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Summary of the risk management plan (RMP) for Voriconazole Hospira (voriconazole)

This is a summary of the risk management plan (RMP) for Voriconazole Hospira, which details the measures to be taken in order to ensure that Voriconazole Hospira is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Voriconazole Hospira, which can be found on Voriconazole Hospira's EPAR page.

Overview of disease epidemiology

Voriconazole Hospira is used to treat adults and children over the age of two years who have the following infections caused by certain types of fungus: invasive aspergillosis, certain types of candidaemia and serious fungal infections caused by *Scedosporium* and *Fusarium*.

- Invasive aspergillosis is an infection caused by fungal spores of *Aspergillus* spp. It often starts in the lungs typically after inhalation of spores from soil or organic matter, or from air-conditioning systems and may then spread to other organs and tissues. The infection affects people whose immune system (the body's natural defenses) is impaired, such as patients undergoing chemotherapy to treat cancer, or receiving bone marrow or organ transplants. Patients with existing lung disease and risk factors are at particular risk of developing invasive aspergillosis. Invasive aspergillosis is extremely rare in patients whose immune system is functioning normally. Invasive aspergillosis is estimated to affect 5-13% of patients following bone marrow transplants, 5-25% of patients following organ transplantation and 10-20% of people with leukaemia who undergo intensive chemotherapy.
- Candidaemia (or invasive candidiasis) is a fungal infection caused by *Candida*. *Candida* yeasts are generally present in healthy humans, however, their growth is normally limited by the human immune system. In extreme cases, superficial infections of the skin or mucous membranes may spread into the bloodstream and cause candidaemia. The rate (per 100,000 population) of candidaemia ranges from 1.4 to 4.9 in Iceland, 3.5 in Spain, 1.7 to 2.9 in Finland, and 2.4 in Norway.
- Fungal infections caused by *Scedosporium* and *Fusarium* are rare. *Scedosporium* is usually found in soil, polluted water or sewage whereas *Fusarium* is an important plant pathogen. Data on the rate of occurrence of these infections in the general population are limited. Patients whose immune system is impaired are at increased risk for these infections.

Summary of treatment benefits

Voriconazole Hospira contains the active substance voriconazole. Voriconazole Hospira is available as a powder to be made up into a solution for infusion (drip) into a vein and is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Vfend.

Voriconazole acts by blocking the production of ergosterol, an essential component of fungal cell membrane. The loss of this component in the fungal cell membrane kills, or stops the growth of the fungi that cause infections.

Because Voriconazole Hospira is a generic medicine, its benefits and risks are taken as being the same as the reference medicine's. Studies in people have been limited to data from the published literature on voriconazole. No additional studies were needed as Voriconazole Hospira is a generic medicine that is given by infusion and contains the same active substance as the reference medicine Vfend.

Unknowns relating to treatment benefits

No unknowns have been identified relating to treatment benefits.

Use in pregnancy and lactation, and use in children below the age of two years, was not studied within the supporting studies.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Liver toxicity (hepatic toxicity)	Voriconazole has been associated with hepatic toxicity (elevations in blood levels of certain liver enzymes and signs of liver damage such as jaundice) and caution is advised in patients with liver problems.	Patients receiving Voriconazole Hospira must be carefully monitored for hepatic toxicity. Liver enzymes should be monitored at the start of treatment and at regular intervals thereafter. Treatment should last for as short a time as possible. 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. Patients who have any pre-existing liver problems should inform their doctor and may need a reduced dose. Detailed guidance can be found in the Summary of Product characteristics
Alteration in heart rhythm (QTc prolongation)	Voriconazole has been associated with QT interval prolongation and caution is advised in patients with heart problems such as heart failure, irregular heartbeat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QT syndrome'. Sometimes the use of voriconazole together with certain medications that can affect the	Patients who have any pre-existing heart problems and who are taking any other medicines must inform their doctor. Voriconazole Hospira must be given with extra care if used together with other medicines known to affect the QT interval. Blood levels of certain electrolytes (such as sodium, potassium and calcium) should be measured before

Risk	What is known	Preventability
	QT interval can increase the risk.	treatment and corrected if necessary.
Problems with vision	There have been rare reports of prolonged visual adverse reactions, including blurred vision, optic neuritis (inflammation of the nerve that sends signals from the eye to the brain) and papilloedema (swelling of the point where the optic nerve joins the retina). In studies most 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.	Events resolve following discontinuation of treatment.
Skin irritation in the presence of light (phototoxicity)	There have been reports of skin reactions that are associated with exposure to light whilst receiving treatment with voriconazole.	It is recommended that all patients, including children, avoid intense or prolonged exposure to direct sunlight during treatment with Voriconazole Hospira and use measures such as protective clothing and sunscreen with high sun protection factor (SPF). Patients who develop a sunburn, severe skin rash while being treated with Voriconazole Hospira should tell their doctor immediately.
Damage to the nerves (peripheral neuropathy)	Peripheral nervous system problems such as tingling or burning in the hands or feet have been observed rarely in patients on treatment with voriconazole.	Patients who experience symptoms that may be related to peripheral neuropathy should inform their doctor so additional examinations can be made or the dosage of Voriconazole Hospira adjusted.
Type of skin cancer (squamous cell carcinoma)	There have been reports of squamous cell carcinoma of the skin in patients treated with Voriconazole Hospira for longer than 6 months, some of whom had previous phototoxic reactions; the mechanism has not been established.	For patients who develop phototoxic reactions, Voriconazole Hospira should be discontinued and the patient should be referred to a dermatologist. Patients who develop bone pain should tell their doctor immediately.

Important potential risks

Risk	What is known
Skin cancers of other types (non-squamous cell carcinoma- type)	Although squamous cell carcinoma type has been reported with voriconazole there is currently limited information on a potential risk of other types of skin cancer (non-squamous cell carcinoma).

Risk	What is known
Suicide-related events (suicide and suicidal thoughts)	In clinical trials with the reference medicine Vfend, two cases related to suicide have been reported (one suicide and one case of suicidal thoughts). No risk factors or cause have currently been identified but neither of the suicide-related events from clinical trials was considered treatment related.

Missing information

Risk	What is known
Use in pregnancy	No adequate information on the use of Voriconazole Hospira in pregnant women is available. Studies in animals have shown reproductive toxicity. 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.
Use in children	There is no information on the use of voriconazole in children under 2 years of age. When studied in children aged 2 to below 12 years (285 patients), the adverse reaction profile was similar to that in adults. Post-marketing data suggest there might be a higher occurrence of skin reactions (especially erythema, redness of the skin) in the children compared to adults.
Unapproved (off-label) use	No information is currently available on off-label use of voriconazole.
Development of drug resistance (when the fungus becomes resistant to treatment with the medicine)	No information is currently available on the development of resistance against voriconazole.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Voriconazole Hospira can be found on Voriconazole Hospira 's EPAR page.

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 II of the product information which is published on Voriconazole Hospira 's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

Hospira will develop additional risk minimisation measures (Patient Alert Card, healthcare professional check list and Q&A document similar to the content of the innovator product Vfend and as agreed by the CHMP) for the following risks:

Liver injury (Hepatic toxicity)

Risk minimisation measure: Healthcare Professional and patient education
Objective and rationale: To increase healthcare professionals' awareness about the risk of liver injury (hepatic toxicity) and recommended ways to manage this risk to minimise its occurrence and its severity.
Description: The Healthcare Professional (HCP) Question and Answer Brochure: • Advises HCPs on the risks of 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 how to obtain additional copies. The Healthcare Professional (HCP) Checklist: • Reminds HCPs of the risks of 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 hepatotoxicity, what to look for, how and when to seek immediate attention.

Skin irritation in the presence of light (phototoxicity) and skin cancer (squamous cell cancer)

Risk minimisation measure: Healthcare Professional and patient education
Objective and rationale: To increase healthcare professionals' patients' awareness on the risk of phototoxicity (skin irritations in the presence of light) and skin cancer (squameous cell cancer) and recommended ways to manage this risk to minimise its occurrence and its severity.
Description: Healthcare Professional (HCP) Question and Answer Brochure: • Advises HCPs on the risks of phototoxicity and squameous cell cancer 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. Healthcare Professional (HCP) Checklist: • Reminds HCPs of the risks of phototoxicity and squameous cell cancer 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 and squameous cell cancer, 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 • Reminds patients of the risk of phototoxicity. • Reminds patients when and how to report relevant signs and symptoms of phototoxicity and squameous cell cancer.

Risk minimisation measure: Healthcare Professional and patient education
• Reminds patients to take steps to minimize the risk of skin reactions (by avoiding exposure to direct sunlight, use of a sunscreen and protective clothing) and inform HCPs if they experience relevant skin abnormalities.

Planned post-authorisation development plan

No post authorisation studies are planned, and no post authorisation studies are identified as being required as conditions of the marketing authorisation approval.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable

This summary was last updated in 06-2015.