VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Voriconazole is an antifungal medicine that belongs to the 'triazole' group. It works by preventing the formation of ergosterol, which is an important part of fungal cell membranes. Without ergosterol, the fungus is killed or prevented from spreading.

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 (a 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.

Invasive aspergillosis (a type of fungal infection due to *Aspergillus)*

Invasive aspergillosis affects 5-13% of patients who have had bone marrow transplants, 5-25% of patients who have received heart or lung transplants, and 10-20% of patients who are receiving chemotherapy for leukemia (cancer of the blood). The incidence of aspergillosis in people with asthma appears to be higher in Great Britain compared with the United States. Invasive aspergillosis is associated with significant mortality, with a rate of 30-95%. The age distribution of aspergillosis is similar to the underlying medical conditions with which it is associated.

Candidaemia (a type of fungal infection due to *Candida*)

Candida species are the most common cause of fungal infection in immunocompromised persons. Oropharyngeal colonization (in the mouth and throat) is found in 30-55% of healthy young adults. Three of every four women experience at least one bout of vulvovaginal candidiasis (genital) during their lifetime. More than 90% of persons infected with HIV who are not receiving highly active antiretroviral treatment eventually develop oropharyngeal candidiasis, and 10% eventually develop at least one episode of oesophageal (gullet) candidiasis. In persons with systemic infections, *Candida* species are now the fourth most common cause. Clinical studies have confirmed the marked increase in the incidence of disseminated candidiasis (spreading in the bloodstream to other areas of the body). Persons at the extremes of age (neonates and adults >65 years of age) are most prone.

Scedosporium infection

Scedosporium is another fungus that causes different types of infections in immunocompetent and immunosuppressed people. The vast majority of infections are fungal infections called mycetomas. This infection causes inflammation in the tissue under the skin, which can extend to the underlying bone. Others include infections of the eye, ear, central nervous system, internal organs and more commonly the lungs. Mycetoma is rare in the United States. Some cases are due to increasing international travel. Mycetoma is endemic in Africa, from Sudan and Somalia through Mauritania and Senegal. Other endemic countries include Mexico and India. Mycetoma causes disfigurement but it rarely causes death.

Fusarium infection

Fusarium is a fungus that may cause a range of opportunistic infections in humans. In humans with normal immune systems, fusarial infections may occur in the nails (onychomycosis) and in the cornea (keratomycosis or mycotic keratitis). In humans whose immune systems are weakened in a particular way,

(neutropenia, i.e. very low neutrophils count), aggressive fusarial infections penetrating the entire body and bloodstream (disseminated infections) may be caused by members of the *Fusarium solani* complex, *Fusarium oxysporum*, *Fusarium verticillioides*, *Fusarium proliferatum* and, rarely, other fusarial species. *Fusarium* species are molds that have a worldwide distribution and are found mainly as saprophytic organisms in soil. In recent years, there have been an increasing number of reports of human infection due to *Fusarium* species, mostly involving immunocompromised hosts. Some consider it the second most common mold pathogen in these patients, causing localized infection, deep skin infections and disseminated disease.

VI.2.2 Summary of treatment benefits

Voriconazole has been tested in several clinical trials worldwide to be effective in each of the indications stated above.

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

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

The study of voriconazole in candidaemia compared voriconazole with a treatment of amphotericin B followed by fluconazole in 370 patients. For candidaemia, the percentage of responders to voriconazole treatment at the end of therapy was the same as for the comparator (72%).

Voriconazole has also been studied in serious refractory *Candida* infections in 55 patients, in scedosporiosis in 38 patients, and in fusariosis in 21 patients. 'Refractory' means that the infections were not responding to treatment. Most patients receiving voriconazole treatment for these rare infections did not tolerate or did not respond to prior treatment with other antifungal medicines. 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.

In the treatment of scedosporiosis and fusariosis, 28 out of 59 patients had a complete or partial response to treatment.

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 and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment.

However as stated in the proposed SmPC, safety in patients who are pregnant and safety of use in children below 2 years of age has not been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Liver damage (Hepatic toxicity)	Changes in liver function tests may affect up to 1 in 10 people. Enlarged liver, gallbladder disease and gallstones may affect up to 1 in 100 people. Deterioration of brain function that is a serious complication of liver disease may affect up to 1 in 1000 people.	Patients suffering from, or have ever suffered from liver disease may need a lower dose of voriconazole. Liver function should be regularly monitored with blood tests.
Abnormality of the electrocardiogram (ECG) (QTc prolongation)	Abnormalities of the ECG may affect up to 1 in 100 people. This may increase the risk of developing abnormal heart rhythms.	Caution is advised in patients known to have cardiomyopathy, irregular heartbeat, slow heart rate or an abnormality of the electrocardiogram called 'long QT syndrome'.
Visual effects	Change in vision may affect more than 1 in 10 people. 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 may affect uptp 1 in 100 people. Damage to the optic nerve resulting in vision impairment, clouding of the cornea may affect up to 1 in 1000 people.	Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment.
Sunburn or severe skin reaction following exposure to light or sun (Phototoxicity)	Sunburn or severe skin reactions following exposure to light or sun may affect up to 1 in 100 people. Sunburn or severe skin reactions following exposure to light or sun are experienced more frequently in children. There is a small chance that skin cancer could develop with long term treatment with voriconazole.	Patients are advised to avoid any 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. Tell your doctor immediately if you experience sunburn, severe skin rash or blisters. If any skin disorders develop, your doctor may refer you to a dermatologist
Nerve injury resulting in numbness, pain, tingling or burning in the hands or feet	Nerve injuries may affect up to 1 in 100 people.	Patients should be made aware of this risk and if any of these symptoms are experienced,

Risk	What is known	Preventability
(Peripheral neuropathy)		treatment should be stopped and a doctor consulted.
A certain type of skin cancer (Squamous cell carcinoma)	There is a small chance that skin cancer could develop with long-term use of voriconazole.	Patients should tell their doctor immediately if they develop a skin disorder.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Any type of skin cancer (Skin cancer (non-squamous cell carcinoma))	There have been reports of skin cancer in patients treated with voriconazole for long periods of time.
Suicide-related events	Psychiatric disorders have been reported during treatment with voriconazole such as depression, hallucinations, anxiety and confusion which may increase a patient's risk for suicide and suicide-related events.

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. 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.
Effects in children (Effects in paediatrics)	The safety of this product when used in children with liver and kidney problems has not been established.
Use not in accordance with the directions of the SmPC (Off label use)	Voriconazole is indicated for use in children and adults, however the safety and effectiveness in children <2 years of age have not been studied. There is a potential for off label use in this population.
Reduced effect of the drug (Resistance)	It is possible that some infections may not respond to treatment with voriconazole therefore it is highly recommended to identify the species of Candida and test, if possible, the sensitivity of the antifungal medicine.

VI.2.5 Summary of additional 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 and the Package leaflet for voriconazole can be found in Annex 2.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex 11 of the product information; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Liver damage (hepatic toxicity)

Risk minimisation measure(s)
Objective and rationale Health Care Professionals (HCPs) to understand the risk of liver damage and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.
• **Summary description of main additional risk minimisation measures** Proposed action: HCP educational materials to be provided to prescribing physicians and pharmacists. The educational materials will comprise of: • An introductory letter • A Questions and Answers Brochure for HCPs • Several copies of the HCP Checklist • Several copies of the Patient Card The educational materials will include advice on: • Monitoring liver function through blood tests. • Importance of adherence to dosing recommendations • Management of liver damage including dose reduction and treatment discontinuation

Sunburn or severe skin reaction following exposure to light or sun (phototoxicity)

Risk minimisation measure(s)
Objective and rationale Patients and Health Care Professionals (HCPs) to understand the risk of phototoxicity and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.
• **Summary description of main additional risk minimisation measures** Proposed action: HCP educational materials to be provided to prescribing physicians and pharmacists. The educational materials will comprise of: • An introductory letter • A Questions and Answers Brochure for HCPs • Several copies of the HCP Checklist • Several copies of the Patient Card

The education materials will include advice on:

- Management of phototoxicity including treatment discontinuation
- Patient booklet will remind patients of the risks of phototoxicity, when and how to report relevant signs and symptoms and how to minimize the risks.

Certain type of skin cancer (squamous cell carcinoma)

Risk minimisation measure(s)
Objective and rationale Patients and Health Care Professionals (HCPs) to understand the risk of squamous cell carcinoma and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.
• **Summary description of main additional risk minimisation measures** Proposed action: HCP educational materials to be provided to prescribing physicians and pharmacists. The educational materials will comprise: • An introductory letter • A Questions and Answers Brochure for HCPs • Several copies of the HCP Checklist • Several copies of the Patient Card The educational materials will include advice on: • Management of squamous cell carcinoma including dose reduction and treatment discontinuation • Patient booklet will inform patients of the risks of squamous cell carcinoma, when and how to report relevant signs and symptoms and steps to minimize risk

Sigillata Limited have decided not to implement a Direct Health Professional Communication (DHPC) for a number of reasons, namely DHPCs are not described as an additional RMM in the latest innovator EPAR.

VI.2.6 Planned post authorisation development plan (if applicable)

There are no studies in the post authorisation development plan.

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**
Version 1	May 2014	Important Identified Risk • Hepatotoxicity • QT prolongation • Visual effects • Phototoxicity • Peripheral neuropathy Important Potential Risks • Skin cancer • Suicide-related events • Off label use • Drug resistance Missing information • Effects in pregnancy • Use in paediatrics with renal and hepatic insufficiency • Use in paediatrics under 2 years	Updated in line with Authority comments
Version 1.1	November 2014	Important Identified Risk • Hepatotoxicity • QT prolongation • Visual effects • Phototoxicity • Peripheral neuropathy • Squamous cell carcinoma (SCC) Important Potential Risks • Skin cancer (non SCC) • Suicide-related events Missing information • Effects in pregnancy • Effects in paediatrics • Off label use • Resistance	Inclusion of updated PI and annex 11 updated.
Version 1.2	Under review	Important Identified Risk • Hepatotoxicity • QT prolongation • Visual effects • Phototoxicity • Peripheral neuropathy • Squamous cell carcinoma (SCC) Important Potential Risks • Skin cancer (non SCC) • Suicide-related events Missing information • Effects in pregnancy	N/A

Version	Date	Safety Concerns	Comment
		• Effects in paediatrics • Off label use • Resistance	