EU RISK MANAGEMENT PLAN

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Aspergillosis refers to a wide variety of diseases caused by infection by fungi of the genus *Aspergillus*. Invasive aspergillosis is estimated to occur in 5-13% of recipients of bone marrow transplants, 5-25% of patients who have received heart or lung transplants, and 10-20% of patients who are receiving intensive chemotherapy for leukaemia.

Candidiasis is a fungal infection of any species from the genus *Candida*. Candida is an increasing cause of bloodstream infection causing significant mortality and morbidity, especially in critically ill patients. Its overall incidence rose fivefold in the past ten years and *Candida spp*. is currently between the fourth and the sixth most common hospital acquired bloodstream isolate in American and European studies.

Fusariosis is a fungal infection caused by *Fussarium species*. The incidence of fusariosis in humans is not clear, however, because systematic reporting of this infection has not been performed. Since the description of the first case in 1973 reports of this opportunistic mycosis have dramatically increased; invasive fusariosis has emerged in many tertiary-care cancer centres as the second most common invasive mold infection in profoundly immunocompromised patients behind invasive aspergillosis.

Disease states produced by *Scedosporium apiospermum* and *S. prolificans* range from skin infections to disseminated infections in immunocompromised hosts. A report from a single institution reviewed the cases of Scedosporium infection from 1989 to 2006. The authors found that the incidence per 100,000 patient-inpatient days increased from 0.82 case between 1993 and 1998 to 1.33 cases in 1999 to 2005.

Invasive fungal infections are important causes of morbidity and mortality among patients undergoing bone marrow or stem-cell transplantation. Antifungal prophylaxis has been prompted by the rising incidence of life-threatening invasive fungal infections in such patients, the difficulty in establishing the diagnosis early in the course of infection, and the recognition that treatment outcomes are poor if initiation of therapy is delayed.

VI.2.2 Summary of treatment benefits

Based on the available data from clinical studies and clinical experience of several years, voriconazole represents an effective drug in the treatment of invasive aspergillosis, candidemia in non-neutropenic patients, fluconazole-resistant serious invasive Candida infections (including *C. krusei*), serious fungal infections caused by *Scedosporium spp*. *and Fusarium spp,* and for prophylaxis of invasive fungal infections in high risk hematopoietic stem cell transplant recipients.

If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, voriconazole can be considered effective in the approved indications.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Liver damage	In clinical trials there have been reports of serious liver reactions during treatment of voriconazole. Liver dysfunction has usually been reversible after discontinuation of therapy.	The doctor should be informed if 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. Monitoring of liver function by doing blood tests should be carried out during treatment with voriconazole. If jaundice or changes in blood tests of liver function appear, voriconazole should be discontinued and the doctor should be contacted immediately.
Abnormality of electrocardiogram (ECG) (QTc prolongation)	Abnormalities of the electrocardiogram (QT interval prolongation) have been reported with voriconazole treatment. Patients with underlying heart conditions, electrolyte imbalance and patients taking other drugs that affect the heart rhythm are at greater risk of experiencing QT prolongation.	Astemizole, cisapride, pimozide, quinidine and terfenadine must not be taken during course of treatment with voriconazole since concomitant use might lead to ECG abnormalities. You should inform your doctor if you know to have cardiomyopathy, irregular heartbeat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QT syndrome'.
Visual effects (including optic neuritis, papiloedema and other visual concerns)	In clinical trials, voriconazole treatment-related visual disturbances were very common. Approximately 30 % 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 and no significant long-term visual effects were observed	Not known.
Increased sensitivity of skin to sunlight (phototoxicity)	Photosensitivity reactions have been reported, especially during long-term therapy with voriconazole.	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, as an increased sensitivity of skin to the sun's UV rays can occur. If you develop sunburns you should contact your doctor immediately.
A disorder of the nerves which can cause weakness,	Nerve injury resulting in numbness, pain, tingling or burning in the hands	Not known.

Risk	What is known	Preventability
tingling or numbness (Peripheral neuropathy)	or feet has been reported as a rare side effect of voriconazole.	
Squamous cell carcinoma of the skin	There have been reports of skin cancer in patients treated with voriconazole for long periods of time.	Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions. 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, as an increased sensitivity of skin to the sun's UV rays can occur. If you develop sunburns you should contact your doctor immediately.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Skin cancers (non-SCC)	There have been reports of skin cancer in patients treated with voriconazole for long periods of time. The mechanism has not been established.
Suicide-related events	Depression has been reported as a side effect of voriconazole.

Missing information

Risk	What is known
Effects in paediatrics	The adverse reaction profile of children studied was similar to that in adults. Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children. Voriconazole should not be given to children younger than 2 years of age.
Effects in pregnancy	Voriconazole must not be used during pregnancy, unless indicated by your doctor. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.
Product use in unapproved indication (Off-label use)	Voriconazole should be used in approved indications only.
Drug resistance	Voriconazole should be used in approved indications only. Specimens for fungal culture and other relevant laboratory studies should be obtained prior to therapy. 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.

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.

These additional risk minimisation measures are for the following risks:

Squamous cell carcinoma of the skin and Liver damage

Risk minimisation measure(s): **Educational materials:** • **Healthcare Professional Checklist (HCP Checklist)** • **Healthcare Professional Question and Answer Brochure (HCP Q&A Brochure)** • **Patient Alert Card (Squamous cell carcinoma only)**
Objective and rationale
To inform patients and healthcare professionals on the risks of liver damage and squamous cell carcinoma of the skin associated with voriconazole use and to minimise its occurrence.
Proposed action
HCP Checklist and HCP Q&A Brochure The HCP Checklist and HCP Q&A Brochure informs and reminds the prescribing physicians on the risk of liver damage and squamous cell carcinoma of the skin before prescribing voriconazole. It also serves as a reminder to closely monitor patients who develop phototoxicity and refer them to dermatological consultations to minimise the risk of developing SCC of the skin and also to monitor liver function. **Patient Alert Card** Patient alert card helps remind patients about the need of regular dermatological evaluations (if phototoxicity occurs). It also reminds patients on the measure that can be undertaken to minimise the risk of phototoxicity and squamous cell carcinoma of the skin respectively (e.g. avoiding exposure to sunlight, use of sunscreen). The card reminds patients to inform their doctors and report adverse reactions associated with phototoxicity and squamous cell carcinoma.

Proposed format and content of the educational material is available in Annex 11 of the RMP. However, exact format and content and way of distribution are to be discussed locally with the individual authorities prior to the launch, and can therefore be different from the text as described in Annex 11 of the RMP.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Table 1. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	14 Nov 2012	Important identified risks: • Hepatotoxicity • QT prolongation • Visual effects • Phototoxicity • Peripheral neuropathy Important potential risks: • Skin cancer (including squamous cell carcinoma) • Suicide-related events • Bone disorders Important missing information: • Use in pregnant women • Off-label use, especially as related to prophylactic and long-term use (i.e. hepatic toxicity, phototoxicity and skin cancer) • Potential for resistance	For tablet formulation only.
2.0	15 Mar 2013	Same as in v 1.0	Reference to the SmPC text updated for tablet formulation only. **Approved version for voriconazole tablets.**
3.0	10 Dec 2013	Voriconazole 200 mg powder for solution for infusion added as a new formulation in the RMP. Safety concerns updated based on available data from publicly available voriconazole EPAR.	This version was rejected by the RMS.
3.1	28 July 2014	Important identified risks: • Hepatotoxicity • QT prolongation • Visual effects • Phototoxicity • Peripheral neuropathy • Squamous cell carcinoma (SCC) Important potential risks: • Skin cancers (non-SCC) • Suicide-related events Important missing information: • Effects in paediatrics • Effects in pregnancy • Off-label use • Drug resistance	A separate RMP was prepared for powder for solution for infusion formulation. The RMP was aligned with the originator: SCC moved to important identified risks. Effects in paediatrics, pregnancy, off label use and resistance moved to missing information. Additional risk minimisation measures introduced for hepatotoxicity and SCC.

Version	Date	Safety Concerns	Comment
3.2		Same as in v 3.1	Update in SPC and additional risks minimisation communication plan