13.2 Part VI.2 Elements for a Public Summary

13.2.1 Part VI.2.1 Overview of disease epidemiology

Almost 20,000 kidney transplants were performed in the EU in the year 2014. In general, more men than women receive a renal transplant. The conditions that most frequently cause the

kidney to fail and therefore a transplant to be needed are kidney disease due to diabetes, uncontrolled hypertension, glomerulonephritis, and cystic kidney disease.

13.2.2 Part VI.2.2 Summary of treatment benefits

Myfortic gastro-resistant tablets belong to the class of drugs known as immunosuppressants. Immunosuppressants reduce body's response to anything that it sees as "foreign" – which includes transplant organs. Myfortic is used to prevent the body from rejecting a transplanted kidney in adult patients. Myfortic is used together with other medicines containing cyclosporine and corticosteroids.

13.2.3 Part VI.2.3 Unknowns relating to treatment benefits

Not applicable.

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-5 Important identified risks

Risk	What is known	Preventability
Decreased capacity of a part of bone to produce all 3 types of blood cells (white and red blood cells, platelets),infections and bleeding (Bone marrow depression, associated infections and hemorrhages)	Blood dyscrasias (e.g. neutropenia or anemia may be related to MPA itself, concomitant medications, viral infections, or some combination of these causes. Pure red cell aplasia (PRCA) has been reported in patients treated with MPA derivatives in combination with other immunosuppressive agents Leukopenia (decrease in a specific type of white cells in the blood, i.e. so called leukocytes) is observed very commonly (≥ 1/10) in patients treated with MPS (MPS), anaemia (blood disorder in which body doesn't have enough red blood cells) and thrombocytopenia (not enough platelets present in the blood) commonly (≥ 1/100 to < 1/10). Lymphopenia (abnormally low level of a specific type of white cells in the blood, i.e. so called lymphocytes), neutropenia (decrease in a specific type of white blood cells, i.e. so called neutrophils) and lymphadenopathy (swollen or enlarged lymph nodes) have been reported. Agranulocytosis has been identified as adverse drug reactions from post marketing experience.	Patients receiving MPS should be instructed to inform their doctor before taking it as well as during the treatment. If any evidence of infection appears such as a fever or sore throat, unexpected bruising, bleeding or any other manifestation of bone marrow depression, patients should inform their doctors as they may need urgent medical treatment. PRCA may resolve with dose reduction or cessation of therapy. Changes to MPS therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection Regular monitoring of patients taking MPS is advised. Patients taking MPS should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If blood disorders occur (e.g. neutropenia with absolute neutrophil count <1.5 x 10^3/µl or anaemia) it may be appropriate

Risk	What is known	Preventability
	Neutropenia or anaemia may be related to MPS itself, or when co-administered with other medications, viral infections, or some combination of these causes. Isolated cases of abnormal neutrophil structure and form, including the acquired Pelger-Huet anomaly (blood condition in which the nuclei of several types of white blood cells have unusual shape), have been observed in patients treated with MPA derivatives. These changes are not associated with impaired neutrophil function. These changes may suggest the presence of immature neutrophils in blood in haematological investigations, which may be mistakenly interpreted as a sign of infection in immunosuppressed patients such as those that receive MPS. MPS reduces body's defenses which prevents transplant rejection. Furthermore, as a result, the body is not as good as normal at fighting infections. This means patients may catch more infections than usual. This includes infections of the brain, skin, mouth, stomach and gut, lungs and urinary system. Other problems such as bleeding or bruising may also occur.	to interrupt or discontinue the treatment.
Allergic reactions (Hypersensitivity)	Hypersensitivity reactions to MPS have been observed. Reactions like rash, pruritus, hypotension (low blood pressure), and chest pain have been observed in clinical trials and post marketing reports.	Patients should not take MPS if they are allergic to MPA or to any of the other ingredients of this medicine. Patients should immediately inform their doctor if they have a rash, swelling of face, lips, tongue or throat, with difficulty breathing as they may be having a serious allergic reaction to the medicine and may need urgent medical treatment.
Drug interaction when MPS is concomitantly administered with drugs that interfere with the liver circulation wherein the	There is a risk of interaction with other medications (Azathioprine, Live vaccine, Gastroprotective Aciclovir agents,	Concomitant medication not recommended Azathioprine, Live vaccine

Risk	What is known	Preventability
drug is reabsorbed into the blood. (Drug-drug interactions: drugs interfering with enterohepatic circulation)	Ganciclovir, Tacrolimus, and Ciclosporin) Oral contraceptives and drugs that interfere with enterohepatic circulation like cholestyramine or activated charcoal may result in therapeutic failure due to a reduced systemic MPS exposure and reduced efficacy.	Concomitant medication to be considered: Gastroprotective Aciclovir agents, Ganciclovir, Tacrolimus, Ciclosporin Caution should be exercised with medicinal products that interfere with enterohepatic circulation. Patients should inform their doctor or pharmacist if they are taking cholestyramine – used to treat high cholesterol, before starting the treatment with MPS.
Disorders of digestive system including erosion of linings of stomach and gut and associated bleeding (Gastrointestinal disorders including ulceration and hemorrhage)	MPA (mycophenolic acid) derivatives have been associated with an increased occurrence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration and haemorrhage and perforation. Diarrhoea has been observed very commonly (≥ 1/10), abdominal distension (gas or fluid, accumulate in the abdomen causing its outward expansion), abdominal pain, constipation (bowel movements are difficult or happen less often than normal), dyspepsia (indigestion), flatulence (accumulation of gas in stomach or gut), gastritis (inflammation of the lining of the stomach), nausea and vomiting are common (≥1/100), gastrointestinal hemorrhage, peritonitis (swelling of membrane of internal organs), ileus (a painful obstruction of ileum, which is part of small gut, or other parts of the gut), esophagitis (swelling of the lining of the food pipe), pancreatitis (inflammation of pancreas), stomatitis (sore mouth), gingival hyperplasia, gastro-oesophageal reflux disease, eructation, halitosis (bad breath), tongue discoloration, dry mouth are uncommon (≥1/1,000), gastric ulcer (painful open sore or raw area in	MPS should be administered with caution in patients with active serious digestive system disease. Patients should inform their doctor before taking MPS if they have or ever had any problems with their digestive system, such as stomach ulcers. Patients should also inform their doctor or pharmacist if they are taking antacids or proton pump inhibitors – used for acid problems in stomach such as indigestion, before starting the treatment.

Risk	What is known	Preventability
	the lining of the stomach), duodenal ulcer (painful open sore or raw area in the lining of duodenum i.e. part of small gut), colitis (swelling of the lining of the large gut), in which MPS was administered together with ciclosporin microemulsion and corticosteroids.	
Spontaneous abortion and congenital malformations in women(maternal exposure)	Use of Myfortic during pregnancy may harm the unborn child and increase the risk of pregnancy, spontaneous abortion (rate of 45% to 49%) and risk of congenital malformation (rate of 23% to 27%)	Yes, warning physicians and patients (male and female) about avoiding pregnancy during treatment and use of contraceptive.

Table 13-6 Important potential risks

Risk	What is known
Capable of causing cancer (Carcinogenicity)	Patient receiving immunosuppressive regimens involving combinations of drugs, including MPA, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. Micronucleus test in vitro and vivo was positive. However, Mycophenolic acid (as sodium salt) was not tumourigenic in rats and mice in the animal carcinogenicity studies. Lymphoproliferative disease or lymphoma developed in 2 *de novo* (0.9%) patients and in 2 maintenance patients (1.3%) receiving MPS for up to 1 year. Non-melanoma skin carcinomas occurred in 0.9% of de novo and 1.8% of maintenance patients receiving MPS for up to 1 year; other types of malignancy occurred in 0.5% of de novo and 0.6% of maintenance patients.
Genotoxicity	Studies showed a potential of MPA to cause chromosomal aberrations. These effects can be related to the pharmacodynamic mode of action, i.e. inhibition of nucleotide synthesis in sensitive cells. Other in vitro tests for detection of gene mutation did not demonstrate genotoxic activity.
Increased risk of vaccination related diseases	Patients should be advised that during treatment with MPA vaccinations may be less effective and the use of the live attenuated vaccines should be avoided. Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.
Lack of efficacy of vaccination	Patients should be advised that during treatment with MPA vaccinations may be less effective and the use of the live attenuated vaccines should be avoided. Influenza vaccination may be of value. Prescribers should refer to national guidelines for influenza vaccination.

Risk	What is known
Off label use	Myfortic has been used in other indications than that is specified in the SmPC. No additional trend or pattern in safety profile has been identified with available data.
Spontaneous abortion and congenital malformations in men (paternal exposure)	The risk of harmful effects on sperm cells cannot completely be excluded.

Table 13-7 Missing information

Risk	What is known
Use in lactation	No data is available
Use in pediatric population	Myfortic has been used in pediatric patients for different indications. No additional trend or pattern in safety profile has been identified with available data.

13.3 Part VI.2.5 Summary of additional risk minimization 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, their risks and recommendations for minimizing them. An abbreviated version of this information in lay language is provided to patients in the form of the Package Leaflet. The measures in these documents are known as routine risk minimization measures.

These additional risk minimization measures are for the following risks:

Table 13-8 Spontaneous abortion and congenital malformations in women (maternal exposure)

Risk minimization measures: Physician and patient education
Objective and rationale: To closely monitor, evaluate and further characterize symptoms of this risk. To identify and/or characterize the following: • Clinical characteristics of the pregnancy outcomes • Types of patients at risk (demographic factors, underlying diseases) • Risk factors • Characteristics of exposure (dose, duration, exposure during 1st trimester, co-medications) Reporting rates of pregnancy reports **Main additional risk minimization measures:** Physicians and Patient educational materials: An educational material program has been developed and distributed to physicians and patients to ensure an increased understanding of the safe and effective use of Myfortic, including the prevention of pregnancy occurrence whilst on Myfortic and collection of information in the event of pregnancy.

Table 13-9 Spontaneous abortion and congenital malformations in men (paternal exposure)

Risk minimization measures: Physician and patient education
Objective and rationale:

Risk minimization measures: Physician and patient education
To closely monitor, evaluate and further characterize symptoms of this risk. To identify and/or characterize the following: • Clinical characteristics of the pregnancy outcomes • Types of patients at risk (demographic factors, underlying diseases) • Risk factors • Characteristics of exposure female partners of male patients (dose, duration, co-medications) Reporting rates of pregnancy reports **Main additional risk minimization measures:** Physicians and Patient educational materials: An educational material program has been developed and distributed to physicians and patients to ensure an increased understanding of the safe and effective use of Myfortic, including the prevention of pregnancy occurrence whilst on Myfortic and collection of information in the event of pregnancy.

13.4 Part VI.2.6 Planned post authorization development plan

Not applicable.

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

Table 13-10 Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.4	18-Oct-2017	**Important identified risks:** Bone marrow depression, associated infections and hemorrhages Hypersensitivity Drug-drug interactions: drugs interfering with enterohepatic circulation Gastrointestinal disorders including ulceration and hemorrhage Reproductive toxicity (teratogenicity and embryolethality) **Important Potential Risks:** Carcinogenicity Genotoxicity Increase of vaccination related disease Lack of effect of vaccinations Off-label use **Important missing information :** Use in lactation Use in pediatric patients	Pharmacovigilance activities: Pregnancy Questionnaire Risk Minimization activities: Educational Material

Version	Date	Safety Concerns	Comment
2.0	21-Feb-2018	No update on safety concerns	Pharmacovigilance activities: No update Risk Minimization activities: Updated Educational Material
2.1	05-Jul-2018	Based on the PRAC assessment report for procedure PSUSA-10550-201705, the important Identified risk, “Reproductive toxicity (teratogenicity and embryolethality)” was changed to identified risk of “Spontaneous abortion and congenital malformations in women (maternal exposure)” and a potential risk of “Spontaneous abortion and congenital malformations in men (paternal exposure)” .	Pharmacovigilance activities: No update Risk Minimization activities: Updated Educational Material