp*., Coccidioides immitis, Conidiobolus coronatus, Cryptococcus neoformans, Exserohilum rostratum, Exophiala spinifera, Fonsecaea pedrosoi, Madurella mycetomatis, Paecilomyces lilacinus, Penicillium* spp. including *P. marneffei, Phialophora richardsiae, Scopulariopsis brevicaulis* and *Trichosporon* spp. including *T. beigelii* infections.

*In vitro* activity against clinical isolates has been observed for *Acremonium* spp., *Alternaria* spp., *Bipolaris* spp*., Cladophialophora* spp*., Histoplasma capsulatum,* with most strains being inhibited by concentrations of voriconazole in the range 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* spp.

Breakpoints

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.

The species most frequently involved in causing human infections include *C. albicans, C. parapsilosis, C. tropicalis, C. glabrata* and *C. krusei*, all of which usually exhibit minimum inhibitory concentration (MICs) of less than 1 mg/L for voriconazole.

However, the *in vitro* activity of voriconazole against *Candida* species is not uniform. Specifically, for *C. glabrata,* the MICs of voriconazole for fluconazole-resistant isolates are proportionally higher than are those of fluconazole-susceptible isolates. Therefore, every attempt should be made to identify *Candida* to species level. If antifungal susceptibility testing is available, the MIC results may be interpreted using breakpoint criteria established by European Committee on Antimicrobial Susceptibility Testing (EUCAST).

EUCAST Breakpoints

| **Candida Species** | **MIC breakpoint (mg/L)** | |
|---|---|---|
| | **≤S (Susceptible)** | **>R (Resistant)** |
| *Candida albicans*[1] | 0.125 | 0.125 |
| *Candida tropicalis*[1] | 0.125 | 0.125 |
| *Candida parapsilosis*[1] | 0.125 | 0.125 |
| *Candida glabrata*[2] | Insufficient evidence | |
| *Candida krusei*[3] | Insufficient evidence | |
| *Other Candida spp.*[4] | Insufficient evidence | |

[1] Strains with MIC values above the Susceptible (S) breakpoint are rare, or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory.
[2] In clinical studies, response to voriconazole in patients with *C glabrata* infections was 21% lower compared to *C. albicans, C. parapsilosis and C. tropicalis.* However, this reduced response was not correlated with elevated MICs.
[3] In clinical studies, response to voriconazole in *C. krusei* infections was similar to *C. albicans, C. parapsilosis and C. tropicalis.* However, as there were only 9 cases available for EUCAST analysis, there is currently insufficient evidence to set clinical breakpoints for *C. krusei*.
[4] EUCAST has not determined non-species related breakpoints for voriconazole.

Clinical Experience
Successful outcome in this section is defined as complete or partial response.

*Aspergillus* infections – efficacy in aspergillosis patients with poor prognosis
Voriconazole has *in vitro* fungicidal activity against *Aspergillus* spp. The efficacy and survival benefit of voriconazole versus conventional amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in an open, randomised, multicentre study in 277 immunocompromised patients treated for 12 weeks. Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of seven days. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12 hours. Median duration of IV voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of oral voriconazole therapy was 76 days (range 2-232 days).

A satisfactory global response (complete or partial resolution of all attributable symptoms signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53 % of voriconazole-treated patients compared to 31 % of patients treated with comparator. The 84-day survival rate for voriconazole was statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of voriconazole for both time to death and time to discontinuation due to toxicity.

This study confirmed findings from an earlier, prospectively designed study where there was a positive outcome in subjects with risk factors for a poor prognosis, including graft versus host disease, and, in particular, cerebral infections (normally associated with almost 100 % mortality).

The studies included cerebral, sinus, pulmonary and disseminated aspergillosis in patients with bone marrow and solid organ transplants, haematological malignancies, cancer and AIDS.

Candidaemia in non-neutropenic patients
The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidaemia was demonstrated in an open, comparative study. Three hundred and seventy non-neutropenic patients (above 12 years of age) with documented candidaemia were included in the study, of whom 248 were treated with voriconazole. Nine subjects in the voriconazole group and five in the amphotericin B followed by fluconazole group also had mycologically proven infection in deep tissue. Patients with renal failure were excluded from this study. The median treatment duration was 15 days in both treatment arms. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medicinal product was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of *Candida* from blood and infected deep tissue sites at 12 weeks after the end of therapy (EOT). Patients who did not have an assessment 12 weeks after EOT were counted as failures. In this analysis a successful response was seen in 41 % of patients in both treatment arms.

In a secondary analysis, which utilised *DRC* assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT) voriconazole and the regimen of amphotericin B followed by fluconazole had successful response rates of 65 % and 71 %, respectively. The Investigator's assessment of successful outcome at each of these time points is shown in the following table.

| *Timepoint* | *Voriconazole (N=248)* | *Amphotericin B → fluconazole (N=122)* |
|---|---|---|
| ***EOT*** | ***178 (72 %)*** | ***88 (72 %)*** |
| ***2 weeks after EOT*** | ***125 (50 %)*** | ***62 (51 %)*** |
| ***6 weeks after EOT*** | ***104 (42 %)*** | ***55 (45 %)*** |
| ***12 weeks after EOT*** | ***104 (42 %)*** | ***51 (42 %)*** |

Serious refractory *Candida* infections
The study comprised 55 patients with serious refractory systemic *Candida* infections (including candidaemia, disseminated and other invasive candidiasis) where prior antifungal treatment, particularly with fluconazole, had been ineffective. Successful response was seen in 24 patients (15 complete, 9 partial responses). In fluconazole-resistant non *albicans* species, a successful outcome was seen in 3/3 *C. krusei* (complete responses) and 6/8 *C. glabrata* (5 complete, 1 partial response) infections. The clinical efficacy data were supported by limited susceptibility data.

*Scedosporium* and *Fusarium* infections
Voriconazole was shown to be effective against the following rare fungal pathogens:

*Scedosporium* spp.: Successful response to voriconazole therapy was seen in 16 (6 complete, 10 partial responses) of 28 patients with *S. apiospermum* and in 2 (both partial responses) of 7 patients with *S. prolificans* infection. In addition, a successful response was seen in 1 of 3 patients with infections caused by more than one organism including *Scedosporium* spp.

*Fusarium* spp.: Seven (3 complete, 4 partial responses) of 17 patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with fusariosis had an infection caused by several organisms; two of them had a successful outcome.

The majority of patients receiving voriconazole treatment of the above mentioned rare infections were intolerant of, or refractory to, prior antifungal therapy.

Duration of treatment
In clinical trials, 705 patients received voriconazole therapy for greater than 12 weeks, with 164 patients receiving voriconazole for over 6 months.

Paediatric population
Sixty one paediatric patients aged 9 months up to 15 years who had definite or probable invasive fungal infections, were treated with voriconazole. This population included 34 patients 2 to < 12 years old and 20 patients 12 to 15 years of age.

The majority (57/61) had failed previous antifungal therapies. Therapeutic studies included 5 patients aged 12 to15 years, the remaining patients received voriconazole in the compassionate use programmes. Underlying diseases in these patients included haematological malignancies (27 patients) and chronic granulomatous disease (14 patients). The most commonly treated fungal infection was aspergillosis (43/61; 70 %).

Clinical studies examining QTc interval
A placebo-controlled, randomized, single-dose, crossover study to evaluate the effect on the QTc interval of healthy volunteers was conducted with three oral doses of voriconazole and ketoconazole. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600 mg of voriconazole were 5.1, 4.8, and 8.2 msec, respectively and 7.0 msec for ketoconazole 800 mg. No subject in any group had an increase in QTc of ≥60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec.

## 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 ($AUC_\tau$). The oral maintenance dose of 200 mg (or 100 mg for patients less than 40 kg) achieves a voriconazole exposure similar to 3 mg/kg IV. A 300 mg (or 150 mg for patients less than 40 kg) oral maintenance dose achieves an exposure similar to 4 mg/kg IV. 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, 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 rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations ($C_{max}$) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96 %. When multiple doses of voriconazole are administered with high fat meals, $C_{max}$ and $AUC_\tau$ 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 %. Cerebrospinal fluid samples from eight patients in a compassionate programme showed detectable voriconazole concentrations in all patients.

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 ($AUC_\tau$) 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 at 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.

Pharmacokinetics in special patient groups

Gender

In an oral multiple dose study, $C_{max}$ and $AUC_{\tau}$ 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 $AUC_{\tau}$ 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 $AUC_{\tau}$ 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 $AUC_{\tau}$ 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. The safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly (see section 4.2).

Paediatric population

The recommended doses in children and adolescent patients are based on a population pharmacokinetic analysis of data obtained from 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescent patients aged 12 to <17 years. Multiple intravenous doses of 3, 4, 6, 7 and 8 mg/kg twice daily and multiple oral doses (using the powder for oral suspension) of 4 mg/kg, 6 mg/kg, and 200 mg twice daily were evaluated in 3 paediatric pharmacokinetic studies. Intravenous loading doses of 6 mg/kg IV twice daily on day 1 followed by 4 mg/kg intravenous dose twice daily and 300 mg oral tablets twice daily were evaluated in one adolescent pharmacokinetic study. Larger inter-subject variability was observed in paediatric patients compared to adults.

A comparison of the paediatric and adult population pharmacokinetic data indicated that the predicted total exposure ($AUC_{\tau}$) in children following administration of a 9 mg/kg IV loading dose was comparable to that in adults following a 6 mg/kg IV loading dose. The predicted total exposures in children following IV maintenance doses of 4 and 8 mg/kg twice daily were comparable to those in adults following 3 and 4 mg/kg IV twice daily, respectively. The predicted total exposure in children following an oral maintenance dose of 9 mg/kg (maximum of 350 mg) twice daily was comparable to that in adults following 200 mg oral twice daily. An 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.

The higher intravenous maintenance dose in paediatric patients relative to adults reflects the higher elimination capacity in paediatric patients due to a greater liver mass to body mass ratio. Oral bioavailability may, however, be limited in paediatric patients with malabsorption and very low body weight for their age. In that case, intravenous voriconazole administration is recommended.

Voriconazole exposures in the majority of adolescent patients were comparable to those in adults receiving the same dosing regimens. However, lower voriconazole exposure was observed in some young adolescents with low body weight compared to adults. It is likely that these subjects may metabolize voriconazole more similarly to children than to adolescents/adults. Based on the population pharmacokinetic analysis, 12- to 14-year-old adolescents weighing less than 50 kg should receive children's doses (see section 4.2).

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).

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

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

### 5.3 Preclinical safety data

Repeated-dose toxicity studies with voriconazole indicated the liver to be the target organ. Hepatotoxicity occurred at plasma exposures similar to those obtained at therapeutic doses in humans, in common with other antifungal agents. In rats, mice and dogs, voriconazole also induced minimal adrenal changes. Conventional studies of safety pharmacology, genotoxicity or carcinogenic potential did not reveal a special hazard for humans.

In reproduction studies, voriconazole was shown to be teratogenic in rats and embryotoxic in rabbits at systemic exposures equal to those obtained in humans with therapeutic doses. In the pre and postnatal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labour and produced dystocia with consequent maternal mortality and reduced perinatal survival of pups. The effects on parturition are probably mediated by species-specific mechanisms, involving reduction of oestradiol levels, and are consistent with those observed with other azole antifungal agents. Voriconazole administration induced no impairment of male or female fertility in rats at exposures similar to those obtained in humans at therapeutic doses.

Preclinical data on the intravenous vehicle, SBECD indicated that the main effects were vacuolation of urinary tract epithelium and activation of macrophages in the liver and lungs in the repeated-dose toxicity studies. As GPMT (guinea pig maximisation test) result was positive, prescribers should be aware of the hypersensitivity potential of the intravenous formulation. Standard genotoxicity and reproduction studies with the excipient SBECD reveal no special hazard for humans. Carcinogenicity studies were not performed with SBECD. An impurity, present in SBECD, has been shown to be an alkylating mutagenic agent with evidence for carcinogenicity in rodents. This impurity should be considered a substance with carcinogenic potential in humans. In the light of these data the duration of treatment of the intravenous formulation should be no longer than 6 months.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sulphobutylether beta cyclodextrin sodium (SBECD)

### 6.2 Incompatibilities

Voriconazole Hospira must not be infused into the same line or cannula concomitantly with other intravenous products. When the Voriconazole Hospira 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 hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of voriconazole therapy (see sections 4.2 and 4.4). Voriconazole Hospira 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 Voriconazole Hospira, 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 Voriconazole Hospira. Voriconazole Hospira 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

After reconstitution:
Chemical and physical in-use stability has been demonstrated for 36 hours at 2°C to 8° C for the reconstituted solution.

After dilution:
Chemical and physical stability of the of the diluted solutions for infusion has been demonstrated for 36 hours at 2°C to 8°C followed by 3 hours at room temperature.

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

## 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

30 ml clear Type I glass vial closed with a chlorobutyl rubber stopper and sealed with an aluminium flip off seal with a red plastic matte top button. Packs of 1 or 5 vials.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

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

The powder is reconstituted with either 19 ml of water for injections or 19 ml of sodium chloride 9 mg/ml (0.9%) solution 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 (non-automated) syringe be used to ensure that the exact amount (19.0 ml) of water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection is dispensed.

After reconstitution with 19 ml of water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection a clear solution is obtained.

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

For administration, the required volume of the reconstituted 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 Voriconazole Hospira Concentrate***

| **Body Weight (kg)** | **Volume of Voriconazole Hospira 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) | - | - |

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.

## 7. MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway, Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1004/001 1 Pack
EU/1/15/1004/002 5 Pack

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
UK

Hospira Enterprises B.V.
Randstad 22-11
1316 BN Almere
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

- Health Care Professional (HCP) Question and Answer Brochure for Phototoxicity, SCC and Hepatic toxicity;
  - Advises HCPs on the risks of phototoxicity, skin SCC and liver toxicity associated with voriconazole use.
  - Provides HCPs with the current recommendations to monitor and manage these risks.
  - Reminds HCPs of use of the HCP Checklist and the Patient Alert Card and how to obtain additional copies.

- Health Care Professional (HCP) Checklist for Phototoxicity, SCC and Hepatic toxicity:
  - Reminds HCPs of the risks of phototoxicity, skin SCC and hepatotoxicity reported with voriconazole use.
  - Provides HCPs with the current recommendations to monitor and manage these risks.
  - Reminds HCPs to discuss with the patient/care giver the risks of phototoxicity/skin SCC and hepatotoxicity, what to look for, how and when to seek immediate attention.
  - Reminds HCPs to provide a Patient Alert Card to the patient.

- Patient Alert Card for Phototoxicity and SCC:
  - Reminds patients of the risk of phototoxicity and skin SCC.
  - Reminds patients when and how to report relevant signs and symptoms of phototoxicity and skin cancer.
  - Reminds patients to take steps to minimize the risk of skin reactions and skin SCC (by avoiding exposure to direct sunlight, use of a sunscreen and protective clothing) and inform HCPs if they experience relevant skin abnormalities.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer carton 1 (or 5) vials including blue box**

## 1. NAME OF THE MEDICINAL PRODUCT

Voriconazole Hospira 200 mg powder for solution for infusion
Voriconazole

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 200 mg of voriconazole.
After reconstitution each ml contains 10 mg of voriconazole.

## 3. LIST OF EXCIPIENTS

Excipient: Sulphobutylether beta cyclodextrin sodium (SBECD). See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
1 vial
5 vials

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Reconstitute and dilute before use.
Intravenous use only
Single use vial

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway, Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1004/001
EU/1/15/1004/002

## 13. BATCH NUMBER

**BN**

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial label**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Voriconazole Hospira 200 mg powder for infusion
Voriconazole
Intravenous use

## 2. METHOD OF ADMINISTRATION

Reconstitute and dilute before use – see leaflet.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

BN

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Voriconazole Hospira 200 mg powder for solution for infusion**
Voriconazole

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet (see section 4).

**What is in this leaflet**



## 1. What Voriconazole Hospira is and what it is used for

Voriconazole Hospira contains the active substance voriconazole. Voriconazole Hospira is an antifungal medicine. It works by killing or stopping the growth of the fungi that cause infections.

It is used for the treatment of patients (adults and children over the age of 2) with:
- invasive aspergillosis (a type of fungal infection due to *Aspergillus sp.*),
- candidaemia (another type of fungal infection due to *Candida sp.*) in non-neutropenic patients (patients without abnormally low white blood cell count),
- serious invasive *Candida sp.* infections when the fungus is resistant to fluconazole (another antifungal medicine),
- serious fungal infections caused by *Scedosporium sp.* or *Fusarium sp.* (two different species of fungi).

Voriconazole Hospira is intended for patients with worsening, possibly life-threatening, fungal infections.

This medicinal product should only be used under the supervision of a doctor.

## 2. What you need to know before you take Voriconazole Hospira

**Do not take Voriconazole Hospira:**
- if you are allergic to the active ingredient voriconazole or to sulphobutylether beta cyclodextrin sodium (listed in section 6).

It is very important that you inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription, or herbal medicines.

The medicines in the following list must not be taken during your Voriconazole Hospira treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)

- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Rifampicin (used for treating tuberculosis)
- Efavirenz (used for treating HIV) in doses of 400 mg and above once daily
- Carbamazepine (used to treat seizures)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g., ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Ritonavir (used for treating HIV) in doses of 400 mg and more twice daily
- St John's Wort (herbal supplement)

**Warnings and precautions**
Talk to your doctor before taking Voriconazole Hospira if:

- You have had an allergic reaction to other azoles.
- You are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of Voriconazole Hospira. Your doctor should also monitor your liver function while you are being treated with Voriconazole Hospira by doing blood tests.
- You are known to have cardiomyopathy, irregular heart beat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QTc syndrome'.

You should avoid sunlight and sun exposure while being treated. It is important to cover sun exposed areas of skin and use sunscreen with high sun protection factor (SPF), as an increased sensitivity of skin to the sun's UV rays can occur. These precautions are also applicable to children.

While being treated with Voriconazole Hospira:
- Tell your doctor immediately if you develop
    - sunburn
    - severe skin rash or blisters
    - bone pain.

If you develop skin disorders as described above, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you to be seen on a regular basis. There is a small chance that skin cancer could develop with long term use of Voriconazole Hospira.

Your doctor should monitor the function of your liver and kidneys by doing blood tests.

**Children and adolescents**
Voriconazole Hospira should not be given to children younger than 2 years of age.

**Other medicines and Voriconazole Hospira**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those that are obtained without a prescription.

Some medicines, when taken at the same time as Voriconazole Hospira, may affect the way that Voriconazole Hospira works or Voriconazole Hospira may affect the way they work.

Tell your doctor if you are taking the following medicine, as treatment with Voriconazole Hospira at the same time should be avoided if possible:
- Ritonavir (used for treating HIV) in doses of 100 mg twice daily

Tell your doctor if you are taking either of the following medicines, as treatment with Voriconazole Hospira at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:
- Rifabutin (used for treating tuberculosis). If you are already being treated with rifabutin, your blood counts and side effects to rifabutin will need to be monitored.

- Phenytoin (used to treat epilepsy). If you are already being treated with phenytoin, your blood concentration of phenytoin will need to be monitored during your treatment with Voriconazole Hospira and your dose may be adjusted.

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines and/or Voriconazole Hospira are still having the desired effect:

- Warfarin and other anticoagulants (e.g. phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Ciclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulphonylureas (e.g., tolbutamide, glipizide and glyburide) (used for diabetes)
- Statins (e.g., atorvastatin, simvastatin) (used for lowering cholesterol)
- Benzodiazepines (e.g., midazolam, triazolam) (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Oral contraceptives (if you take Voriconazole Hospira whilst using oral contraceptives, you may get side effects such as nausea and menstrual disorders)
- Vinca alkaloids (e.g., vincristine and vinblastine) (used in treating cancer)
- Indinavir and other HIV protease inhibitors (used for treating HIV)
- Non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, delavirdine, nevirapine) (used for treating HIV) (some doses of efavirenz can NOT be taken at the same time as Voriconazole Hospira)
- Methadone (used to treat heroin addiction)
- Alfentanil and fentanyl and other short acting opiates such as sufentanil (painkillers used for surgical procedures)
- Oxycodone and other long acting opiates such as hydrocodone (used for moderate to severe pain)
- Non-steroidal anti-inflammatory drugs (e.g., ibuprofen, diclofenac) (used for treating pain and inflammation)
- Fluconazole (used for treating fungal infections)
- Everolimus (used for treating advanced kidney cancer and in transplant patients)

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Voriconazole Hospira must not be used during pregnancy, unless indicated by your doctor. Effective contraception must be used in women of childbearing potential. Contact your doctor immediately if you become pregnant while being treated with Voriconazole Hospira.

**Driving and using machines**
Voriconazole Hospira may cause blurring of vision or uncomfortable sensitivity to light. While affected, do not drive or operate any tools or machines. Tell your docotor if you experience this.

**Voriconazole Hospira contains sodium**
Each vial of Voriconazole Hospira contains 217.6 mg of sodium per vial. This should be taken into consideration if you are on a strictly controlled sodium diet.

## 3. How to take Voriconazole Hospira

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Your doctor will determine your dose depending on your weight and the type of infection you have.

Your doctor may change your dose depending upon your condition.

The recommended dose for adults (including elderly patients) is as follows:

| | **Intravenous** |
|---|---|
| **Dose for the first 24 hours** (Loading Dose) | 6 mg/kg every 12 hours for the first 24 hours |
| **Dose after the first 24 hours** (Maintenance Dose) | 4 mg/kg twice a day |

Depending on your response to treatment, your doctor may decrease the dose to 3 mg/kg twice daily.

The doctor may decide to decrease the dose if you have mild to moderate cirrhosis.

**Use in children and adolescents**
The recommended dose for children and teenagers is as follows:

| | **Intravenous** | |
|---|---|---|
| | Children aged 2 to less than 12 years and teenagers aged 12 to 14 years weighing less than 50 kg | Teenagers aged 12 to 14 years weighing 50 kg or more; and all teenagers older than 14 |
| **Dose for the first 24 hours** (Loading Dose) | 9 mg/kg every 12 hours for the first 24 hours | 6 mg/kg every 12 hours for the first 24 hours |
| **Dose after the first 24 hours** (Maintenance Dose) | 8 mg/kg twice a day | 4 mg/kg twice a day |

Depending upon your response to treatment, your doctor may increase or decrease the daily dose.

Voriconazole Hospira powder for solution for infusion will be reconstituted and diluted to the correct concentration by your hospital pharmacist or nurse. (Please refer to the end of this leaflet for further information).

This will be given to you by intravenous infusion (into a vein) at a maximum rate of 3 mg/kg per hour over 1 to 3 hours.

**If a dose of Voriconazole Hospira has been forgotten:**
As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However, tell your doctor or pharmacist if you think that a dose has been forgotten.

**If you stop taking Voriconazole Hospira**
Voriconazole Hospira treatment will continue for as long as your doctor advises, however the duration of treatment with voriconazole should be no more than 6 months.

Patients with a weakened immune system or those with difficult infections may require long term treatment to prevent the infection from returning. You may be switched from the intravenous infusion to tablets once your condition improves.

When Voriconazole Hospira treatment is stopped by your doctor you should not experience any effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

**Serious side effects – Stop taking Voriconazole Hospira and see a doctor immediately**
- Rash

- Jaundice; changes in blood tests of liver function
- Pancreatitis which may present with severe abdominal pain

**Other side effects**

Very common side effects (may affect more than 1 in 10 people) are:
- Visual impairment (change in vision)
- Fever
- Rash
- Nausea, vomiting, diarrhoea
- Headache
- Swelling of the extremities
- Stomach pains
- Breathing difficulties.

Common side effects (may affect up to 1 in 10 people) are:
- Flu-like symptoms, irritation and inflammation of the gastrointestinal tract, inflammation of the sinuses, inflammation of the gums, chills, weakness
- Low numbers of some types of red or white blood cells, low numbers of cells called platelets that help blood to clot
- Allergic reaction or exaggerated immune response
- Low blood sugar, low blood potassium, low sodium in the blood
- Anxiety, depression, confusion, agitation, inability to sleep, hallucinations
- Seizures, tremors or uncontrolled muscle movements, tingling or abnormal skin sensations, increase in muscle tone, sleepiness, dizziness
- Bleeding in the eye
- Heart rhythm problems including very fast heartbeat, very slow heartbeat, fainting
- Low blood pressure, inflammation of a vein (which may be associated with the formation of a blood clot)
- Breathing difficulty, chest pain, swelling of the face, fluid accumulation in the lungs
- Constipation, indigestion, inflammation of the lips
- Jaundice, inflammation of the liver, redness of the skin
- Skin rashes which may lead to severe blistering and peeling of the skin characterized by a flat, red area on the skin that is covered with small confluent bumps
- Itchiness
- Hair loss
- Back pain
- Kidney failure, blood in the urine, changes in blood tests of kidney function

Uncommon side effects (may affect up to 1 in 100 people) are:
- Inflammation of the gastrointestinal tract causing antibiotic associated diarrhoea, inflammation of the lymphatic vessels
- Inflammation of the thin tissue that lines the inner wall of the abdomen and covers the abdominal organs
- Enlarged lymph glands (sometimes painful), disorder of blood clotting system, failure of blood marrow, other blood cell changes (increased eosinophil and low white blood cells in blood)
- Depressed function of the adrenal gland, underactive thyroid gland
- Abnormal brain function, Parkinson-like symptoms, nerve injury resulting in numbness, pain, tingling or burning in the hands or feet
- Problems with balance or coordination
- Swelling of the brain
- Double vision, serious conditions of the eye including: pain and inflammation of the eyes and eyelids, involuntary movement of the eye, abnormal eye movement, damage to the optic nerve resulting in vision impairment, optic disc swelling
- Decreased sensitivity to touch

- Abnormal sense of taste
- Hearing difficulties, ringing in the ears, vertigo
- Inflammation of certain internal organs- pancreas and duodenum, swelling and inflammation of the tongue
- Enlarged liver, liver failure, gallbladder disease, gallstones
- Joint inflammation, inflammation of the veins under the skin (which may be associated with the formation of a blood clot)
- Inflammation of the kidney, proteins in the urine
- Very fast heart rate or skipped heartbeats
- Abnormal electrocardiogram (ECG)
- Blood cholesterol increased, blood urea increased
- Allergic skin reactions (sometimes severe), including widespread blistering rash and skin peeling, inflammation of the skin, the rapid swelling (edema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues, itchy or sore patches of thick, red skin with silvery scales of skin, hives, sunburn or severe skin reaction following exposure to light or sun, skin redness and irritation, red or purple discoloration of the skin which may be caused by low platelet count, eczema
- Injection site reaction
- Life threatening allergic reaction

Rare side effects (may affect up to 1 in 1000 people) are:
- Overactive thyroid gland
- Deterioration of brain function that is a serious complication of liver disease
- Damage to the optic nerve resulting in vision impairment, clouding of the cornea
- Bullous photosensitivity
- A disorder in which the body's immune system attacks part of the peripheral nervous system
- Severe heart rhythm problems that may be life threatening

Other significant side effects whose frequency is not known, but should be reported to your doctor immediately:
- Skin cancer
- Inflammation of the tissue surrounding the bone
- Red, scaly patches or ring-shaped skin lesions that may be a symptom of an autoimmune disease called cutaneous lupus erythematosus

Reactions during the infusion have occurred uncommonly with Voriconazole Hospira (including flushing, fever, sweating, increased heart rate and shortness of breath). Your doctor may stop the infusion if this occurs.

As Voriconazole Hospira has been known to affect the liver and the kidney, your doctor should monitor the function of your liver and kidneys by doing blood tests. Please advise your doctor if you have any stomach pains or if your stools have a different consistency.

There have been reports of skin cancer in patients treated with voriconazole for long periods of time

Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children. If you or your child develops skin disorders, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you or your child to be seen on a regular basis.

If any of these side effects persist or are troublesome, please tell your doctor.

**Reporting of side effects**
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Voriconazole Hospira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Voriconazole Hospira contains**

- The active substance is voriconazole. Each vial contains 200 mg voriconazole, equivalent to 10 mg/ml solution when reconstituted as directed by your hospital pharmacist or nurse.
- The other ingredient is sulphobutylether beta cyclodextrin sodium.

**What Voriconazole Hospira looks like and contents of the pack**

Voriconazole Hospira is a white to off-white lyophilised cake.

Voriconazole Hospira is presented in packs of 1 or 5 glass vials as a powder for solution for infusion. Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Hospira UK Limited
Queensway, Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**AT / DE**
Hospira Deutschland GmbH
Tel: + 49 (0) 89 43 77 77 0

**BE / LX / NL**
Hospira Benelux BVBA
Tél/Tel: + 32 3 231 90 09

**BG / CZ / EE / EL / HU / IE / LT / LV / MT / PL / RO / SI / SK / UK**
Hospira UK Limited
Тел/Tel/Τηλ: + 44 (0) 1926 820820

**CY**
Pharmaceutical Trading Co Ltd
Τηλ: +357 246 56 165

**DK / FI / IS / NO / SE**
Hospira Nordic AB
Tlf/Puh/Tel/Sími: + 46 (0) 8 672 85 00

**ES**
Hospira Productos Farmacéuticos y Hospitalarios S.L.
Tel: + 34 914847100

**FR**
Hospira France

**IT**
Hospira Italia Srl

Tél: + 33 (0) 1 40 83 82 00

Tel: + 39 0812405912

**PT**
Hospira Portugal Lda
Tel: + 351 214857434

**This leaflet was last revised in MM/YYYY**.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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The following information is intended for healthcare professionals only:

**Reconstitution and dilution information**
Voriconazole Hospira powder for solution for infusion needs to first be reconstituted with either 19 ml of water for injections or 19 ml of sodium chloride 9 mg/ml (0.9%) solution for injection to obtain an extractable volume of 20 ml of clear concentrate containing 10 mg/ml voriconazole.

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 of sodium chloride 9 mg/ml (0.9%) solution for injection is dispensed.

After reconstitution with 19 ml of water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection, a clear solution is obtained.

The required volume of the reconstituted concentrate is then added to a recommended compatible infusion solution listed below to obtain a final Voriconazole Hospira solution containing 0.5 to 5 mg/ml of voriconazole.

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

Not for administration as a bolus injection.

Prior to use this medicine does not require any special temperature storage conditions. Store in the original package in order to protect from light.

*Required volumes of 10 mg/ml Voriconazole Hospira Concentrate*

| Body Weight (kg) | Volume of Voriconazole Hospira 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) | - | - |

Voriconazole Hospira is a single dose unpreserved sterile lyophile.

Stability after reconstitution:
Chemical and physical in-use stability has been demonstrated for 36 hours at 2°C to 8° C for the reconstituted solution.

Stability after dilution:
Chemical and physical stability of the of the diluted solutions for infusion has been demonstrated for 36 hours at 2°C to 8°C followed by 3 hours at room temperature.

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

**Compatible Infusion Solutions:**
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 Hospira with diluents other than listed above (or listed below under 'Incompatibilities') is unknown.

**Incompatibilities:**

Voriconazole Hospira must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition (e.g. Aminofusin 10% Plus).

Infusions of blood products must not occur simultaneously with Voriconazole Hospira.

Infusion of total parenteral nutrition can occur silmultaneously with Voriconazole Hospira but not in the same line or cannula.

Voriconazole Hospira must not be diluted with 4.2% Sodium Bicarbonate Infusion.