Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sandimmun 50 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The concentrate for solution for infusion contains 50 mg/ml. Each ampoule of 1 ml contains 50 mg of ciclosporin. Each ampoule of 5 ml contains 250 mg of ciclosporin.

Excipients with known effect:
Ethanol: 278 mg/ml. Sandimmun 50 mg/ml concentrate for solution for infusion contains around 34% v/v ethanol (27.8% m/v ethanol).
Macrogolglycerol ricinoleate/ Polyoxyl 35 castor oil: 650 mg/ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for Solution for Infusion
Clear brown-yellow oleaginous concentrate for infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Transplantation indications
Solid organ transplantation
Prevention of graft rejection following solid organ transplantation.

Treatment of transplant cellular rejection in patients previously receiving other immunosuppressive agents.

Bone marrow transplantation
Prevention of graft rejection following allogeneic bone marrow and stem cell transplantation.

Prevention or treatment of graft-versus-host disease (GVHD).

4.2 Posology and method of administration

Posology
The dose ranges given for oral administration are intended to serve as guidelines only.

Sandimmun should only be prescribed by, or in close collaboration with, a physician with experience of immunosuppressive therapy and/or organ transplantation.

Transplantation
Solid organ transplantation
The recommended dose of Sandimmun concentrate for solution for infusion is approximately one-third of the corresponding oral dose, and it is recommended that patients be switched to oral therapy as soon as possible.

For reference the initial dose of Sandimmun or Neoral is 10 to 15 mg/kg given in 2 divided doses which should be initiated within 12 hours before surgery. This dose should be maintained as the daily dose for 1 to 2 weeks post-operatively, being gradually reduced in accordance with blood levels according to local immunosuppressive protocols until a recommended maintenance dose of about 2 to 6 mg/kg given in 2 divided doses is reached.

When oral Sandimmun or Neoral is given with other immunosuppressants (e.g., with corticosteroids or as part of a triple or quadruple medicinal product therapy), lower doses (e.g., 3 to 6 mg/kg given in 2 divided doses for the initial treatment) may be used.

Bone marrow transplantation
The initial dose should be given on the day before transplantation. In most cases, Sandimmun concentrate for solution for infusion is preferred for this purpose. The recommended intravenous dose is 3 to 5 mg/kg/day. Infusion is continued at this dose level during the immediate post-transplant period of up to 2 weeks, before a change is made to oral maintenance therapy with Sandimmun or Neoral at daily oral doses of about 12.5 mg/kg given in 2 divided doses.

Maintenance treatment should be continued for at least 3 months (and preferably for 6 months) before the dose is gradually decreased to zero by 1 year after transplantation.

If oral Sandimmun or Neoral is used to initiate therapy, the recommended daily dose is 12.5 to 15 mg/kg given in 2 divided doses, starting on the day before transplantation.

Higher doses of oral Sandimmun or Neoral, or the use of Sandimmun intravenous therapy, may be necessary in the presence of gastrointestinal disturbances which might decrease absorption.

In some patients, GVHD occurs after discontinuation of ciclosporin treatment, but usually responds favourably to re-introduction of therapy. In such cases an initial oral loading dose of 10 to 12.5 mg/kg should be given, followed by daily oral administration of the maintenance dose previously found to be satisfactory. Low doses of Sandimmun should be used to treat mild, chronic GVHD.

Special populations
Patients with renal impairment
All indications
Ciclosporin undergoes minimal renal elimination, and its pharmacokinetics are not extensively affected by renal impairment (see section 5.2). However, due to its nephrotoxic potential (see section 4.8), careful monitoring of renal function is recommended (see section 4.4).

Patients with hepatic impairment
Ciclosporin is extensively metabolised by the liver. An approximate 2- to 3-fold increase in ciclosporin exposure may be observed in patients with hepatic impairment. Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see sections 4.4 and 5.2) and it is recommended that ciclosporin blood levels are monitored until stable levels are reached.

Paediatric population
Clinical studies have included children from 1 year of age. In several studies, paediatric patients required and tolerated higher doses of ciclosporin per kg body weight than those used in adults.

Use of Sandimmun in children for non-transplantation indications other than nephrotic syndrome cannot be recommended (see section 4.4).

Elderly population (age 65 years and above)
Experience with Sandimmun in the elderly is limited.

In rheumatoid arthritis clinical trials with ciclosporin, patients aged 65 or older were more likely to develop systolic hypertension on therapy, and more likely to show serum creatinine rises ≥ 50% above the baseline after 3 to 4 months of therapy.
Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or medication and increased susceptibility for infections.

Method of administration
Intravenous administration.

Types of containers suitable for the infusion solution are mentioned in section 6.2.

Because of the risk of anaphylaxis (see section 4.4) the use of Sandimmun concentrate for solution for infusion should be reserved for organ transplant patients who are unable to take the medicinal product orally (e.g., shortly after surgery), or in whom absorption of the oral forms might be impaired during episodes of gastrointestinal disorders. In such cases, it is recommended to switch to oral administration as soon as feasible. Another well-established use of the concentrate for solution for infusion is the initial treatment of patients undergoing bone marrow transplantation.

The concentrate for solution for infusion should be diluted 1:20 to 1:100 with normal saline or 5% glucose and given as a slow intravenous infusion over 2 to 6 hours.

Once an ampoule is opened, the contents should be used immediately. Diluted infusion solutions must be discarded after 24 hours.

Precautions to be taken before handling or administering the medicinal product
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Combination with products containing *Hypericum perforatum* (St John´s Wort) (see section 4.5).

Combination with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g. bosentan, dabigatran etexilate and aliskiren (see section 4.5).

4.4 Special warnings and precautions for use

Medical supervision
Sandimmun should be prescribed only by physicians who are experienced in immunosuppressive therapy and can provide adequate follow-up, including regular full physical examination, measurement of blood pressure and control of laboratory safety parameters. Transplantation patients receiving this medicinal product should be managed in facilities with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should receive complete information for the follow-up of the patient.

Polyoxyl castor oil and anaphylactoid reactions
Sandimmun concentrate for solution for infusion contains polyoxyl castor oil, which has been reported to cause anaphylactoid reactions following intravenous administration. These reactions can consist of flushing of the face and upper thorax, and non-cardiogenic pulmonary oedema, with acute respiratory distress, dyspnoea, wheezing, blood pressure changes and tachycardia. Special caution is therefore necessary in patients who have previously received preparations containing polyoxylcastor oil (e.g., a preparation containing Cremophor® EL) by intravenous injection or infusion, and in patients with an allergic predisposition. Thus, patients receiving Sandimmun concentrate for solution for infusion should be under continuous observation for at least the first 30 minutes after the start of the infusion and at frequent intervals thereafter. If anaphylaxis occurs, the infusion should be discontinued. An aqueous solution of adrenaline 1:1000 and a source of oxygen should be available by the bedside. Prophylactic administration of an antihistamine (H_1 + H_2 blocker) prior to Sandimmun concentrate for solution for infusion has also been successfully employed to prevent the occurrence of anaphylactoid reactions.

Lymphomas and other malignancies
Like other immunosuppressants, ciclosporin increases the risk of developing lymphomas and other malignancies, particularly those of the skin. The increased risk appears to be related to the degree and duration of immunosuppression rather than to the use of specific agents.

A treatment regimen containing multiple immunosuppressants (including ciclosporin) should therefore be used with caution as this could lead to lymphoproliferative disorders and solid organ tumours, some with reported fatalities.

In view of the potential risk of skin malignancy, patients on Sandimmun, in particular those treated for psoriasis or atopic dermatitis, should be warned to avoid excess unprotected sun exposure and should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

Infections

Like other immunosuppressants, ciclosporin predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections, often with opportunistic pathogens. Activation of latent polyomavirus infections that may lead to polyomavirus associated nephropathy (PVAN), especially to BK virus nephropathy (BKVN), or to JC virus associated progressive multifocal leukoencephalopathy (PML), have been observed in patients receiving ciclosporin. These conditions are often related to a high total immunosuppressive burden and should be considered in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Serious and/or fatal outcomes have been reported. Effective pre-emptive and therapeutic strategies should be employed, particularly in patients on multiple long-term immunosuppressive therapy.

Renal toxicity

A frequent and potentially serious complication, an increase in serum creatinine and urea, may occur during Sandimmun therapy. These functional changes are dose-dependent and are initially reversible, usually responding to dose reduction. During long-term treatment, some patients may develop structural changes in the kidney (e.g., interstitial fibrosis) which, in renal transplant patients, must be differentiated from changes due to chronic rejection. Frequent monitoring of renal function is therefore required according to local guidelines for the indication in question (see sections 4.2 and 4.8).

Hepatotoxicity

Sandimmun may also cause dose-dependent, reversible increases in serum bilirubin and in liver enzymes (see section 4.8). There have been solicited and spontaneous reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients treated with ciclosporin. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and co-medications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see section 4.8). Close monitoring of parameters that assess hepatic function is required and abnormal values may necessitate dose reduction (see sections 4.2 and 5.2).

Elderly population (age 65 years and above)

In elderly patients, renal function should be monitored with particular care.

Monitoring ciclosporin levels (see section 4.2)

When Sandimmun is used in transplant patients, routine monitoring of ciclosporin blood levels is an important safety measure. For monitoring ciclosporin levels in whole blood, a specific monoclonal antibody (measurement of parent compound) is preferred; a high-performance liquid chromatography (HPLC) method, which also measures the parent compound, can be used as well. If plasma or serum is used, a standard separation protocol (time and temperature) should be followed. For the initial monitoring of liver transplant patients, either the specific monoclonal antibody should be used, or parallel measurements using both the specific monoclonal antibody and the non-specific monoclonal antibody should be performed, to ensure a dosage that provides adequate immunosuppression.

Hypertension

Regular monitoring of blood pressure is required during Sandimmun therapy. If hypertension develops, appropriate antihypertensive treatment must be instituted. Preference should be given to an antihypertensive agent that does not interfere with the pharmacokinetics of ciclosporin, e.g., isradipine (see section 4.5).

Blood lipids increased

Since Sandimmun has been reported to induce a reversible slight increase in blood lipids, it is advisable to perform lipid determinations before treatment and after the first month of therapy. In the event of increased lipids being found, restriction of dietary fat and, if appropriate, a dose reduction, should be considered.

Hyperkalaemia

Ciclosporin enhances the risk of hyperkalaemia, especially in patients with renal dysfunction. Caution is also required when ciclosporin is co-administered with potassium-sparing drugs (e.g., potassium-sparing diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists) or potassium-containing medicinal products as well as in patients on a potassium rich diet. Control of potassium levels in these situations is advisable.

Hypomagnesaemia

Ciclosporin enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplant period. Control of serum magnesium levels is therefore recommended in the peri-transplant period, particularly in the presence of neurological symptom/signs. If considered necessary, magnesium supplementation should be given.

Hyperuricaemia

Caution is required when treating patients with hyperuricaemia.

Live-attenuated vaccines
During treatment with ciclosporin, vaccination may be less effective. The use of live attenuated vaccines should be avoided (see section 4.5).

Interactions
Caution should be observed when co-administering ciclosporin with drugs that substantially increase or decrease ciclosporin plasma concentrations, through inhibition or induction of CYP3A4 and/or P-gp (see section 4.5).

Renal toxicity should be monitored when initiating ciclosporin use together with active substances that increase ciclosporin levels or with substances that exhibit nephrotoxic synergy (see section 4.5). The clinical condition of the patient should be monitored closely. Monitoring of ciclosporin blood levels and adjustment of the ciclosporin dose may be required.

Concomitant use of ciclosporin and tacrolimus should be avoided (see section 4.5).

Ciclosporin is an inhibitor of CYP3A4, the multidrug efflux transporter P-gp and organic anion transporter proteins (OATP) and may increase plasma levels of co-medications that are substrates of this enzyme and/or transporter.Caution should be observed while co-administering ciclosporin with such drugs or concomitant use should be avoided (see section 4.5).
Ciclosporin increases the exposure to HMG-CoA reductase inhibitors (statins). When concurrently administered with ciclosporin, the dosage of the statins should be reduced, and concomitant use of certain statins should be avoided according to their label recommendations. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis (see section 4.5).
Following concomitant administration of ciclosporin and *lercanidipine*, the AUC of lercanidipine was increased three-fold and the AUC of ciclosporin was increased 21%. Therefore, the simultaneous combination of ciclosporin and lercanidipine should be avoided. Administration of ciclosporin 3 hours after lercanidipine yielded no change of the lercanidipine AUC, but the ciclosporin AUC was increased by 27%. This combination should therefore be given with caution with an interval of at least 3 hours.

Paediatric use in non-transplantation indications
Except for the treatment of nephrotic syndrome, there is no adequate experience available with Sandimmun. Its use in children under 16 years of age for non-transplantation indications other than nephrotic syndrome cannot be recommended.

Special excipients: Polyoxyl 35 castor oil
Sandimmun contains polyoxyl 35 castor oil, which may cause severe allergic reactions.

Special excipients: Ethanol
Sandimmun contains 278 mg of alcohol (ethanol) in each ml which is equivalent to 34.4 % v/v. A 100 mg dose of Sandimmun contains 556 mg ethanol, equivalent to nearly 14 ml beer or 6 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions
Of the many drugs reported to interact with ciclosporin, those for which the interactions are adequately substantiated and considered to have clinical implications are listed below.

Various agents are known to either increase or decrease plasma or whole blood ciclosporin levels usually by inhibition or induction of enzymes involved in the metabolism of ciclosporin, in particular CYP3A4.

Ciclosporin is also an inhibitor of CYP3A4, the multidrug efflux transporter P-gp and organic anion transporter proteins (OATP) and may increase plasma levels of co-medications that are substrates of this enzyme and/or transporters.

Medicinal products known to reduce or increase the bioavailability of ciclosporin: In transplant patients, frequent measurement of ciclosporin levels and, if necessary, ciclosporin dosage adjustment is required, particularly during the introduction or withdrawal of the co-administered medication. In non-transplant patients, the relationship between blood level and clinical effects is less well established. If medicinal products known to increase ciclosporin levels are given concomitantly, frequent

assessment of renal function and careful monitoring for ciclosporin-related side effects may be more appropriate than blood level measurement.

Drugs that decrease ciclosporin levels
All inducers of CYP3A4 and/or P-gp are expected to decrease ciclosporin levels. Examples of drugs that decrease ciclosporin levelsare:
Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, intravenous sulfadimidine, probucol, orlistat, hypericum perforatum (St. John's wort), ticlopidine, sulfinpyrazone, terbinafine, bosentan.

Products containing *Hypericum perforatum* (St John´s Wort) must not be used concomitantly with Sandimmun due to the risk of decreased blood levels of ciclosporin and thereby reduced effect (see section 4.3).

Rifampicin induces ciclosporin intestinal and liver metabolism. Ciclosporin doses may need to be increased 3- to 5-fold during co-administration.

Octreotide decreases oral absorption of ciclosporin and a 50% increase in the ciclosporin dose or a switch to intravenous administration could be necessary.

Drugs that increase ciclosporin levels
All inhibitors of CYP3A4 and/or P-gp may lead to increased levels of ciclosporin. Examples are:
Nicardipine, metoclopramide, oral contraceptives, methylprednisolone (high dose), allopurinol, cholic acid and derivatives, protease inhibitors, imatinib, colchicine, nefazodone.

Macrolide antibiotics: Erythromycin can increase ciclosporin exposure 4- to 7-fold, sometimes resulting in nephrotoxicity. *Clarithromycin* has been reported to double the exposure of ciclosporin. *Azitromycin* increases ciclosporin levels by around 20%.

Azole antimyotics: Ketoconazole, fluconazole, itraconazole and voriconazole could more than double ciclosporin exposure.

Verapamil increases ciclosporin blood concentrations 2- to 3-fold.

Co-administration with *telaprevir* resulted in approximately 4.64- fold increase in ciclosporin dose normalised exposure (AUC).

Amiodarone substantially increases the plasma ciclosporin concentration concurrently with an increase in serum creatinine. This interaction can occur for a long time after withdrawal of amiodarone, due to its very long half-life (about 50 days).

Danazol has been reported to increase ciclosporin blood concentrations by approximately 50%.

Diltiazem (at doses of 90 mg/day)can increase ciclosporin plasma concentrations by up to 50%.

Imatinib could increase ciclosporin exposure and C_{max} by around 20%.

Cannabidiol (P-gp inhibitor): There have been reports of increased blood levels of another calcineurin inhibitor during concomitant use with cannabidiol. This interaction may occur due to inhibition of intestinal P-gp efflux, leading to increased bioavailability of the calcineurin inhibitor. Ciclosporin and cannabidiol should therefore be co-administered with caution, closely monitoring for side effects. In transplant recipients, monitor ciclosporin whole blood trough concentrations and adjust the ciclosporin dose if needed. In non-transplant patients, monitoring of ciclosporin blood levels, with dose adjustment if needed, should be considered (see sections 4.2 and 4.4).

Food interactions
The concomitant intake of grapefruit and grapefruit juice has been reported to increase the bioavailability of ciclosporin.

Combinations with increased risk for nephrotoxicity
Care should be taken when using ciclosporin together with other active substances that exhibit nephrotoxic synergy such as:
aminoglycosides (including gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); fibric acid derivatives (e.g., bezafibrate, fenofibrate); NSAIDs (including diclofenac, naproxen, sulindac); melphalan histamine H_2-receptor antagonists (e.g., cimetidine, ranitidine); methotrexate (see section 4.4).

During the concomitant use of a drug that may exhibit nephrotoxic synergy, close monitoring of renal function should be performed. If a significant impairment of renal function occurs, the dosage of the co-administered medicinal product should be reduced, or alternative treatment considered.

Concomitant use of ciclosporin and tacrolimus should be avoided due to the risk for nephrotoxicity and pharmacokinetic interaction via CYP3A4 and/or P-gp (see section 4.4).

Impact of DAA therapy

The pharmacokinetics of ciclosporin may be impacted by changes in liver function during DAA therapy, related to clearance of HCV virus. A close monitoring and potential dose adjustment of ciclosporin is warranted to ensure continued efficacy.

Effects of ciclosporin on other drugs

Ciclosporin is an inhibitor of CYP3A4, the multidrug efflux transporter P-gp and organic anion transporter proteins (OATP). Co-administration of drugs that are substrates of CYP3A4, P-gp and OATP with ciclosporinmay increase plasma levels of co-medications that are substrates of this enzyme and/or transporter.

Some examples are listed below:

Ciclosporin may reduce the clearance of *digoxin, colchicine, HMG-CoA reductase inhibitors (statins)* and etoposide. If any of these drugs are used concurrently with ciclosporin, close clinical observation is required in order to enable early detection of toxic manifestations of the medicinal products, followed by reduction of its dosage or its withdrawal. When concurrently administered with ciclosporin, the dosage of the statins should be reduced, and concomitant use of certain statins should be avoided according to their label recommendations. Exposure changes of commonly used statins with ciclosporin are summarised in Table 1. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis.

Table 1 Summary of exposure changes of commonly used statins with ciclosporin

Statin	**Doses available**	**Fold change in exposure with ciclosporin**
Atorvastatin	10-80 mg	8-10
Simvastatin	10-80 mg	6-8
Fluvastatin	20-80 mg	2-4
Lovastatin	20-40 mg	5-8
Pravastatin	20-80 mg	5-10
Rosuvastatin	5-40 mg	5-10
Pitavastatin	1-4 mg	4-6

Caution is recommended when co-administering ciclosporin with lercanidipine (see section 4.4).

Following concomitant administration of ciclosporin and *aliskiren*, a P-gp substrate, the C_{max} of aliskiren was increased approximately 2.5-fold and the AUC approximately 5-fold. However, the pharmacokinetic profile of ciclosporin was not significantly altered. Co-administration of ciclosporin and aliskiren is not recommended (see section 4.3).

Concomitant administration of dabigatran etexilate is not recommended due to the P-gp inhibitory activity of ciclosporin (see section 4.3).

The concurrent administration of *nifedipine* with ciclosporin may result in an increased rate of gingival hyperplasia compared with that observed when ciclosporin is given alone.

The concomitant use of *diclofenac* and ciclosporin has been found to result in a significant increase in the bioavailability of diclofenac, with the possible consequence of reversible renal function impairment. The increase in the bioavailability of diclofenac is most probably caused by a reduction of its high first-pass effect. If *NSAIDs* with a low first-pass effect (e.g., acetylsalicylic acid) are given together with ciclosporin, no increase in their bioavailability is to be expected.

Elevations in serum creatinine were observed in the studies using *everolimus* or *sirolimus* in combination with full-dose ciclosporin for microemulsion. This effect is often reversible with ciclosporin dose reduction. Everolimus and sirolimus had only a minor influence on ciclosporin pharmacokinetics. Co-administration of ciclosporin significantly increases blood levels of everolimus and sirolimus.

Caution is required with concomitant use of *potassium-sparing medicinal products (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists*) or *potassium-containing medicinal products* since they may lead to significant increases in serum potassium (see section 4.4).

Ciclosporin may increase the plasma concentrations of *repaglinide* and thereby increase the risk of hypoglycaemia.

Co-administration of *bosentan* and ciclosporin in healthy volunteers increases the bosentan exposure several-fold and there was a 35% decrease in ciclosporin exposure. Co-administration of ciclosporin with bosentan is not recommended (see above subsection "Drugs that decrease ciclosporin levels" and section 4.3).

Multiple dose administration of *ambrisentan* and ciclosporin in healthy volunteers resulted in an approximately 2-fold increase in ambrisentan exposure, while the ciclosporin exposure was marginally increased (approximately 10%).

A significantly increased exposure to *anthracycline antibiotics (e.g., doxorubicine, mitoxanthrone, daunorubicine*) was observed in oncology patients with the intravenous co-administration of anthracycline antibiotics and very high doses of ciclosporin.

During treatment with ciclosporin, vaccination may be less effective, and the use of live attenuated vaccines should be avoided.

Interactions resulting in decrease of other drug levels

Concomitant administration of ciclosporin and mycophenolate sodium or mycophenolate mofetil in transplant patients may decrease the mean exposure of mycophenolic acid by 20-50% when compared with other immunosuppressants. This information should be taken into consideration especially in case of interruption or discontinuation of ciclosporin therapy.

The coadministration of a single dose of ciclosporin (200 mg or 600 mg) with a single dose of eltrombopag (50 mg) decreased plasma eltrombopag AUCinf by 18% to 24% and Cmax by 25% to 39%. Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count. Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with ciclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate or well-controlled clinical studies in pregnant women using ciclosporin. There is a moderate amount of data on the use of ciclosporin in pregnant patients from postmarketing experience, including transplantation registries and published literature with majority of cases available from transplant recipients. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks).

Embryo-foetal developmental (EFD) studies in rats and rabbits with ciclosporin have shown embryofoetal toxicity at dose levels below the maximum recommended human dose (MRHD) based on body surface area (BSA) (see section 5.3).

Sandimmun should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. The ethanol content of the Sandimmun formulations should also be taken into account in pregnant women (see section 4.4).

Published data from the National Transplantation Pregnancy Registry (NTPR), described pregnancy outcomes in female kidney (482), liver (97), and heart (43) transplant recipients receiving ciclosporin. The data indicated successful pregnancies with a live birth rate of 76% and 76.9%, and 64% in kidney, liver, and heart transplant recipients, respectively. Premature delivery (< 37 weeks) was reported in 52%, 35%, and 35% of kidney, liver, and heart transplant recipients, respectively.
The rates of miscarriages and major birth defects were reported to be comparable to the rates observed in the general population. A potential direct effect of ciclosporin on maternal hypertension, preeclampsia, infections or diabetes could not be excluded given the limitations inherent to registries and postmarketing safety reporting.

A limited number of observations in children exposed to ciclosporin *in utero* are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal.

Breast-feeding
Ciclosporin is transferred into breast milk. Mothers receiving treatment with Sandimmun should not breast-feed because of the potential of Sandimmun to cause serious adverse drug reactions in breast-fed newborns/infants. A decision should be made whether to abstain from breastfeeding or to abstain from using the medicinal drug, taking into account the benefit of breastfeeding for the newborn/infant and the importance of the medicinal product to the mother.

Limited data showed that the milk to maternal blood concentration ratio of ciclosporin was in the range of 0.17 to 1.4. Based on the infant milk intake, the highest estimated ciclosporin dose ingested by fully breastfed infant was approximately 2% of maternal weight-adjusted dose.

The ethanol content of the Sandimmun formulations should also be taken into account in women who are breast-feeding (see section 4.4).

Fertility
There is limited data on the effect of Sandimmun on human fertility (see section 5.3). No adverse effects on fertility were observed in male and female rats up to 15 mg/kg/day (below MRHD based on BSA) (see section 5.3).

4.7 Effects on ability to drive and use machines

Sandimmun may cause neurological and visual disturbances (see section 4.8). Sandimmun may have a moderate influence on the ability to drive and use machines. Caution should be exercised when driving a motor vehicle or operating machines.
No studies on the effects of Sandimmun on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile
The principal adverse reactions observed in clinical trials and associated with the administration of ciclosporin include renal dysfunction, tremor, hirsutism, hypertension, diarrhoea, anorexia, nausea and vomiting.

Many side effects associated with ciclosporin therapy are dose-dependent and responsive to dose reduction. In the various indications the overall spectrum of side effects is essentially the same; there are, however, differences in incidence and severity. As a consequence of the higher initial doses and longer maintenance therapy required after transplantation, side effects are more frequent and usually more severe in transplant patients than in patients treated for other indications.

Anaphylactoid reactions have been observed following intravenous administration (see section 4.4).

Infections and infestations
Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic) (see section 4.4). Both generalised and localised infections can occur. Pre-existing infections may also be aggravated and reactivation of polyomavirus infections may lead to polyomavirus-associated nephropathy (PVAN) or to JC virus associated progressive multifocal leukopathy (PML). Serious and/or fatal outcomes have been reported.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin containing regimens, are at increased risk of developing lymphomas or lymphoproliferative disorders and other malignancies, particularly of the skin. The frequency of malignancies increases with the intensity and duration of therapy (see section 4.4). Some malignancies may be fatal.

Tabulated summary of adverse drug reactions from clinical trials
Adverse drug reactions from clinical trials (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 2: Adverse drug reactions from clinical trials **Blood and lymphatic system disorders**	
Common	Leucopenia
Uncommon	Thrombocytopenia, anaemia
Rare	Haemolytic uraemic syndrome, microangiopathic haemolytic anaemia
Not known*	Thrombotic microangiopathy, thrombotic thrombocytopenic purpura
Metabolism and nutrition disorders	
Very common	Hyperlipidaemia
Common	Hyperglycaemia, anorexia, hyperuricaemia, hyperkalaemia, hypomagnesaemia
Nervous system disorders	
Very common	Tremor, headache
Common	Convulsions, paraesthesia
Uncommon	Encephalopathy including Posterior Reversible Encephalopathy Syndrome (PRES), signs and symptoms such as convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis and cerebellar ataxia
Rare	Motor polyneuropathy
Very rare	Optic disc oedema, including papilloedema, with possible visual impairment secondary to benign intracranial hypertension
Not known*	Migraine
Ear and labyrinth disorders	
Not known*	Hearing impairment[#]
Vascular disorders	
Very common	Hypertension
Common	Flushing
Gastrointestinal disorders	
Common	Nausea, vomiting, abdominal discomfort/pain, diarrhoea, gingival hyperplasia, peptic ulcer
Rare	Pancreatitis
Hepatobiliary disorders	
Common	Hepatic function abnormal (see section 4.4)
Not known*	Hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure with some fatal outcome (see section 4.4)
Skin and subcutaneous tissue disorders	
Very common	Hirsutism
Common	Acne, hypertrichosis
Uncommon	Allergic rashes
Musculoskeletal and connective tissue disorders	
Common	Myalgia, muscle cramps
Rare Not known*	Muscle weakness, myopathy Pain of lower extremities
Renal and urinary disorders	
Very common	Renal dysfunction (see section 4.4)
Reproductive system and breast disorders	
Rare	Menstrual disturbances, gynaecomastia
General disorders and administration site conditions	
Common	Pyrexia, fatigue
Uncommon	Oedema, weight increase

* Adverse events reported from post marketing experience where the ADR frequency is not known due to the lack of a real denominator.

[#] Hearing impairment has been reported in the post-marketing phase in patients with high levels of ciclosporin.

Other adverse drug reactions from post-marketing experience
There have been solicited and spontaneous reports of hepatotoxicity and liver injury including cholestasis, jaundice hepatitis and liver failure in patients treated with ciclosporin. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and co-medications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see section 4.4).

Acute and chronic nephrotoxicity
Patients receiving calcineurin inhibitor (CNI) therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of acute or chronic nephrotoxicity. There have been reports from clinical trials and from the post-marketing setting associated with the use of Sandimmun. Cases of acute nephrotoxicity reported disorders of ion homeostasis, such as hyperkalaemia, hypomagnesaemia, and hyperuricaemia. Cases reporting chronic morphological changes included arteriolar hyalinosis, tubular atrophy and interstitial fibrosis (see section 4.4).

Pain of lower extremities
Isolated cases of pain of lower extremities have been reported in association with ciclosporin. Pain of lower extremities has also been noted as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS).

Paediatric population
Clinical studies have included children from 1 year of age using standard ciclosporin dosage with a comparable safety profile to adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie;

4.9 Overdose

The oral LD_{50} of ciclosporin is 2,329 mg/kg in mice, 1,480 mg/kg in rats and > 1,000 mg/kg in rabbits. The intravenous LD_{50} is 148 mg/kg in mice, 104 mg/kg in rats, and 46 mg/kg in rabbits.

Symptoms
Experience with acute overdosage of ciclosporin is limited. Oral doses of ciclosporin of up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia and in a few patients moderately severe, reversible impairment of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with ciclosporin in premature neonates.

Treatment
In all cases of overdosage, general supportive measures should be followed and symptomatic treatment applied. Forced emesis and gastric lavage may be of value within the first few hours after oral intake. Ciclosporin is not dialysable to any great extent, nor is it well cleared by charcoal haemoperfusion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressive agents, calcineurin inhibitors, ATC code: L04AD01

Ciclosporin (also known as ciclosporin A) is a cyclic polypeptide consisting of 11 amino acids. It is a potent immunosuppressive agent, which in animals prolongs survival of allogeneic transplants of skin, heart, kidney, pancreas, bone marrow, small intestine or lung. Studies suggest that ciclosporin inhibits the development of cell-mediated reactions, including allograft immunity, delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, graft-versus-host disease (GVHD), and also T-cell dependent antibody production. At the cellular level it inhibits production and release of lymphokines including interleukin 2 (T-cell growth factor, TCGF). Ciclosporin appears to block the resting

lymphocytes in the G_0 or G_1 phase of the cell cycle, and inhibits the antigen-triggered release of lymphokines by activated T-cells.

All available evidence suggests that ciclosporin acts specifically and reversibly on lymphocytes. Unlike cytostatic agents, it does not depress haemopoiesis and has no effect on the function of phagocytic cells.

Successful solid organ and bone marrow transplantations have been performed in man using ciclosporin to prevent and treat rejection and GVHD. Ciclosporin has been used successfully both in hepatitis C virus (HCV) positive and HCV negative liver transplants recipients. Beneficial effects of ciclosporin therapy have also been shown in a variety of conditions that are known, or may be considered to be of autoimmune origin.

Paediatric population: Ciclosporin has been shown to be efficacious in steroid-dependent nephrotic syndrome.

5.2 Pharmacokinetic properties

Distribution
Ciclosporin is distributed largely outside the blood volume, with an average apparent distribution volume of 3.5 l/kg. In the blood, 33 to 47% is present in plasma, 4 to 9% in lymphocytes, 5 to 12% in granulocytes, and 41 to 58% in erythrocytes. In plasma, approximately 90% is bound to proteins, mostly lipoproteins.

Biotransformation
Ciclosporin is extensively metabolised to approximately 15 metabolites. Metabolism mainly takes place in the liver via cytochrome P450 3A4 (CYP3A4), and the main pathways of metabolism consist of mono- and dihydroxylation and N-demethylation at various positions of the molecule. All metabolites identified so far contain the intact peptide structure of the parent compound; some possess weak immunosuppressive activity (up to one-tenth that of the unchanged drug).

Elimination
There is a high variability in the data reported on the terminal half-life of ciclosporin depending on the assay applied and on the target population. The terminal half-life ranged from 6.3 hours in healthy volunteers to 20.4 hours in patients with severe liver disease. Excretion is primarily biliary, with only 6% of an oral dose excreted in the urine, and with less than 1% in the unchanged form (see sections 4.2 and 4.4). The elimination half-life in kidney-transplanted patients was approximately 11 hours, with a range between 4 and 25 hours.

Special populations
Patients with renal impairment
In a study performed in patients with terminal renal failure, the systemic clearance was approximately two thirds of the mean systemic clearance in patients with normally functioning kidneys. Less than 1% of the administered dose is removed by dialysis.

Patients with hepatic impairment
An approximate 2- to 3-fold increase in ciclosporin exposure may be observed in patients with hepatic impairment. In a study performed in severe liver disease patients with biopsy-proven cirrhosis, the terminal half-life was 20.4 hours (range between 10.8 to 48.0 hours) compared to 7.4 to 11.0 hours in healthy subjects.

Paediatric population
Pharmacokinetic data from paediatric patients given Neoral or Sandimmun are very limited. In 15 renal transplant patients aged 3 -16 years, ciclosporin whole blood clearance after intravenous administration of Sandimmun was 10.6±3.7 ml/min/kg (assay: Cyclo-trac specific RIA). In a study of 7 renal transplant patients aged 2-16 years, the ciclosporin clearance ranged from 9.8 to15.5 ml/min/kg. In 9 liver transplant patients aged 0.65-6 years, clearance was 9.3±5.4 ml/min/kg (assay: HPLC). In comparison to adult transplant populations, the differences in bioavailability between Neoral and Sandimmun in paediatrics are comparable to those observed in adults.

5.3 Preclinical safety data

Ciclosporin gave no evidence of teratogenic effects in rats and rabbits with oral application (up to 300 mg/kg/day). Ciclosporin was embryo- and foetotoxic as indicated by reduced foetal weight together with related skeletal retardations. The NOELs are

below the maximum recommended human dose (MRHD) based on the body surface area (BSA). Pregnant rats, which received 6 and 12 mg/kg/day of ciclosporin intravenously (below the MRHD based on BSA), had foetuses with an increased incidence of ventricular septal defect.
In two published research studies, rabbits exposed to ciclosporin *in utero* (10 mg/kg/day subcutaneously) demonstrated reduced numbers of nephrons, renal hypertrophy, systemic hypertension, and progressive renal insufficiency up to 35 weeks of age. These findings have not been demonstrated in other species and their relevance for humans is unknown.

In a peri- and postnatal development study in rats, ciclosporin increased pre- and post-implantation mortality of off-spring and reduced body weight gain of surviving pups at the highest dose of 45 mg/kg/day. The NOEL is below the MRHD based on BSA.

In a fertility study in rats, no adverse effects on fertility and reproduction were observed up to 15 mg/kg/day (below the MRHD based on BSA) in male and female rats.

Ciclosporin was tested in a number of *in vitro* and *in vivo* tests for genotoxicity with no evidence for a clincally relevant mutagenic potential.

Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate at the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol anhydrous
Macrogolglycerol ricinoleate/polyoxyl 35 castor oil

6.2 Incompatibilities

Sandimmun concentrate for solution for infusion contains macrogolglycerol ricinoleate/polyoxyl 35 castor oil, which can cause phthalate stripping from polyvinyl chloride. If available, glass containers should be used for infusion. Plastic bottles should be used only if they conform to the requirements for “Sterile plastic containers for human blood and blood components” or “Empty sterile containers of plasticised polyvinyl chloride for human blood and blood components” of the current European Pharmacopoeia. Containers and stoppers should be free of silicone oil and fatty substances.

6.3 Shelf life

4 years.
Use immediately after first opening of the ampoule.
Use immediately after dilution or store in a refrigerator (2°C – 8°C) for 24 hours unless dilution has been carried out under controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. For storage conditions after dilution and first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1 ml and 5 ml, colorless glass (type I) ampoule.

Pack with 10 ampoules of 1 ml.
Pack with 10 ampoules of 5 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The concentrate should be diluted 1:20 to 1:100 with normal saline or 5% glucose, and given as a slow intravenous infusion over approximately 2 to 6 hours. Diluted infusion solutions must be discarded after 24 hours.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Ireland Limited
Vista Building
Elm Park
Merrion Road, Ballsbridge
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0896/027/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 31st March 2009

10 DATE OF REVISION OF THE TEXT

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