VI.B.2 Elements for a public summary

VI.B.2.1 Overview of disease epidemiology

Product therapeutic indications:

Invasive fungal infections are serious infections from various types of fungal species and often life threatening. The most common invasive fungal infections include invasive candidosis, aspergillosis, and cryptococcosis. The incidence of invasive fungal infections (IFIs) has increased significantly over the past two decades, as the populations of patients at risk have continued to rise. The mortality rate for invasive fungal infections in neutropenic subjects is 50% for subjects with Candida infection and may approach 100% for those with invasive aspergillosis, fusariosis, or trichosporonosis.

Early and accurate diagnosis and the subsequent usage of appropriate antifungal therapy are difficult, which leads to a high mortality rate in patients with IFI. Traditional microbiological studies (direct microscopy and culture of respiratory specimens) have low sensitivity and appear positive only in the late stage of IFI. Furthermore, positive cultures do not discriminate between colonization and contamination.
Increasing use of aggressive chemotherapy, increasing number of stem cell transplantation, widespread use of antifungal prophylaxis, increasing number of organ transplant recipients and emergence of human immunodeficiency virus infection are major factors contributing to higher frequency of fungal infections.

VI.B.2.2 Summary of treatment benefits

Voriconazole is a triazole derivative of fluconazole with potent broad-spectrum activity against fungi, including filamentous fungi, serious infections caused by *Aspergillus*, *Fusarium*, *Scedosporium* as well as fluconazole-resistant *Candida albicans* and other fluconazole-resistant *Candida spp*, such as *Candida krusei*. Voriconazole is intended for patients with worsening, possibly life-threatening, fungal infections.

VI.B.2.3 Unknowns relating to treatment benefits

Safety and effectiveness in paediatric subjects below the age of two years has not been established.

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

VI.B.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Patients known to be allergic to voriconazole, other azoles or excipients of the medicinal product *(Hypersensitivity to the active substance, other azoles or to any of the excipients)*	Allergic reactions (sometimes severe), including widespread blistering rash and skin peeling have been reported with voriconazole use.	Yes, by discontinuation of the treatment and immediate medical consultation.
Liver damage *(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). 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.	Yes. Monitoring of hepatic function should be carried out in both children and adults. 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. If the liver function tests become markedly elevated, voriconazole should be discontinued, unless the medical judgment of the risk-benefit of the treatment for the patient justifies continued use.

Prolongation of the QT interval on the electrocardiogram which results in delayed repolarization of the heart *(QTc prolongation)*	Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as • Congenital or acquired QT-prolongation • Cardiomyopathy, in particular when heart failure is present • Sinus bradycardia • Existing symptomatic arrhythmias • Concomitant medicinal product that is known to prolong QT interval. Coadministration with CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine is contraindicated.	Physicians should be aware on the other medicinal products administered to the patient. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy.
Changes in vision *(Visual events (including blurred vision, optic neuritis and papilloedema))*	There have been reports of prolonged visual adverse reactions, including blurred vision, optic neuritis and papilloedema. In clinical trials, voriconazole treatment-related visual disturbances were very common. 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.	Voriconazole may cause blurring of vision or uncomfortable sensitivity to light. While affected, do not drive or operate any tools or machines. The doctor should be informed in such cases. Usually the visual disturbances are transient and fully reversible, with the majority spontaneously resolving within 60 minutes.
A chemically induced skin irritation requiring light (a type of photosensitivity) *(Phototoxicity)*	Voriconazole has been associated with phototoxicity in both children and adults. The lesions are typical of a phototoxic mechanism: painful erythema restricted to photo-exposed skin areas (without pruritus or extension) followed after several months by sequel pigmentary lesions such as lentigines and ephelides.	Yes, by avoiding intense or prolonged exposure to direct sunlight during voriconazole treatment and by using measures such as protective clothing and sunscreen with high sun protection factor (SPF). If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Voriconazole discontinuation should be considered.

Damage or disease affecting nerves, which may affect sensation, movement and other aspects of health *(Peripheral neuropathy)*	Peripheral neuropathy is a rare but reported side effect of triazole therapy in the acute management of invasive fungal infections. It manifests as a burning pain, tingling, numbness, sensitivity to touch and weakness.	Patients with commencing long-term triazole 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. Physicians treating patients with voriconazole should be aware of this association and closely monitor their patients for this potentially incapacitating and serious adverse effect.
A type of skin cancer *(Squamous cell carcinoma of the skin (SCC))*	Squamous cell carcinoma of the skin has been reported in patients, some of whom have reported prior phototoxic reactions. Prescribing voriconazole should be made with specific precautions because of its phototoxicity. First, the patient's phototype and dermatological history should be documented; second, photoprotection is mandatory; finally, given the occurrence of squamous cell carcinoma and probably of melanoma, any manifestation of phototoxicity should be acknowledged and assessed by a dermatologist and any chronic lesion should be subject to specialized follow-up, with surgical sampling and histological documentation if malignancy is suspected.	Yes, by avoiding sunlight exposure while taking voriconazole and by wearing protective clothing and using sunscreen with a high sun protection factor. In case of phototoxic reactions a dermatologist should be consulted. The doctor should check the skin frequently and thoroughly to detect and manage pre-cancerous lesions as early as possible.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Patients with risk factors for acute pancreatitis	Patients, especially children, with risk factors for acute pancreatitis (e.g. recent chemotherapy, haematopoietic stem cell translplantation (HSCT)), should be monitored closely during voriconazole treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.

Stevens-Johnson syndrome	There have been cases of exfoliative cutaneous reactions, such as Stevens-Johnson Syndrome (uncommon), toxic epidermal necrolysis (rare) and erythema multiforme (rare) during treatment with voriconazole. Stevens-Johnson Syndrome and toxic epidermal necrolysis should be considered as a differential diagnosis if patients develop prodromal flu-like symptoms (fever, malaise, rhinitis, chest pain. vomiting, sore throat, cough, diarrhea, headache, myalgia and arthralgia). If a patient develops an exfoliative cutaneous reaction voriconazole should be discontinued.
Development of resistant strains	Voriconazole drug resistance development has not been adequately studied in vitro against *Candida*, *Aspergillus*, *Scedosporium* and *Fusarium* species. The frequency of drug resistance development for the various fungi for which this drug is indicated is not known. Fungal isolates exhibiting reduced susceptibility to fluconazole or itraconazole may also show reduced susceptibility to voriconazole, suggesting cross-resistance can occur among these azoles. The relevance of cross-resistance and clinical outcome has not been fully characterized. Clinical cases where azole cross-resistance is demonstrated may require alternative antifungal therapy.
Skin cancers (non-SCC)	Premalignant skin lesions might occur particularly during long-term treatment with voriconazole. Long term exposure (treatment or prophylaxis) greater than 180 days (6 months) requires careful assessment of the benefit-risk balance.
Suicidal events	Suicidal events less commonly have been associated with voriconazole use. Spontaneous reports of “suicide attempt”, “suicidal ideation” and “completed suicide” exist. Currently only the American Prescribing Information and the product monograph mention suicidal events.
Off-label use (especially as	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. The following severe adverse events have been reported in relation with long-term voriconazole treatment: Squamous cell carcinoma of the skin (SCC) 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 discontinuation and use of alternative antifungal agents 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. Furthermore, voriconazole can also be used “off-label” to prevent and treat other opportunistic infections of HIV infection

Important missing information	
Risk	**What is known**
Use of voriconazole during pregnancy and in women of child-bearing potential	No adequate information on the use of voriconazole in pregnant women is available. 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 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. Women of child-bearing potential must always use effective contraception during treatment.
Use in breastfeeding women	The excretion of voriconazole into breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with voriconazole. In an animal study, no impairment of fertility was demonstrated in male and female rats.
Safety and efficacy in children below 2 years	Safety and effectiveness in paediatric subjects below the age of two years has not been established and no recommendations on a posology can be made. Voriconazole is indicated for paediatric patients aged two years or older. Hepatic function should be monitored in both children and adults.

VI.B.2.5 Summary of risk minimisation measures by safety concern

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures).

These additional risk minimisation measures are for the following risks:

- **A type of skin cancer (Squamous cell carcinoma of the skin)**

Risk minimisation measure(s)
These measures will enable the HCP to understand what [voriconazole] is used for, be aware of important identified risks of phototoxicity, squamous cell carcinoma of the skin of voriconazole and how they should be mitigated and managed and understand what other tools are available to communicate and remind patients of these risks.

• Summary description of main additional risk minimisation measures ▯ Voriconazole is associated with a risk of phototoxicity and skin squamous cell carcinoma (SCC). It is therefore important to adhere to the advice on the precautions against phototoxic reactions and monitoring for SCC given in the product information. If phototoxic reactions occur, refer the patient to consult a dermatologist and consider stopping voriconazole treatment ▯ If voriconazole treatment is continued despite a phototoxic reaction, the skin should be checked frequently and thoroughly to detect and manage precancerous lesions as early as possible. Stop voriconazole treatment if precancerous skin lesions or SSC are identified
A type of skin cancer (Squamous cell carcinoma of the skin) Healthcare Professional and patient education Objective and rationale Patients and HCPs to understand the risk of squamous cell carcinoma of the skin and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. Proposed action: • HCP educational materials to be provided to prescribing physicians and pharmacists including advice on: ✓ the precautions against phototoxic reactions and monitoring for SCC given in the product information ✓ when they should refer a patient for dermatologic consultation ✓ when the treatment should be stopped • Direct HCP communication prior to launch (‘Dear HCP’ letter). • Patient alert card will inform patients about the risk of SCC and the measures that should undertake

- **Liver toxicity (Hepatic toxicity)**

Risk minimisation measure(s)
These measures will enable the HCP to understand what [voriconazole] is used for, be aware of important identified risks of hepatic toxicity adverse reactions of voriconazole and how they should be mitigated and managed and understand what other tools are available to communicate and remind patients of these risks.
• Summary description of main additional risk minimisation measures Voriconazole is associated with a risk of liver toxicity. Advice on monitoring liver function in the product information has been revised. It is also important to adhere to this advice.
Liver toxicity (Hepatic toxicity) Healthcare Professional and patient education Objective and rationale Patients and HCPs to understand the risk of hepatic toxicity and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. Proposed action: • HCP educational materials to be provided to prescribing physicians and pharmacists including advice on: ✓ The frequency of monitoring for hepatic toxicity. ✓ When the treatment should be stopped. • Direct HCP communication prior to launch (‘Dear HCP’ letter).

VI.B.2.6 Planned post authorization development plan

Not applicable

VI.2.A Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Change
1.0	15.02.2014	**Important identified risks** • Hypersensitivity to the active substance, other azoles or to any of the excipients of the product • Hepatic toxicity • QTc prolongation • Visual events (including blurred vision, optic neuritis and papilloedema) • Phototoxicity • Peripheral neuropathy • Carbamazepine and long acting barbiturates induce decrease plasma concentrations of voriconazole • Significantly decreased plasma voriconazole concentrations when coadministered with high efavirenz (400 mg once daily or higher) or ritonavir (400 mg and above twice daily) doses • Increased plasma concentrations of sirolimus or everolimus when co-administered with voriconazole • Decreased plasma concentrations of voriconazole when co-administered with St John's Wort • Potential induction of ergotism when co-administration of voriconazole with ergot alkaloids **Important potential risks** • Renal adverse reactions • Patients with risk factors for acute pancreatitis • Squamous cell carcinoma of the skin • Non-infectious periostitis in transplant patients • Stevens-Johnson syndrome • Increased phenytoin plasma concentrations if used in coadministration with voriconazole • Potential uveitis (rifabutin adverse reactions) due to coadministration with rifabutin • Risk of voriconazole associated adverse reactions when coadministered with fluconazole (or other CYP2C9, CYP2C19, CYP3A4 inhibitors) • Risk of adverse reactions if coadministered with CYP2C9 and CYP3A4 substrates • Development of resistant strains **Missing information** • Use of voriconazole during pregnancy and in women of child-bearing potential • Use in breastfeeding women • Safety and efficacy in children below 2 years	Initial version

2.0	23.09.2014	**Important identified risks** • Hypersensitivity to the active substance, other azoles or to any of the excipients of the product • Hepatic toxicity • QTc prolongation • Visual events (including blurred vision, optic neuritis and papilloedema) • Phototoxicity • Peripheral neuropathy • Squamous cell carcinoma of the skin (SCC) **Important potential risks** • Patients with risk factors for acute pancreatitis • Stevens-Johnson syndrome • Development of resistant strains • Skin cancers (non-SCC) • Suicidal events • Off-label use (especially as related to prophylactic and long-term use, i.e., hepatic toxicity, phototoxicity, and skin cancer) **Missing information** • Use of voriconazole during pregnancy and in women of child-bearing potential • Use in breastfeeding women • Safety and efficacy in children below 2 years	Day 70 RMS Assessment