5.2 Part VI.2 Elements for a Public Summary

5.2.1 Part VI.2.1 Overview of disease epidemiology

Aspergillosis which spreads to many organ systems (Invasive aspergillosis)

The mold Aspergillus primarily affects the lungs, causing 4 main syndromes: allergic aspergillosis of the lung and bronchia (ABPA), chronic cell-destructing Aspergillus pneumonia (CNPA), aspergilloma (a clump of fungus in a cavity like the lung), and invasive aspergillosis. However, in patients whose immunity is severely compromised, Aspergillus may spread via the blood stream beyond the lungs. 0.25-0.8% of people with asthma and approximately 7% of patients with cystic fibrosis/mucoviscidosis are estimated to have ABPA. The frequency of ABPA in people with asthma who take steroids or have associated enlargement of the bronchia (bronchiectasis) is higher, estimated at 7-10%. CNPA is rare. The frequency may be underestimated. 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 leukemia. Although it has been described in individuals who have a healthy immunity, invasive aspergillosis is exceedingly uncommon in this population. Aspergilloma is not rare in patients with chronic cavity-forming lung disease and cystic fibrosis. In one survey of patients with cavitary lung disease due to tuberculosis, 17% developed aspergilloma. [Harman EM, 2014]

Candidemia in non-neutropenic patients (Candida in the blood in patients without decreased white blood cells)

Candida are the most common cause of fungal infection in patients with compromised immunity. In persons with systemic infections, Candida are the fourth most commonly detected pathogens from blood cultures. Clinical and autopsy studies show a marked increase in the frequency of disseminated candidiasis, a diffuse disease process by pathogen spread via blood stream. Persons at the extremes of age (neonates and adults >65 years) are most susceptible to candidal colonization. Very-low-birth-weight and extremely-low-birth-weight infants are at high risk for candida sepsis developing after the age of 3 days. [Hidalgo JA, 2014]

Fluconazole-resistant serious *Candida* infections (including *C. krusei*), which spread to many organ systems

Fungi are a major causes of human disease, especially among patients with compromised immunity and those hospitalized with serious underlying diseases. Candida species, a group of yeasts, are the fourth leading cause of bloodstream infection (BSI) occurring in hospitals in the United States (US), accounting for 8% to 10% of all BSIs acquired in the hospital. 29 of 100,000 US people were diagnosed with BSI in 2003, 24 of 10,000 who were discharged from hospitals. Annually 10,500 to 42,000 US Americans suffer a BSI caused by Candida. The type *Candida krusei* is an important germ among patients with blood cell cancer and among patients who receive blood and bone marrow transplants. This yeast accounts for 2% to 4% worldwide of all *Candida* bloodstream infections, although higher frequencies have been reported for cancer patients in Europe and the United States. [Pfaller MA, 2007].

Fungal infections caused by *Scedosporium* spp. and *Fusarium* spp

Scedosporium fungi are increasingly recognized as causes of therapy-resistant life-threatening infections in patients with compromised immunity. They also cause mycetoma, a disease with granuloma formation by *Scedosporium*. [Cortez KJ, 2008] Mycetoma caused by fungi is more common in areas where the average rainfall is scarce (ie, < 350 mm). In Sudanese hospitals, at least 300-400 patients are diagnosed with mycetoma (caused by different germs) every year. Mycetoma is typical for Africa, from Sudan and Somalia through Mauritania and Senegal and also typical for Mexico and India and can be found in natives of areas of Central and South America and the Middle or Far East between latitudes 15°S and 30°N. In the US, mycetoma is rare. Some cases are due to increasing international travel. Rarely, mycetoma is acquired on US soil. [Anía BJ, 2013] *Scedosporium* fungi can also cause colonization of the airways, infections of the lung and sinuses (cavities in the bones near the nose), other localized infections, and extended, diffuse infections. The most common sites of infection are the lungs, sinuses, bones, joints, eyes, and brain. [Cortez KJ, 2008]

Fusarium fungi are widely distributed in soil and in association with plants. They may cause infections penetrating the entire body and bloodstream, infections of the lung and the blood stream, which usually do not occur in a healthy human. In healthy people, infections of the nails and the front part of the eye can occur. [Walsh TJ, 1996; Singh D, 2013]

5.2.2 Part VI.2.2 Summary of treatment benefits

Aspergillosis which spreads to many organ systems (Invasive aspergillosis)

The efficacy and survival benefit of voriconazole compared to amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in a study in 277 patients with compromised immunity treated for 12 weeks. Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of 7 days. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12 hours. Median duration of IV voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of oral voriconazole therapy was 76 days (range 2-232 days). 53% of voriconazole-treated patients compared to 31% of patients treated with amphotericin B had complete or partial resolution of all attributable symptoms and abnormalities in related investigations. The survival rate for voriconazole was higher than that for amphotericin B and a clinical benefit was shown in favour of voriconazole.

Also a previous study showed a positive outcome in patients with risk factors for a poor prognosis, including graft versus host disease (a condition where transplanted immune cells attack the patient's body cells), and cerebral infections (normally associated with almost 100% mortality).

Candidemia in non-neutropenic patients (Candida in the blood in patients without decreased white blood cells)

The efficacy of voriconazole compared to amphotericin B followed by fluconazole in the primary treatment of candidemia was demonstrated in a study with 370 non-neutropenic patients (above 12 years of age) with candidemia. 248 of them were treated with voriconazole. The treatment duration was 15 days in both treatment groups. Successful therapy was defined as resolution/improvement in all clinical symptoms of infection with elimination of Candida

from blood and infected deep tissue 12 weeks after the end of therapy (EOT). A successful response was seen in 41% of patients in both treatment groups. In a secondary analysis with inclusion of assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT), voriconazole and the therapy with amphotericin B followed by fluconazole had successful response rates of 65% and 71%, respectively.

Serious intractable *Candida* infections

A study comprised 55 patients with serious intractable *Candida* infections (including bloodstream infection with Candida and extended, diffuse and other invasive candidiasis) where prior antifungal treatment, particularly with fluconazole, had been ineffective. Successful therapy was seen in 24 patients (15 complete successes, 9 partial successes). In 3 of 3 infections with fluconazole-resistant Candida krusei a complete therapy success was observed, and in 6 of 8 patients with *Candida glabrata* infections 5 complete and 1 partial therapy success was seen.

***Scedosporium* and *Fusarium* infections**

Scedosporium spp.: Successful response to voriconazole therapy was seen in 16 (6 complete, 10 partial therapy successes) of 28 patients with *S. apiospermum* and in 2 (both partial therapy successes) of 7 patients with *S. prolificans* infection. In addition, a successful therapy was seen in 1 of 3 patients with infections caused by more than one organism including *Scedosporium* spp.

Fusarium spp.: Seven (3 complete, 4 partial therapy successes) of 17 patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had extended, diffuse infection. Four additional patients with *Fusarium* caused infections had an infection caused by several organisms; 2 of them had a successful outcome.

The majority of patients receiving voriconazole treatment of the above mentioned rare infections were intolerant of, or not susceptible to, prior antifungal therapy.

Prophylaxis of fungal infections which spread to many organ systems

Voriconazole was compared to itraconazole as prophylaxis in a study of adult and adolescent recipients of blood cell forming stem cell transplant (HSCT) without prior proven or probable fungal infection spreading to many organ systems (IFI). Success was defined as the ability to continue the study drug prophylaxis for 100 days after HSCT (without stopping for >14 days) and survival with no proven or probable IFI for 180 days after HSCT. The treatment group included 465 patients with 45% of patients having acute myeloid leukemia (AML). 224 received voriconazole and 241 received itraconazole. The median duration of study drug prophylaxis was 96 days for voriconazole and 68 days for itraconazole in the treatment group. Success at day 180 was observed in 48.7% of the patients treated with voriconazole and 33.2% of those treated with itraconazole. In patients with AML,56.1% of patients treated with voriconazole and 41.3% of patients treated with intraconazole showed therapy success at day 180.

In patients with prior proven or probable IFI, voriconazole was investigated as prophylaxis in a study of adult HSCT recipients. The primary endpoint was the rate of occurrence of proven

and probable IFI during the first year after HSCT. The therapy group included 40 patients with prior IFI, including 31 with infection with Aspergillus, 5 with infection with Candida, and 4 with other IFI. The median duration of study drug prophylaxis was 95.5 days. Proven or probable IFIs developed in 7.5% of patients during the first year after HSCT. 80.0% of patients had survived at day 180 and at 1 year 70.0%.

5.2.3 Part VI.2.3 Unknowns relating to treatment benefits

Laboratory activity of voriconazole against the fungi Curvularia and Sporothrix has been shown, but the clinical value is unknown.

5.2.4 Part VI.2.4 Summary of safety concerns

The following safety concerns apply for all Voriconazole formulations:

Table 0-5 Important identified risks

Risk	What is known	Preventability
Skin irritation due to light (Phototoxicity)	An increased sensitivity of skin to the sun's UV rays can occur. Bullous photosensitivity is a rare side effect of voriconazole. Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children.	The patient should 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). These precautions are also applicable to children. While being treated with voriconazole the doctor should be contacted immediately if the patient develops sunburn or a severe skin rash or blisters. Voriconazole may cause … or uncomfortable sensitivity to light. If affected, patient is advised not to drive or operate any tools or machines and inform the doctor regarding this situation.
Cancer of outermost layers of skin cells (Squamous cell carcinoma)	There is a small chance that skin cancer could develop with long-term use of voriconazole.	If a patient develops skin disorders, the doctor should refer him/her to a dermatologist, who after consultation may decide that it is important for the patient to be seen on a regular basis. Doctor should be informed regarding the simultaneous use of voriconazole with vinca alkaloids eg. vincristine and vinblastine (drugs used in treating cancer) and everolimus

Risk	What is known	Preventability
		(used for treating advanced kidney cancer and in transplant patients) so that a dose adjustment or monitoring may be required to ensure that the medicines still have the desired effect.
Liver toxicity (Hepatic toxicity)	Voriconazole is known to affect the liver. Jaundice, inflammation of the liver and changes in blood test of liver function occur commonly (may affect up to 1 in 10 people) under voriconazole therapy. Enlarged liver, hepatitis, and liver failure occur uncommonly (may affect up to 1 in 100 people) under voriconazole therapy. Deterioration of brain function occurs that is a serious complication of liver disease and loss of consciousness due to liver failure occurs rarely (may affect up to 1 in 1000 people) under voriconazole therapy.	The doctor should monitor the function of the liver by doing blood tests. The patient should advise the doctor if he/she has any stomach pains or if the stools have a different consistency. A patient should talk to his/her doctor if he/she is suffering from, or has ever suffered from liver disease. If he/she has liver disease, the doctor may prescribe a lower dose of voriconazole. The doctor should also monitor the liver function while the patient is being treated with voriconazole by doing blood tests. If jaundice and changes in blood tests of liver function occur, the treatment should be stopped and a doctor should be consulted immediately.
Typical changes of the electrocardiogram (ECG) (QTc prolongation)	Heart rhythm problems including very fast heartbeat, very slow heartbeat, fainting and abnormal ECG occurs uncommonly (may affect up to 1 in 100 people)and severe heart rhythm problems that may be life threatening occur rarely (may affect up to 1 in 1000 people) under voriconazole therapy.	A patient should talk to his/her doctor if he/she is known to have heart muscle disease, irregular heartbeat, slow heart rate or an abnormality of ECG called ‘long QTc syndrome’. A patient is advised not to take voriconazole along with quinidine (drug used to treat irregular heart beat) and doctor or pharmacist should be informed if the patient had taken the drug recently. Doctor should be informed if the patient experiences increased heart rate after the voriconazole infusion so that the doctor may stop the infusion.

Risk	What is known	Preventability
Drug induced eye-related side effects (Visual events)	Voriconazole may cause blurring of vision or uncomfortable sensitivity to light. While affected, do not drive or operate any tools or machines. Visual impairment/disturbances (change in vision) occurs very commonly (may affect more than 1 in 10 people) under voriconazole therapy. Bleeding in the eye occurs commonly (may affect up to 1 in 10 people) under voriconazole therapy. 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 and optic disc swelling occur uncommonly (may affect up to 1 in 100 people) under voriconazole therapy. Damage to the optic nerve resulting in vision impairment, and clouding of the cornea occurs rarely (may affect up to 1 in 1000 people) under voriconazole therapy.	The doctor should be contacted if the patient experiences impairment of vision or uncomfortable sensitivity to light.
Disorder of nerves which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected (Peripheral neuropathy)	Nerve injury resulting in numbness, pain, tingling or burning in the hands or feet and problems with balance or coordination are uncommon side effects of voriconazole, a disorder in which the body's immune system attacks part of the peripheral nervous system a rare side effect.	Like all medicines, voriconazole can cause side effects, although not everybody gets them. If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention. If any of the side effects persist or are troublesome, the doctor should be contacted.

Table 0-6 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Skin cancer (other than the cancer of outermost layers of skin cells) (Skin cancer (non-SCC)	Patient 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 patients develop skin disorders, doctor may refer patients to a dermatologist (skin specialist), who after consultation may decide that it is important for patient to be seen on a regular basis. The frequency of skin cancer is not known and should be reported to the doctor immediately if any changes in the skin occur. There have been reports of skin cancer in patients treated with voriconazole for long periods of time. There is a small chance that skin cancer could develop with the long-term use of voriconazole.
Suicide-related events	Between January 2004 and October 2012, 1 individuals taking voriconazole reported suicidal ideation to the Food and Drug Administration (FDA) (Health Authority of the United States of America). A total of 4,233 voriconazole drug adverse event reports were made with the FDA during this time period. [MedsFacts, 2013]

Table 0-7 Missing information

Risk	What is known
Effects in pregnancy	There are no adequate data on the use of voriconazole in pregnant women available. Voriconazole must not be taken during pregnancy, unless indicated by the doctor. Effective contraception must be used in women of childbearing potential. The doctor should be contacted immediately if a woman becomes pregnant while taking voriconazole.
Effects in pediatrics	Voriconazole should not be given to children younger than 2 years of age. The safety and efficacy of children below 2 years has not been established. Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children. If the child develops skin disorders, doctor may refer you to a dermatologist, who after consultation may decide that it is important for the child to be seen on a regular basis. If any of these side effects persist or are troublesome, please tell your doctor.

Risk	What is known
	It is recommended to initiate the therapy with intravenous regimen, and oral regimen should be considered only after there is a significant clinical improvement. Use in children aged 2 to <12 years with liver or kidney disease has not been studied. Regularly monitoring of liver function should be done. In case of treatment related side effects discontinuation of voriconazole and use of alternative antifungal agents must be considered.
Use of medications other than their intended indications (Off-label use)	Voriconazole should not be given to children younger than 2 years of age. There are recommended doses for children teenagers and adults. Tablets must only be given if the child is able to swallow tablets. If a patient is taking voriconazole for prevention of fungal infections, the doctor may stop giving voriconazole if the patient develops treatment related side effects.
Non-susceptibility of a fungus to voriconazole (Resistance)	The activity of voriconazole against Candida is not uniform. More voriconazole is necessary to treat infections with fluconazole-resistant fungi than for those with fluconazole-susceptible fungi. The fungus should be identified and therapy performed according to an antifungal susceptibility testing performed prior to therapy.

5.2.5 Part VI.2.5 Summary of risk minimization measures by safety concern

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

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

These additional risk minimization measures are for the following risks:

Table 0-8 (Liver toxicity) Hepatic toxicity

Risk minimization measure(s)
The following educational material will be provided: 1) HCP Q&A Brochure 2) HCP checklist
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.

Proposed actions:
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.

Table 0-9 (Skin irritation due to light) Phototoxicity

Risk minimization measure(s)

The following educational material will be provided:

1) HCP Q&A Brochure
2) HCP checklist
3) Patient Alert Card

Objective and rationale:
To increase healthcare professionals' patients' awareness on the risk of phototoxicity (skin irritations in the presence of light) and recommended ways to manage this risk to minimise its occurrence and its severity.

Proposed actions:
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.

• 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.

Table 0-10 Cancer of outermost layers of skin cells (Squamous cell carcinoma)

Risk minimization measure(s)
The following educational material will be provided: 1) HCP Q&A Brochure 2) HCP checklist 3) Patient Alert Card
Objective and rationale: To increase healthcare professionals' patients' awareness on the risk of skin cancer (squamous cell carcinoma) and recommended ways to manage this risk to minimise its occurrence and its severity. Proposed actions: 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. • 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.

5.2.6 Part VI.2.6 Planned post authorization development plan

None

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

Table 0-11 Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
RMP Voriconazole 200 mg film-coated tablet; 50 mg film-coated tablet; 200 mg powder for solution for infusion. Version 1.0	22 Feb 2013	**Identified risks:** QT prolongation and Torsade de Pointes Hepatic toxicity Visual effects (optic neuritis, papilloedema) Phototoxicity Peripheral neuropathy Periostitis **Potential risks:** Skin cancer (including squamous cell carcinoma) Cardiac failure Suicide-related events Resistance Interaction with CYP450 inducers (Phenytoin, Efavirenz, Rifabutin, Ritonavir) **Missing information:** Long-term use impact focusing on hepatic toxicity, Phototoxicity, and skin cancer Off-label use in pediatric population Pregancy and Lactation	None
RMP Voriconazole 200 mg film-coated tablet; 50 mg film-coated tablet; 200 mg powder for solution for infusion. Version 2.0	17 Nov 2014	None	Inclusion of applicable RMP content in the valid EU-RMP template. Update of the currently available information on all included risks. No new risk, additional pharmacovigilance or risk minimization activity added.
RMP Voriconazole 200 mg film-coated tablet; 50 mg film-coated tablet; 200 mg powder for solution for	17 Nov 2014	Skin cancer (including squamous cell carcinoma) Resistance Interaction with CYP450 inducers (Phenytoin, Efavirenz, Rifabutin, Ritonavir) Long-term use impact focusing on hepatic toxicity, phototoxicity, and skin cancer	Changed to important identified risks

Version	Date	Safety Concerns	Comment
infusion. Version 2.0			
RMP Version 3.0	17 Nov 2015	Additional risk minimization measures for the risks hepatic toxicity, phototoxicity, Skin cancer (including cancer of outermost layers of skin cells) and long-term use impact focusing on hepatic toxicity, phototoxicity, and skin cancer	Addition of Q&A brochure, HCP checklist and patient alert material Inclusion of new figures in sales and MA status in chapters according to the current time point
RMP Version 3.1	29 Feb 2016		Following the RMS preliminary assessment report of NL/H/2583/001-002/IB/005 and NL/H/2584/001-002/IB/003 for Voriconazole 50 mg and 200 mg film-coated tablets received on 17 Feb 2016 and NL/H/2835/001/IB/003 for voriconazole 200 mg powder for solution for infusion received on 22 Feb 2016, the following changes were made.
		Important identified risks: • Phototoxicity • Squamous cell carcinoma • Hepatic toxicity • QTc prolongation • Visual events • Peripheral neuropathy **Important potential risks:** • Skin cancer (non-SCC) • Suicide-related events **Missing information:** • Effects in pregnancy • Effects in pediatrics • Off-label use • Resistance	The safety concerns were updated in Part II Module SVIII, Part V.1, Part V.3, Part VI.1.1, and Part VI.1.4. Part VI.2.4 Summary of safety concerns was updated for safety concerns. Updated SmPC and PIL were included in the Annex 2 Annex 3 was updated with the current marketing authorization data Annex 10 was updated with the key elements of the educational material.