VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Transplantation is the act of transferring cells, tissues, or organs from one site to another. The malfunction of an organ system can be corrected with transplantation of an organ (eg, kidney, liver,

heart, lung, or pancreas) from a donor. However, the immune system remains the most formidable barrier to transplantation as a routine medical treatment. The immune system has developed elaborate and effective mechanisms to combat foreign agents. These mechanisms are also involved in the rejection of transplanted organs, which are recognized as foreign by the recipient's immune system (Malhotra and Malu 2013). In some cases, recipient's tissue can be attacked by the immune cells (white blood cells) in the tissue (the graft) as they recognize the recipient (the host) as "foreign". This is called Graft-versus-host disease (GVHD) (Sweetman SC ed, 2013). Acute attack usually develops during the first 100 days after transplantation and has been estimated to develop in 6% to 90% of recipients. Chronic graft-versus-host disease (GVHD) is the most common late-occurring complication of allogeneic stem cell transplantation and is the most common cause of nonrelapse mortality more than 2 years after allogeneic transplantation. In patients surviving beyond 100 days posttransplant, chronic GVHD develops in up to 60% of patients with marrow transplants from HLA-matched siblings and in up to 70% of those with unrelated donors (Sweetman SC ed, 2013).

Psoriasis is a chronic inflammatory, genetic skin disorder that is spread throughout the system, affected by environmental factors, and characterized by reddened, scaly patches with small bumps on the skin that fill with fluid or pus and plaques that are frequently itchy (Sweetman SC ed, 2013). The prevalence of psoriasis is considered to be about 2% of the population; more specifically, 0.6% to 4.8% in the United States (US), while in Northern Europe and Scandinavia it is estimated to be between 1.5% and 3%. Psoriatic arthritis affects approximately 0.1% to 0.25% of the general US population and may affect as many as 42% of patients with psoriasis. Psoriasis is most commonly a disease of white persons, affecting up to 3% of whites in the US with study rates that range from 1.4% to 4.6%. The annual incidence rate for psoriasis in whites is estimated to be 60 cases per 100,000 persons (Sweetman SC ed, 2013).

Rheumatoid arthritis is an inflammatory, system-wide spread autoimmune disorder characterized by symmetric, erosive synovitis that frequently leads to joint destruction, deformity, and disability (Sweetman SC ed, 2013). In the United States, nearly 1.3 million adults aged 18 years and older have been estimated to have rheumatoid arthritis. Prevalence estimates from developed countries range from approximately 0.5% to 1% of the adult population; however, in certain populations such as the Pima Indians, the prevalence is higher. The prevalence of rheumatoid arthritis is approximately 2 times higher in women than in men. The onset of rheumatoid arthritis is earlier for women, frequently occurring during the childbearing years. The incidence of rheumatoid arthritis increases with advancing age with peak incidence occurring between the ages of 60 and 69 for both men and women. Approximately 2% to 3% of persons over 60 years of age are affected by rheumatoid arthritis (Sweetman SC ed, 2013).

Atopic dermatitis (AD) is a disease with acute skin flare-ups with itchy rash that usually presents in infancy or childhood, but can persist or start in adulthood – 40% patients are aged 16 or older (Sweetman SC ed, 2013). AD occurs during the first year of life in 50% to 70% of patients, 90% of children are affected by age 5 and late onset is unusual. AD affects 10% to 20% of children and 1% to 3% of adults worldwide. The prevalence has dramatically increased in recent years in industrialized countries and urban regions. Increased exposure to pollutants, indoor allergens, and the use of antibiotics may contribute to the rise. AD is more common among small families and in higher socioeconomic groups. A large population study reported the prevalence of atopic dermatitis (AD) to be 10% in children younger than 2 years, 2% in 12 to 15 year olds, and 10% in adults over 40 years of age (Sweetman SC ed, 2013).

Endogenous uveitis (incl. Behçet disease) is inflammation of the iris (the pigmented middle of the three concentric layers that make up an eye) caused by non-infectious or autoimmune diseases. It affects approx. 1 out of 4,500 people and appears more often in people between 20 and 60 years of age; affects men and women equally (MorphoSys AG, 2013). In western countries, anterior uveitis

accounts for between 50% and 90% of uveitis cases. In Asian countries the proportion is between 28% and 50% (Chang and Wakefield, 2002).

Nephrotic syndrome (NS) is kidney disease with excess of serum proteins in the urine, decreased serum albumin, and swelling (Cohen and Sinnakirouchenan, 2013). It may affect adults and children, of both sexes and of any race. It occurs in typical form, or in association with nephritic syndrome (disorders affecting the kidneys). Kidney disease due to diabetes with NS is most common, at an estimated rate of at least 50 cases per million population. However, that is an underestimation, since the rate of end-stage renal disease from diabetes has reached 100 cases per million population in some Western countries. In children, NS may occur at a rate of 20 cases per million children. Because diabetes is major cause of NS, American Indians, Hispanics, and African Americans have a higher incidence of NS than do white persons. There is a male predominance in the occurrence of NS (Cohen and Sinnakirouchenan, 2013).

VI.2.2 Summary of treatment benefits

Based on the available data and clinical experience of several years, ciclosporin represents an effective drug in the prevention of rejection of newly transplanted organs like liver, kidney, heart, lung or pancreas or bone marrow transplants. Ciclosporin is also used for the treatment of severe psoriasis, kidney disease due to some forms of nephrotic syndrome, endogenous uveitis, severe rheumatoid arthritis and severe eczema (atopic dermatitis).

The existing evidence indicates that ciclosporin acts specifically and reversibly on white blood cells. Contrary to cytostatic agents, ciclosporin does not impair the number nor the development of blood cells that give rise to all the other blood cells (haemopoietic stem cells) and has no effect on function of the white blood cells other than lymphocytes.

Successful organ and bone marrow transplantations have been carried out in humans, where ciclosporin has been used to prevent and treat rejection and complication following a transplant of allogeneic tissue from a genetically non-identical donor.

If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, ciclosporin can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Lymphomas and other malignancies (Tumours)	Like other medicines that act on the immune system, ciclosporin may increase the risk of developing tumours or other cancers, particularly of the skin and lymphoid system.	Ciclosporin should not be taken by non-transplant patients with any type of cancer. Exposure to sunlight and UV light should be limited by wearing appropriate protective clothing and with a high protection factor sunscreen

Risk	What is known	Preventability
		applied often.
Concomitant ultraviolet B irradiation or PUVA photochemotherapy	Ciclosporin may increase the risk of developing cancers, particularly of the skin.	Exposure to sunlight and UV light should be limited by wearing appropriate protective clothing and with a high protection factor sunscreen applied often.
Infections	Like other medicines that act on the immune system, ciclosporin may influence the body's ability to fight against infection. Signs of infection might be fever or sore throat.	Before and during treatment with ciclosporin, patients should inform their doctor if they have any signs of infection, such as fever or a sore throat. Ciclosporin should not be taken by non-transplant patients with infection which is not under control with medication. Doctor should be notified about any changes in the sight, loss of coordination, being clumsy, memory loss, difficulty speaking or understanding what others say, and muscle weakness. These might be signs of an infection of the brain called progressive multifocal leukoencephalopathy
Renal toxicity (Kidney damage)	More than one in ten people treated with ciclosporin will experience kidney problems. Too much of the medicine can affect the kidneys. Some medicines that are sometimes taken during treatment with ciclosporin may affect the kidneys. These include: anti-bacterial medicines (gentamycin, tobramycin, ciprofloxacin), anti-fungal medicines which contain amphotericin B, medicines used for urinary tract infections which contain trimethoprim, medicines for cancer which contain melphalan, medicines used to lower the amount of acid in the stomach (acid secretion inhibitors of the H2-receptor antagonist type), tacrolimus, pain killers (non-steroid anti-inflammatory medicines such as diclofenac), fibric acid medicines (used to lower the amount of fat in the blood).	Before taking ciclosporin, patients should notify the doctor straight away if they have kidney problems. The doctor will carry out regular blood tests and may change the dose if necessary. The doctor will check how well the kidneys are working and will check the levels of ciclosporin in blood, especially if patient has had a transplant. Patients should notify the doctor straight away if they notice kidney problems which may greatly reduce the amount of produced urine. Ciclosporin should not be taken by patients with kidney problems (except for nephrotic syndrome).
Hepatotoxicity	Up to one in ten people treated with	Before and during the

Risk	What is known	Preventability
(Liver damage)	ciclosporin will experience liver problems. Some people (frequency cannot be estimated) have had serious liver problems both with and without yellowing of the eyes or skin nausea (feeling sick), loss of appetite, dark coloured urine, swelling of the face, feet, hands and/or the whole body.	treatment with ciclosporin, patients should notify the doctor straight away if they have liver problems. The doctor will check how well the liver is working. The doctor will check the levels of ciclosporin in blood, especially if patient has had a transplant.
Hypertension (High blood pressure)	More than one in ten people treated with ciclosporin will experience high blood pressure.	The doctor will check the blood pressure before the start of the treatment and regularly during the treatment and may give the patient a medicine to lower blood pressure if necessary. Before and during the treatment with ciclosporin, patients should notify the doctor straight away if they are suffering from high blood pressure. Ciclosporin should not be taken by non-transplant patients with high blood pressure (hypertension) which is not under control with medication.
Increased blood lipids	More than 1 in 10 people may experience high level of lipids in the blood.	The doctor will monitor the blood lipids (fats) during the treatment, and should be notified about any side effects that severely affect the patient.
Electrolyte disturbance including hyperkalaemia, hypomagnesaemia, hyperuricaemia (Electrolyte disturbance including high levels of potassium, low levels of magnesium and high levels of uric acid in the blood)	Up to one in ten people treated with ciclosporin will experience high level of uric acid or potassium in the blood or low levels of magnesium in the blood.	Before and during treatment with ciclosporin, patients should notify the doctor straight away if they have high levels of potassium in the blood or low levels of magnesium in the body or if they have gout. The doctor may give magnesium supplements to such patients, especially just after the operation if they have had a transplant. Patients should tell their doctor if they are taking medicines that may affect the potassium levels. These include medicines

Risk	What is known	Preventability
		which contain potassium, potassium supplements, water tablets (diuretics) called potassium-sparing diuretics and some medicines which lower the blood pressure.
Encephalopathy including posterior reversible encephalopathy syndrome (Brain disorders)	Up to 1 in 100 people may experience symptoms of brain disorders including sudden fits, mental confusion, sleeplessness, disorientation, disturbance of vision, unconsciousness, sense of weakness in the limbs and impaired movements.	Doctor should be notified about any brain problems with signs such as seizures, confusion, feeling disorientated, being less responsive, personality changes, feeling agitated, sleeplessness, changes to your sight, blindness, coma, paralysis of part or all of the body, stiff neck, loss of coordination with or without unusual speech or eye movements.
Administration of live attenuated vaccines	Vaccination with live attenuated vaccines may be ineffective.	Patients should notify the doctor if they need to have a vaccination before or during the treatment.
Drug-drug interactions e.g. with inhibitors or inducers of CYP3A4 and/or P-glycoprotein (P-gp) and with substrates of CYP3A4, P-gp and organic anion transporter proteins (Situations when one drug affects the activity of another drug when both are administered together)	Some medicines may increase or decrease the level of ciclosporin in blood. Medicines which may increase the level of ciclosporin in blood include: antibiotics (such as erythromycin or azythromycin), antifungals (voriconazole, itraconazole), medicines used for heart problems or high blood pressure (diltiazem, nicardipine, verapamil, amiodarone), metoclopramide (used to stop sickness), oral contraceptives, danazol (used to treat menstrual problems), medicines used to treat gout (allopurinol), cholic acid and derivatives (used to treat gallstones), protease inhibitors used to treat HIV, imatinib (used to treat leukaemia or tumours), colchicine, telaprevir (used to treat hepatitis C). Medicines which may decrease the level of ciclosporin in blood include: barbiturates (used to help you to sleep), some anti-convulsant medicines (such as carbamazepine or phenytoine), octreotide (used to treat acromegaly or neuroendocrine tumours in the gut),	Patients should inform their doctor if they are taking, have recently taken or might take any other medicines. Ciclosporin must not be used with products containing dabigatran etexilate (used to avoid blood clots after surgery) or bosentan and aliskiren (used to reduce high blood pressure) or products/herbal medicines which contain Hypericum perforatum (St. John's Wort). Doctor might check the level of ciclosporin in blood when starting or stopping treatment with other medicines.

Risk	What is known	Preventability
	anti-bacterial medicines used to treat tuberculosis, orlistat (used to help weight loss), herbal medicines containing St. John's wort, ticlopidine (used after a stroke), certain medicines which lower blood pressure (bosentan), and terbinafine (an anti-fungal medicine used to treat infections of the toes and nails). Interaction with food and drink is possible (e.g. grapefruit/grapefruit juice).	
Interaction with grapefruit/grapefruit juice	Grapefruit or grapefruit juice may affect how ciclosporin works, by increasing the levels of ciclosporin in the body.	Grapefruit or grapefruit juice should not be used with ciclosporin.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Increased risk of nephrotoxicity when combined with other drugs that are nephrotoxic (Increased risk of kidney damage when combined with other drugs that may cause kidney damage)	Some medicines may affect the kidneys. These include: anti-bacterial medicines (gentamycin, tobramycin, ciprofloxacin), anti-fungal medicines which contain amphotericin B, medicines used for urinary tract infections which contain trimethoprim, medicines for cancer which contain melphalan, medicines used to lower the amount of acid in the stomach (acid secretion inhibitors of the H2-receptor antagonist type), tacrolimus, pain killers (non-steroid anti-inflammatory medicines such as diclofenac), fibric acid medicines (used to lower the amount of fat in the blood). Doctor or pharmacist should be notified if the patient is taking any of the above mentioned medicines.
Increased risk of hyperkalaemia (increased potassium levels in the blood) **when combined with potassium-sparing medicinal products**	Some medicines may affect the potassium levels. These include medicines which contain potassium, potassium supplements, water tablets (diuretics) called potassium-sparing diuretics and some medicines which lower the blood pressure. Doctor or pharmacist should be notified if the patient is taking any of the above mentioned medicines.
Reproductive toxicity (Adverse effects on reproduction)	Animal studies have shown reproductive toxicity in rats and rabbits. There are no adequate and well-controlled studies in pregnant women and therefore ciclosporin should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.
Use in breast-feeding women	Ciclosporin, the active substance, passes into breast milk. This may affect the baby. Therefore, breast-feeding is not recommended during treatment with ciclosporin.

Missing information

Risk	What is known
Use in children under 16 years of age for non-transplant indications other than nephrotic syndrome (kidney disorder)	Experience with ciclosporin in children is still limited. Ciclosporin use in children for non-transplant indications other than nephrotic syndrome cannot be recommended.
Effect on human fertility	There is limited data on the effect of ciclosporin on human fertility. Changes in menstrual cycle have been reported.
Use in pregnancy	The experience with ciclosporin in pregnant women is limited. There are no adequate and well-controlled studies in pregnant women and therefore ciclosporin should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus. The ethanol content of the ciclosporin formulations should also be taken into account in pregnant women. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks).

VI.2.5 Summary of risk minimisation measures by safety concern

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Table 3. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	30 Dec 2013	**Important identified risks** • Interactions • Infections and infestations • Neoplasms benign, malignant and unspecified (including cysts and polyps) • Hepatotoxicity • Renal toxicity • Hypertension • Electrolyte disturbance • Safety experience in transplant patients **Important potential risks** None **Missing information** • Use in children under 16 years of age for non-transplant indications (other than nephrotic syndrome)	Not applicable.
1.1	18 Jul 2014	**Important identified risks**	Safety concerns

Version	Date	Safety Concerns	Comment
		• Lymphomas and other malignancies • Infections • Renal toxicity • Hepatotoxicity • Hypertension • Increased blood lipids • Electrolyte disturbances including hyperkalaemia, hypomagnesaemia, hyperuricaemia • Encephalopathy including posterior reversible encephalopathy syndrome • Administration of live attenuated vaccines • Drug-drug interactions e.g. with inhibitors or inducers of CYP3A4 and/or P-glycoprotein (P-gp) and with substrates of CYP3A4, P-gp and organic anion transporter proteins **Important potential risks** • Increased risk of nephrotoxicity when combined with other drugs that are nephrotoxic • Increased risk of hyperkalaemia when combined with potassium-sparing medicinal products • Reproductive toxicity • Use in breast-feeding women **Missing information** • Use in children under 16 years of age for non-transplant indications (other than nephrotic syndrome) • Effect on human fertility • Use in pregnancy	are updated according to the RMS Generic Risk Management Plan (RMP) Preliminary Assessment Report
1.2	28 Oct 2014	**Important identified risks** • Lymphomas and other malignancies • Concomitant ultraviolet B irradiation or PUVA photochemotherapy • Infections • Renal toxicity • Hepatotoxicity • Hypertension • Increased blood lipids • Electrolyte disturbances including hyperkalaemia, hypomagnesaemia, hyperuricaemia • Encephalopathy including posterior reversible encephalopathy syndrome • Administration of live attenuated vaccines • Drug-drug interactions e.g. with inhibitors or inducers of CYP3A4 and/or P-glycoprotein (P-gp) and with substrates of CYP3A4, P-gp and organic anion transporter proteins • Interaction with grapefruit/grapefruit juice **Important potential risks**	Safety concerns are updated according to the Request for Further Information (UK/H/5195/01-04/II/05; dated 13 October 2014)

Version	Date	Safety Concerns	Comment
		• Increased risk of nephrotoxicity when combined with other drugs that are nephrotoxic • Increased risk of hyperkalaemia when combined with potassium-sparing medicinal products • Reproductive toxicity • Use in breast-feeding women **Missing information** • Use in children under 16 years of age for non-transplant indications (other than nephrotic syndrome) • Effect on human fertility • Use in pregnancy	