EU RISK MANAGEMENT PLAN

Active substance(s) (INN or common name):	Voriconazole
Pharmacotherapeutic group (ATC Code):	Antimycotics for systemic use, triazole derivatives (J02A C03)
Name of Marketing Authorisation Holder or Applicant:	Fresenius Kabi Deutschland GmbH
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Voriconazole Fresenius Kabi 200 mg powder for solution for infusion

Data lock point for this RMP	30 Apr. 2014	Version number	3.0
Date of final sign off	03 Jun. 2015		

VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 Overview of Disease Epidemiology

Voriconazole is an antifungal medicine. It is used for the treatment of adults and children over the age of two years with:

- invasive aspergillosis (a type of fungal infection due to Aspergillus);
- candidaemia (another type of fungal infection due to Candida) in non-neutropenic patients (patients with a normal white blood cell count);
- serious invasive Candida infections when the fungus is resistant to fluconazole (another antifungal medicine);
- serious fungal infections caused by Scedosporium or Fusarium (two different types of fungus).

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

Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

The medicine can only be obtained with a prescription.

Due to the inconsistency in the population treated (children and adults of different age groups), the indications (treatment of several different fungal infection types), and different underlying diseases no data on disease epidemiology are available.

VI.2.2 Summary of Treatment Benefits

Voriconazole was studied in various different fungal infections such as invasive aspergillosis, candidaemia, serious refractory candida infections (‘Refractory’ means that the infections were not responding to treatment), scedosporiosis and fusariosis. Voriconazole has also been studied in 285 children.

Voriconazole studies in invasive aspergillosis involved 277 immunocompromised patients (patients whose immune system was not working properly). Voriconazole was compared with amphotericin B (another antifungal medicine).

The study of Voriconazole in candidaemia compared voriconazole with a treatment of amphotericin B followed by fluconazole in 370 patients.

Voriconazole has also been studied in serious refractory Candida infections in 55 patients, in scedosporiosis in 38 patients, and in fusariosis in 21 patients.

Most patients receiving Voriconazole treatment for these rare infections did not tolerate or did not respond to prior treatment with other antifungal medicines.

The main measure of effectiveness in all studies was the number of patients who had a complete or partial response to treatment.

In invasive aspergillosis, the proportion of patients responding to treatment was higher with Voriconazole than with amphotericin B (53% versus 31%). The survival for voriconazole was significantly greater than that for amphotericin B.

For candidaemia, the percentage of responders to Voriconazole treatment at the end of therapy was the same as for the comparator (72%).

A successful outcome was seen in 44% of the patients with serious refractory Candida infections (24 out of 55). In most of these (15 out of 24), the response was complete.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Safety Concern	What is known	Preventability
Important Identified Risks		
Hepatic Toxicity	In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with vorionazole (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.	Patients taking 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 duration should be as short as possible; however, if based on the benefit-risk assessment the treatment is continued, monitoring frequency can be reduced to monthly if there are no changes in the liver function tests. If the liver function tests

Safety Concern	What is known	Preventability
		become markedly elevated, voriconazole 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. This has been explained in the Health Care Professional Checklist (HCP Checklist) under important information regarding voriconazole and liver function monitoring.
QTc prolongation	Voriconazole may have an effect on the electrical activity of the heart known as QT/QTc prolongation and torsades de pointes. This effect can be measured as a change in the electrocardiogram (ECG). In infrequent cases, drugs with this effect on the ECG can lead to disturbances in heart rhythm that could result in dizziness, rapid or slow heartbeat or fainting.	Yes, voriconazole should be carefully administered in patients with cardiomyopathy, irregular heartbeat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QTc syndrome' and monitoring of ECG is recommended in such patients. In addition voriconazole should be administered with caution in patients with concomitant medication that is known to prolong QT interval. When there is also a potential for voriconazole to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide) co-

Safety Concern	What is known	Preventability
		administration is contraindicated.
Visual events (including optic neuritis, papiloedema and other visual concerns)	In clinical trials, 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	Patients with visual disturbances should consult with their doctor. In addition Patients must avoid potentially hazardous tasks, such as driving or operating machinery while experiencing these symptoms.

Safety Concern	What is known	Preventability
	reversible on withdrawal of voriconazole. There have been post-marketing reports of prolonged visual adverse events.	
Phototoxicity	Phototoxicity is a known side effect reported for voriconazole. 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.	Yes, it is recommended that all patients, including children, avoid intense or prolonged exposure to direct sunlight during voriconazole treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF). This has been explained in the Health Care Professional Checklist (HCP Checklist). Further, a Patient Alert Card has been provided which helps to remind patients about the need of dermatological evaluations.
Peripheral neuropathy	Peripheral neuropathy (PN) is damage to or disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected Peripheral neuropathy is a known side effect classified under nervous system disorder for voriconazole.	Yes, Patients with long-term voriconazole therapy should have a baseline neuropathy assessment before commencing therapy and regular review thereafter. Early detection and exclusion of alternative causes is important to prevent progression of potentially irreversible symptoms.
Squamous cell carcinoma (SCC)	Squamous cell carcinoma of the skin is a cancer of a kind of epithelial cell, the squamous cell. These cells are the main part of the epidermis of the skin, and this cancer is one of the	If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Voriconazole

Safety Concern	What is known	Preventability
	major forms of skin cancer. It has been reported in patients treated with voriconazole, some of whom have reported prior phototoxic reactions. An underlying mechanism has not yet been established.	discontinuation should be considered. Dermatologic evaluation should be performed on a systematic and regular basis. Whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. Voriconazole should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified. This has been explained in the Health Care Professional Checklist (HCP Checklist). Further, a Patient Alert Card has been provided which helps to remind patients about the need of dermatological evaluations.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Skin Cancers (non-SCC)	Voriconazole has been associated with phototoxicity and pseudoporphyria. 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. Moreover, there have been reports of long term treatment with voriconazole has been associated with phototoxicity and

Risk	What is known (Including reason why it is considered a potential risk)
	squamous cell carcinoma of the skin in patients
Suicide-related events	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. It is recommend referring to the SPC specifying 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.

Missing information

Risk	What is known
Effects in pregnancy	No adequate information on the use of voriconazole in pregnant women is available. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Voriconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. The excretion of voriconazole into breast milk has not been investigated. Breast-feeding must be stopped on voriconazole initiation. In an animal study, no impairment of fertility was demonstrated in male and female rats.
Effects in paediatrics	The safety and efficacy of children below 2 years has not been established. Therefore voriconazole should not be administered to children below 2 years of age. Use in paediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied. It is recommended to refer to the SPC before prescribing voriconazole in children and adolescent patients. Voriconazole is indicated for paediatric patients aged two years or older. Hepatic function should be monitored in children. Oral bioavailability may be limited in pediatric patients aged 2 to <12 years with malabsorption and very low body weight for age. In that case, intravenous voriconazole administration is recommended. Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. Prophylaxis should be as short as possible depending on the risk for developing invasive fungal infection (IFI) as defined by neutropenia or immunosuppression. It may only be continued up to 180 days after transplantation in case of continuing immunosuppression or graft versus host disease (GvHD) 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. The frequency of phototoxicity reactions is higher in the

Risk	What is known
	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.
Off-label use	There is no information available regarding off-label use.
Resistance	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 MICs of less than 1 mg/L for voriconazole.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics for Voriconazole can be found in Annex 2 of this RMP.

There are additional risks minimisation measures described below, are established relating to hepatotoxicity, squamous cell carcinoma and phototoxicity:

- Health Care Professional Checklist for phototoxicity, squamous cell carcinoma and hepatic toxicity (Annex 11a)
- Health Care Professional Question and Answer brochure for phototoxicity, squamous cell carcinoma and hepatic toxicity (Annex 11b)
- Patient Alert Card for squamous cell carcinoma (Annex 11c)

These additional risk minimisation measures are for the following risks:

Phototoxicity squamous cell carcinoma and hepatic toxicity

Health Care Professional Checklist

Objective and rationale

For HCPs to evaluate and discuss the risks of phototoxicity, SCC of the skin and hepatic toxicity before prescribing Voriconazole Fresenius Kabi. This will remind the HCPs to closely monitor patients who develop phototoxicity and to refer them for regular dermatological consultation to minimize the risk of developing SCC of the skin, as well as to monitor liver function at the initiation and on a regular basis during Voriconazole Fresenius Kabi treatment.

Proposed actions

- Health Care Professional Checklist to be provided to the prescribing physicians.
- HCPs are to be encouraged to fill the details in each patient receiving Voriconazole Fresenius Kabi treatment.

Health Care Professional Question and Answer brochure

Objective and rationale

For HCPs to

- Understand what Voriconazole Fresenius Kabi is used for and how it should be used
- Be aware of important identified risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity adverse reactions of Voriconazole Fresenius Kabi and how they should be mitigated and managed
- Understand what other tools are available to communicate and remind patients of these risks
- Provide important safety information to patients

Proposed actions

Health Care Professional Question and Answer brochure to be provided to the prescribing physicians.

Patient Alert Card for squamous cell carcinoma

Objective and rationale

This card will help to remind patients about the need for dermatological evaluations on a regular basis (if phototoxic reactions occur and Voriconazole Fresenius Kabi is not discontinued). It also urges the patient to report phototoxic symptoms that increase the risk of SCC of the skin.

Additionally, it reminds patients:

- to avoid exposure to sunlight
- to use protective clothing and sufficient sunscreen with high SPF
- to inform their doctor if they develop sunburn or severe skin reactions

Proposed actions

- Patient Alert Card to be provided to the prescribing physicians.
- HCPs are to be encouraged to fill the details in each patient receiving Voriconazole Fresenius Kabi treatment.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.