ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note:

This summary of product characteristics, labelling and package leaflet is the version valid at the time of Commission Decision.

After the Commission Decision the National Competent Authorities will update the product information as required.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sandimmun and associated names (see Annex I) 25 mg soft capsules
Sandimmun and associated names (see Annex I) 50 mg soft capsules
Sandimmun and associated names (see Annex I) 100 mg soft capsules
[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 25 mg ciclosporin.
Excipients with known effect:
Ethanol: 25 mg/capsule. Sandimmun soft capsules contain 12.8% v/v ethanol (10.2% m/v).
Each capsule contains 50 mg ciclosporin.
Excipients with known effect:
Ethanol: 50 mg/capsule. Sandimmun soft capsules contain 12.8% v/v ethanol (10.2% m/v).
Each capsule contains 100 mg ciclosporin.
Excipients with known effect:
Ethanol: 100 mg/capsule. Sandimmun soft capsules contain 12.8% v/v ethanol (10.2% m/v).

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Capsule,soft

Pink, oval soft gelatin capsules
Corn yellow, oblong soft gelatin capsules
Dusty rose, oblong soft gelatin capsules

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).

Non-transplantation indications
Endogenous uveitis
Treatment of sight-threatening intermediate or posterior uveitis of non-infectious aetiology in patients in whom conventional therapy has failed or caused unacceptable side effects.

Treatment of Behçet uveitis with repeated inflammatory attacks involving the retina in patients without neurological manifestations.

Nephrotic syndrome
Steroid-dependent and steroid-resistant nephrotic syndrome, due to primary glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis, or membranous glomerulonephritis.

Sandimmun can be used to induce and maintain remissions. It can also be used to maintain steroid-induced remission, allowing withdrawal of steroids.

Rheumatoid arthritis
Treatment of severe, active rheumatoid arthritis.

Psoriasis
Treatment of severe psoriasis in patients in whom conventional therapy is inappropriate or ineffective.

Atopic dermatitis
Sandimmun is indicated in patients with severe atopic dermatitis when systemic therapy is required.

4.2 Posology and method of administration

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

The daily doses of Sandimmun should be given in two divided doses equally distributed throughout the day. It is recommended that Sandimmun be administered on a consistent schedule with regard to time of day and in relation to meals.

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
Treatment with Sandimmun should be initiated within 12 hours before surgery at a dose of 10 to 15 mg/kg given in 2 divided doses. 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 Sandimmun 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 at daily 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 Sandimmun 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 Sandimmun, 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.

Non-transplantation indications
When using Sandimmun in any of the established non-transplantation indications, the following general rules should be adhered to:

Before initiation of treatment a reliable baseline level of renal function should be established by at least two measurements. The estimated glomerular filtration rate (eGFR) by the MDRD formula can be used for estimation of renal function in adults and an appropriate formula should be used to assess eGFR in paediatric patients. Since Sandimmun can impair renal function, it is necessary to assess renal function frequently. If eGFR decreases by more than 25% below baseline at more than one measurement, the dosage of Sandimmun should be reduced by 25 to 50%. If the eGFR decrease from baseline exceeds 35%, further reduction of the dose of Sandimmun should be considered. These recommendations apply even if the patient`s values still lie within the laboratory`s normal range. If dose reduction is not successful in improving eGFR within one month, Sandimmun treatment should be discontinued (see section 4.4).

Regular monitoring of blood pressure is required.

The determination of bilirubin and parameters that assess hepatic function are required prior to starting therapy and close monitoring during treatment is recommended. Determinations of serum lipids, potassium, magnesium and uric acid are advisable before treatment and periodically during treatment.

Occasional monitoring of ciclosporin blood levels may be relevant in non-transplant indications, e.g. when Sandimmun is co-administered with substances that may interfere with the pharmacokinetics of ciclosporin, or in the event of unusual clinical response (e.g. lack of efficacy or increased drug intolerance such as renal dysfunction).

The normal route of administration is by mouth. If the concentrate for solution for infusion is used, careful consideration should be given to administering an adequate intravenous dose that corresponds to the oral dose. Consultation with a physician with experience of use of ciclosporin is recommended.

Except in patients with sight-threatening endogenous uveitis and in children with nephrotic syndrome, the total daily dose must never exceed 5 mg/kg.

For maintenance treatment the lowest effective and well tolerated dosage should be determined individually.

In patients in whom within a given time (for specific information see below) no adequate response is achieved or the effective dose is not compatible with the established safety guidelines, treatment with Sandimmun should be discontinued.

Endogenous uveitis
For inducing remission, initially 5 mg/kg/day orally given in 2 divided doses are recommended until remission of active uveal inflammation and improvement in visual acuity are achieved. In refractory cases, the dose can be increased to 7 mg/kg/day for a limited period.

To achieve initial remission, or to counteract inflammatory ocular attacks, systemic corticosteroid treatment with daily doses of 0.2 to 0.6 mg/kg prednisone or an equivalent may be added if Sandimmun alone does not control the situation sufficiently. After 3 months, the dose of corticosteroids may be tapered to the lowest effective dose.

For maintenance treatment, the dose should be slowly reduced to the lowest effective level. During the remission phases, this should not exceed 5 mg/kg/day.

Infectious causes of uveitis should be ruled out before immunosuppressants can be used.

Nephrotic syndrome
For inducing remission, the recommended daily dose is given in 2 divided oral doses.

If the renal function (except for proteinuria) is normal, the recommended daily dose is the following:
- adults: 5 mg/kg
- children: 6 mg/kg

In patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day.

The combination of Sandimmun with low doses of oral corticosteroids is recommended if the effect of Sandimmun alone is not satisfactory, especially in steroid-resistant patients.

Time to improvement varies from 3 to 6 months depending on the type of glomerulopathy. If no improvement has been observed after this time to improvement period, Sandimmun therapy should be discontinued.

The doses need to be adjusted individually according to efficacy (proteinuria) and safety, but should not exceed 5 mg/kg/day in adults and 6 mg/kg/day in children.

For maintenance treatment, the dose should be slowly reduced to the lowest effective level.

Rheumatoid arthritis
For the first 6 weeks of treatment the recommended dose is 3 mg/kg/day orally given in 2 divided doses. If the effect is insufficient, the daily dose may then be increased gradually as tolerability permits, but should not exceed 5 mg/kg. To achieve full effectiveness, up to 12 weeks of Sandimmun therapy may be required.

For maintenance treatment the dose has to be titrated individually to the lowest effective level according to tolerability.

Sandimmun can be given in combination with low-dose corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs) (see section 4.4). Sandimmun can also be combined with low-dose weekly methotrexate in patients who have insufficient response to methotrexate alone, by using 2.5 mg/kg Sandimmun in 2 divided doses per day initially, with the option to increase the dose as tolerability permits.

Psoriasis
Sandimmun treatment should be initiated by physicians with experience in the diagnosis and treatment of psoriasis. Due to the variability of this condition, treatment must be individualised. For inducing remission, the recommended initial dose is 2.5 mg/kg/day orally given in 2 divided doses. If there is no improvement after 1 month, the daily dose may be gradually increased, but should not exceed 5 mg/kg. Treatment should be discontinued in patients in whom sufficient response of psoriatic lesions cannot be achieved within 6 weeks on 5 mg/kg/day, or in whom the effective dose is not compatible with the established safety guidelines (see section 4.4).

Initial doses of 5 mg/kg/day are justified in patients whose condition requires rapid improvement. Once satisfactory response is achieved, Sandimmun may be discontinued and subsequent relapse managed with re-introduction of Sandimmun at the previous effective dose. In some patients, continuous maintenance therapy may be necessary.

For maintenance treatment, doses have to be titrated individually to the lowest effective level, and should not exceed 5 mg/kg/day.

Atopic dermatitis
Sandimmun treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis. Due to the variability of this condition, treatment must be individualised. The recommended dose range is 2.5 to 5 mg/kg/day given in 2 divided oral doses. If a starting dose of 2.5 mg/kg/day does not achieve a satisfactory response within 2 weeks, the daily dose may be rapidly increased to a maximum of 5 mg/kg. In very severe cases, rapid and adequate control of the disease is more likely to occur with a starting dose of 5 mg/kg/day. Once satisfactory response is achieved, the dose should be reduced gradually and, if possible, Sandimmun should be discontinued. Subsequent relapse may be managed with a further course of Sandimmun.

Although an 8-week course of therapy may be sufficient to achieve clearing, up to 1 year of therapy has been shown to be effective and well tolerated, provided the monitoring guidelines are followed.

Switching between oral ciclosporin formulations
The switch from one oral ciclosporin formulation to another should be made under physician supervision, including monitoring of blood levels of ciclosporin for transplantation patients.

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).

Non-transplantation indications
With the exception of patients being treated for nephrotic syndrome, patients with impaired renal function should not receive ciclosporin (see subsection on additional precautions in non-transplantation indications in section 4.4). In nephrotic syndrome patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day.

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
Oral use
Sandimmun capsules should be swallowed whole.

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.

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.

In non-transplant patients, occasional monitoring of ciclosporin blood levels is recommended, e.g. when Sandimmun is co-administered with substances that may interfere with the pharmacokinetics of ciclosporin, or in the event of unusual clinical response (e.g. lack of efficacy or increased drug intolerance such as renal dysfunction).
It must be remembered that the ciclosporin concentration in blood, plasma, or serum is only one of many factors contributing to the clinical status of the patient. Results should therefore serve only as a guide to dosage in relationship to other clinical and laboratory parameters.

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-glycoprotein (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).

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

Ciclosporin is an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein 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.

Special excipients: Polyoxyl 40 hydrogenated castor oil
Sandimmun contains polyoxyl 40 hydrogenated castor oil, which may cause stomach upsets and diarrhoea.

Special excipients: Ethanol
Sandimmun contains around 12% vol. ethanol. A 500 mg dose of Sandimmun contains 500 mg ethanol, equivalent to nearly 15 ml beer or 5 ml wine. This may be harmful in alcoholic patients and should be taken into account in pregnant or breast-feeding women, in patients presenting with liver disease or epilepsy, or if the patients is a child.

Special excipients: Sorbitol

If you have fructose intolerance, inform your doctor before taking this medicine, as it contains sorbitol.

Additional precautions in non-transplantation indications
Patients with impaired renal function (except nephrotic syndrome patients with a permissible degree of renal impairment), uncontrolled hypertension, uncontrolled infections, or any kind of malignancy should not receive ciclosporin.

Before initiation of treatment a reliable baseline assessment of renal function should be established by at least two measurements of eGFR. Renal function must be assessed frequently throughout therapy to allow dosage adjustment (see section 4.2).

Additional precautions in endogenous uveitis
Sandimmun should be administered with caution in patients with neurological Behcet`s syndrome. The neurological status of these patients should be carefully monitored.

There is only limited experience with the use of Sandimmun in children with endogenous uveitis.

Additional precautions in nephrotic syndrome
Patients with abnormal baseline renal function should initially be treated with 2.5 mg/kg/day and must be monitored very carefully.

In some patients, it may be difficult to detect Sandimmun-induced renal dysfunction because of changes in renal function related to the nephrotic syndrome itself. This explains why, in rare cases, Sandimmun-associated structural kidney alterations have been observed without increases in serum creatinine. Renal biopsy should be considered for patients with steroid-dependent minimal-change nephropathy, in whom Sandimmun therapy has been maintained for more than 1 year.

In patients with nephrotic syndrome treated with immunosuppressants (including ciclosporin), the occurrence of malignancies (including Hodgkin's lymphoma) has occasionally been reported.

Additional precautions in rheumatoid arthritis
After 6 months of therapy, renal function needs to be assessed every 4 to 8 weeks depending on the stability of the disease, its co- medication, and concomitant diseases. More frequent checks are necessary when the Sandimmun dose is increased, or concomitant treatment with an NSAID is initiated or its dosage increased. Discontinuation of Sandimmun may also become necessary if hypertension developing during treatment cannot be controlled by appropriate therapy.

As with other long-term immunosuppressive treatments, an increased risk of lymphoproliferative disorders must be borne in mind. Special caution should be observed if Sandimmun is used in combination with methotrexate due to nephrotoxic synergy.

Additional precautions in psoriasis
Discontinuation of Sandimmun therapy is recommended if hypertension developing during treatment cannot be controlled with appropriate therapy.

Elderly patients should be treated only in the presence of disabling psoriasis, and renal function should be monitored with particular care.

There is only limited experience with the use of Sandimmun in children with psoriasis.

In psoriatic patients on ciclosporin, as in those on conventional immunosuppressive therapy, development of malignancies (in particular of the skin) has been reported. Skin lesions not typical for psoriasis, but suspected to be malignant or pre-malignant should be biopsied before Sandimmun treatment is started. Patients with malignant or pre-malignant alterations of the skin should be treated

with Sandimmun only after appropriate treatment of such lesions, and if no other option for successful therapy exists.

In a few psoriatic patients treated with Sandimmun, lymphoproliferative disorders have occurred. These were responsive to prompt discontinuation.

Patients on Sandimmun should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

Additional precautions in atopic dermatitis
Discontinuation of Sandimmun is recommended if hypertension developing during treatment cannot be controlled with appropriate therapy.

Experience with Sandimmun in children with atopic dermatitis is limited.

Elderly patients should be treated only in the presence of disabling atopic dermatitis and renal function should be monitored with particular care.

Benign lymphadenopathy is commonly associated with flares in atopic dermatitis and invariably disappears spontaneously or with general improvement in the disease.

Lymphadenopathy observed on treatment with ciclosporin should be regularly monitored.

Lymphadenopathy which persists despite improvement in disease activity should be examined by biopsy as a precautionary measure to ensure the absence of lymphoma.

Active herpes simplex infections should be allowed to clear before treatment with Sandimmun is initiated, but are not necessarily a reason for treatment withdrawal if they occur during therapy unless infection is severe.

Skin infections with *Staphylococcus aureus* are not an absolute contraindication for Sandimmun therapy, but should be controlled with appropriate antibacterial agents. Oral erythromycin, which is known to have the potential to increase the blood concentration of ciclosporin (see section 4.5), should be avoided. If there is no alternative, it is recommended to closely monitor blood levels of ciclosporin, renal function, and for side effects of ciclosporin.

Patients on Sandimmun should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

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.

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-glycoprotein 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-glycoprotein are expected to decrease ciclosporin levels. Examples of drugs that decrease ciclosporin levels are:
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-glycoprotein may lead to increased levels of cyclosporine. 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 antibiotics: 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%.

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).

Effects of ciclosporin on other drugs
Ciclosporin is an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein (P-gp) and organic anion transporter proteins (OATP). Co-administration of drugs that are substrates of CYP3A4, P-gp and OATP with ciclosporin may 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 extexilate 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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies have shown reproductive toxicity in rats and rabbits.

Experience with Sandimmun in pregnant women is limited. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks).

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. However, there are no adequate and well-controlled studies in pregnant women and therefore Sandimmun 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 Sandimmun formulations should also be taken into account in pregnant women (see section 4.4).

Breast-feeding
Ciclosporin passes into breast milk. The ethanol content of the Sandimmun formulations should also be taken into account in women who are breast-feeding (see section 4.4). 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 breast-feeding or to abstain from using the medicinal drug, taking into account the importance of the medicinal product to the mother.

Fertility
There is limited data on the effect of Sandimmun human fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No data exist on the effects of Sandimmun on the ability to drive and use machines.

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 1) 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 1: 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
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	Muscle weakness, myopathy
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.

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).

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

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

Absorption
Following oral administration of Sandimmun peak blood concentrations are reached within 1 to 6 hours. The absolute oral bioavailability following administration of Sandimmun is 20 to 50%. The absorption of ciclosporin is variable and may be influenced by intake of food. About 37% increase in AUC C_{max} was observed when Sandimmun was administered with high-fat meal. Within the therapeutic dose range the peak plasma concentration and the area under the plasma concentration/time curve are proportional to the dose; for whole blood, however, the relationship is non-linear. Sandimmun oral solution and soft gelatin capsules are bioequivalent. The inter- and intra-subject variability ranges between 18 to 74%.

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 elimination half-life of ciclosporin, depending on the assay applied and 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. The 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 Sandimmun 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 Sandimmun Neoral and Sandimmun in paediatrics are comparable to those observed in adults.

5.3 Preclinical safety data

Ciclosporin gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg/day and rabbits up to 30 mg/kg/day orally). At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day orally), ciclosporin was embryo- and foetotoxic as indicated by increased prenatal and postnatal mortality, and reduced foetal weight together with related skeletal retardations.

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. Pregnant rats which received 12 mg/kg/day of ciclosporin intravenously (twice the recommended human intravenous dose) had foetuses with an increased incidence of ventricular septal defect. These findings have not been demonstrated in other species and their relevance for humans is unknown. No impairment in fertility was demonstrated in studies 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

Capsule contents
Ethanol anhydrous
Maize oil interesterified
Maize oil refined

Capsule shell
Iron oxide red (E172)
Titanium dioxide (E 171)
Glycerol 85%
Sorbitol syrup special
Gelatin

Capsule content
Ethanol anhydrous
Maize oil interesterified
Maize oil refined

Capsule shell
Iron oxide yellow (E172)
Titanium dioxide (E171)
Glycerol 85%
Sorbitol syrup special
Gelatin

Capsule content
Ethanol anhydrous
Maize oil interesterified
Maize oil refined

Capsule shell
Iron oxide red (E172)
Titanium dioxide (E171)
Glycerol 85%
Sorbitol syrup special
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

The capsules should be left in the blister pack until required for use and stored at a temperature not exceeding 30°C. When a blister is opened, a characteristic smell is noticeable; this is normal and does not mean that there is anything wrong with the capsule.

6.5 Nature and contents of container

Blister packs of double-sided aluminium consisting of aluminium foil on the bottom side and aluminium foil on the upper side.

[To be completed nationally]

6.6 Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}

{e-mail}

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

1. NAME OF THE MEDICINAL PRODUCT

Sandimmun and associated names (see Annex I) 100 mg/ml oral solution
[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral solution contains 100 mg ciclosporin.

Excipient with known effect:
Ethanol: 100 mg/ml. Sandimmun oral solution contains 12.6% v/v ethanol (10.0% m/v ethanol).

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Yellow to brownish yellow liquid, clear or with a small amount of very fine sediment.

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).

Non-transplantation indications
Endogenous uveitis
Treatment of sight-threatening intermediate or posterior uveitis of non-infectious aetiology in patients in whom conventional therapy has failed or caused unacceptable side effects.

Treatment of Behçet uveitis with repeated inflammatory attacks involving the retina in patients without neurological manifestations.

Nephrotic syndrome
Steroid-dependent and steroid-resistant nephrotic syndrome, due to primary glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis, or membranous glomerulonephritis.

Sandimmun can be used to induce and maintain remissions. It can also be used to maintain steroid-induced remission, allowing withdrawal of steroids.

Rheumatoid arthritis
Treatment of severe, active rheumatoid arthritis.

Psoriasis
Treatment of severe psoriasis in patients in whom conventional therapy is inappropriate or ineffective.

Atopic dermatitis
Sandimmun is indicated in patients with severe atopic dermatitis when systemic therapy is required.

4.2 Posology and method of administration

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

The daily doses of Sandimmun should be given in two divided doses equally distributed throughout the day. It is recommended that Sandimmun be administered on a consistent schedule with regard to time of day and in relation to meals.

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
Treatment with Sandimmun should be initiated within 12 hours before surgery at a dose of 10 to 15 mg/kg given in 2 divided doses. 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 Sandimmun 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 at daily 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 Sandimmun 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 Sandimmun, 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.

Non-transplantation indications
When using Sandimmun in any of the established non-transplantation indications, the following general rules should be adhered to:

Before initiation of treatment a reliable baseline level of renal function should be established by at least two measurements. The estimated glomerular filtration rate (eGFR) by the MDRD formula can be used for estimation of renal function in adults and an appropriate formula should be used to assess eGFR in paediatric patients. Since Sandimmun can impair renal function, it is necessary to assess renal function frequently. If eGFR decreases by more than 25% below baseline at more than one measurement, the dosage of Sandimmun should be reduced by 25 to 50%. If the eGFR decrease from baseline exceeds 35%, further reduction of the dose of Sandimmun should be considered. These recommendations apply even if the patient`s values still lie within the laboratory`s normal range. If dose reduction is not successful in improving eGFR within one month, Sandimmun treatment should be discontinued (see section 4.4).

Regular monitoring of blood pressure is required.

The determination of bilirubin and parameters that assess hepatic function are required prior to starting therapy and close monitoring during treatment is recommended. Determinations of serum lipids, potassium, magnesium and uric acid are advisable before treatment and periodically during treatment.

Occasional monitoring of ciclosporin blood levels may be relevant in non-transplant indications, e.g. when Sandimmun is co-administered with substances that may interfere with the pharmacokinetics of ciclosporin, or in the event of unusual clinical response (e.g. lack of efficacy or increased drug intolerance such as renal dysfunction).

The normal route of administration is by mouth. If the concentrate for solution for infusion is used, careful consideration should be given to administering an adequate intravenous dose that corresponds to the oral dose. Consultation with a physician with experience of use of ciclosporin is recommended.

Except in patients with sight-threatening endogenous uveitis and in children with nephrotic syndrome, the total daily dose must never exceed 5 mg/kg.

For maintenance treatment the lowest effective and well tolerated dosage should be determined individually.

In patients in whom within a given time (for specific information see below) no adequate response is achieved or the effective dose is not compatible with the established safety guidelines, treatment with Sandimmun should be discontinued.

Endogenous uveitis
For inducing remission, initially 5 mg/kg/day orally given in 2 divided doses are recommended until remission of active uveal inflammation and improvement in visual acuity are achieved. In refractory cases, the dose can be increased to 7 mg/kg/day for a limited period.

To achieve initial remission, or to counteract inflammatory ocular attacks, systemic corticosteroid treatment with daily doses of 0.2 to 0.6 mg/kg prednisone or an equivalent may be added if Sandimmun alone does not control the situation sufficiently. After 3 months, the dose of corticosteroids may be tapered to the lowest effective dose.

For maintenance treatment, the dose should be slowly reduced to the lowest effective level. During the remission phases, this should not exceed 5 mg/kg/day.

Infectious causes of uveitis should be ruled out before immunosuppressants can be used.

Nephrotic syndrome
For inducing remission, the recommended daily dose is given in 2 divided oral doses.

If the renal function (except for proteinuria) is normal, the recommended daily dose is the following:
- adults: 5 mg/kg
- children: 6 mg/kg

In patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day.

The combination of Sandimmun with low doses of oral corticosteroids is recommended if the effect of Sandimmun alone is not satisfactory, especially in steroid-resistant patients.

Time to improvement varies from 3 to 6 months depending on the type of glomerulopathy. If no improvement has been observed after this time to improvement period, Sandimmun therapy should be discontinued.

The doses need to be adjusted individually according to efficacy (proteinuria) and safety, but should not exceed 5 mg/kg/day in adults and 6 mg/kg/day in children.

For maintenance treatment, the dose should be slowly reduced to the lowest effective level.

Rheumatoid arthritis
For the first 6 weeks of treatment the recommended dose is 3 mg/kg/day orally given in 2 divided doses. If the effect is insufficient, the daily dose may then be increased gradually as tolerability permits, but should not exceed 5 mg/kg. To achieve full effectiveness, up to 12 weeks of Sandimmun therapy may be required.

For maintenance treatment the dose has to be titrated individually to the lowest effective level according to tolerability.

Sandimmun can be given in combination with low-dose corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs) (see section 4.4). Sandimmun can also be combined with low-dose weekly methotrexate in patients who have insufficient response to methotrexate alone, by using 2.5 mg/kg Sandimmun in 2 divided doses per day initially, with the option to increase the dose as tolerability permits.

Psoriasis
Sandimmun treatment should be initiated by physicians with experience in the diagnosis and treatment of psoriasis. Due to the variability of this condition, treatment must be individualised. For inducing remission, the recommended initial dose is 2.5 mg/kg/day orally given in 2 divided doses. If there is no improvement after 1 month, the daily dose may be gradually increased, but should not exceed 5 mg/kg. Treatment should be discontinued in patients in whom sufficient response of psoriatic lesions cannot be achieved within 6 weeks on 5 mg/kg/day, or in whom the effective dose is not compatible with the established safety guidelines (see section 4.4).

Initial doses of 5 mg/kg/day are justified in patients whose condition requires rapid improvement. Once satisfactory response is achieved, Sandimmun may be discontinued and subsequent relapse managed with re-introduction of Sandimmun at the previous effective dose. In some patients, continuous maintenance therapy may be necessary.

For maintenance treatment, doses have to be titrated individually to the lowest effective level, and should not exceed 5 mg/kg/day.

Atopic dermatitis
Sandimmun treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis. Due to the variability of this condition, treatment must be

individualised. The recommended dose range is 2.5 to 5 mg/kg/day given in 2 divided oral doses. If a starting dose of 2.5 mg/kg/day does not achieve a satisfactory response within 2 weeks, the daily dose may be rapidly increased to a maximum of 5 mg/kg. In very severe cases, rapid and adequate control of the disease is more likely to occur with a starting dose of 5 mg/kg/day. Once satisfactory response is achieved, the dose should be reduced gradually and, if possible, Sandimmun should be discontinued. Subsequent relapse may be managed with a further course of Sandimmun.

Although an 8-week course of therapy may be sufficient to achieve clearing, up to 1 year of therapy has been shown to be effective and well tolerated, provided the monitoring guidelines are followed.

Switching between oral ciclosporin formulations
The switch from one oral ciclosporin formulation to another should be made under physician supervision, including monitoring of blood levels of ciclosporin for transplantation patients.

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).

Non-transplantation indications
With the exception of patients being treated for nephrotic syndrome, patients with impaired renal function should not receive ciclosporin (see subsection on additional precautions in non-transplantation indications in section 4.4). In nephrotic syndrome patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day.

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
Oral administration
Sandimmun oral solution should be diluted in a glass (not plastic) container with cold chocolate drink, milk, fruit juice or cola immediately before being taken, stirred well and drunk at once. Owing to its

possible interference with the cytochrome P450 enzyme system, grapefruit juice should be avoided for dilution (see section 4.5). The syringe should not come in contact with the diluent. The glass must be rinsed well with some more diluent to ensure that all of the dose is taken. The syringe should not be rinsed, but wiped on the outside with a dry tissue to remove remaining drops of the solution (see section 6.6).

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.

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.

In non-transplant patients, occasional monitoring of ciclosporin blood levels is recommended, e.g. when Sandimmun is co-administered with substances that may interfere with the pharmacokinetics of ciclosporin, or in the event of unusual clinical response (e.g. lack of efficacy or increased drug intolerance such as renal dysfunction).
It must be remembered that the ciclosporin concentration in blood, plasma, or serum is only one of many factors contributing to the clinical status of the patient. Results should therefore serve only as a guide to dosage in relationship to other clinical and laboratory parameters.

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-glycoprotein (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).

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

Ciclosporin is an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein 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.

Special excipients: Polyoxyl 40 hydrogenated castor oil
Sandimmun contains polyoxyl 40 hydrogenated castor oil, which may cause stomach upsets and diarrhoea.

Special excipients: Ethanol
Sandimmun contains around 12% vol. ethanol. A 500 mg dose of Sandimmun contains 500 mg ethanol, equivalent to nearly 15 ml beer or 5 ml wine. This may be harmful in alcoholic patients and should be taken into account in pregnant or breast-feeding women, in patients presenting with liver disease or epilepsy, or if the patients is a child.

Additional precautions in non-transplantation indications

Patients with impaired renal function (except nephrotic syndrome patients with a permissible degree of renal impairment), uncontrolled hypertension, uncontrolled infections, or any kind of malignancy should not receive ciclosporin.

Before initiation of treatment a reliable baseline assessment of renal function should be established by at least two measurements of eGFR. Renal function must be assessed frequently throughout therapy to allow dosage adjustment (see section 4.2).

Additional precautions in endogenous uveitis
Sandimmun should be administered with caution in patients with neurological Behcet`s syndrome. The neurological status of these patients should be carefully monitored.

There is only limited experience with the use of Sandimmun in children with endogenous uveitis.

Additional precautions in nephrotic syndrome
Patients with abnormal baseline renal function should initially be treated with 2.5 mg/kg/day and must be monitored very carefully.

In some patients, it may be difficult to detect Sandimmun-induced renal dysfunction because of changes in renal function related to the nephrotic syndrome itself. This explains why, in rare cases, Sandimmun-associated structural kidney alterations have been observed without increases in serum creatinine. Renal biopsy should be considered for patients with steroid-dependent minimal-change nephropathy, in whom Sandimmun therapy has been maintained for more than 1 year.

In patients with nephrotic syndrome treated with immunosuppressants (including ciclosporin), the occurrence of malignancies (including Hodgkin's lymphoma) has occasionally been reported.

Additional precautions in rheumatoid arthritis
After 6 months of therapy, renal function needs to be assessed every 4 to 8 weeks depending on the stability of the disease, its co- medication, and concomitant diseases. More frequent checks are necessary when the Sandimmun dose is increased, or concomitant treatment with an NSAID is initiated or its dosage increased. Discontinuation of Sandimmun may also become necessary if hypertension developing during treatment cannot be controlled by appropriate therapy.

As with other long-term immunosuppressive treatments, an increased risk of lymphoproliferative disorders must be borne in mind. Special caution should be observed if Sandimmun is used in combination with methotrexate due to nephrotoxic synergy.

Additional precautions in psoriasis
Discontinuation of Sandimmun therapy is recommended if hypertension developing during treatment cannot be controlled with appropriate therapy.

Elderly patients should be treated only in the presence of disabling psoriasis, and renal function should be monitored with particular care.

There is only limited experience with the use of Sandimmun in children with psoriasis.

In psoriatic patients on ciclosporin, as in those on conventional immunosuppressive therapy, development of malignancies (in particular of the skin) has been reported. Skin lesions not typical for psoriasis, but suspected to be malignant or pre-malignant should be biopsied before Sandimmun treatment is started. Patients with malignant or pre-malignant alterations of the skin should be treated with Sandimmun only after appropriate treatment of such lesions, and if no other option for successful therapy exists.

In a few psoriatic patients treated with Sandimmun, lymphoproliferative disorders have occurred. These were responsive to prompt discontinuation.

Patients on Sandimmun should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

Additional precautions in atopic dermatitis
Discontinuation of Sandimmun is recommended if hypertension developing during treatment cannot be controlled with appropriate therapy.

Experience with Sandimmun in children with atopic dermatitis is limited.

Elderly patients should be treated only in the presence of disabling atopic dermatitis and renal function should be monitored with particular care.

Benign lymphadenopathy is commonly associated with flares in atopic dermatitis and invariably disappears spontaneously or with general improvement in the disease.

Lymphadenopathy observed on treatment with ciclosporin should be regularly monitored.

Lymphadenopathy which persists despite improvement in disease activity should be examined by biopsy as a precautionary measure to ensure the absence of lymphoma.

Active herpes simplex infections should be allowed to clear before treatment with Sandimmun is initiated, but are not necessarily a reason for treatment withdrawal if they occur during therapy unless infection is severe.

Skin infections with *Staphylococcus aureus* are not an absolute contraindication for Sandimmun therapy, but should be controlled with appropriate antibacterial agents. Oral erythromycin, which is known to have the potential to increase the blood concentration of ciclosporin (see section 4.5), should be avoided. If there is no alternative, it is recommended to closely monitor blood levels of ciclosporin, renal function, and for side effects of ciclosporin.

Patients on Sandimmun should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

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.

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-glycoprotein 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-glycoprotein are expected to decrease ciclosporin levels. Examples of drugs that decrease ciclosporin levels are:
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-glycoprotein may lead to increased levels of cyclosporine. 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 antibiotics: 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%.

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).

Effects of ciclosporin on other drugs
Ciclosporin is an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein (P-gp) and organic anion transporter proteins (OATP). Co-administration of drugs that are substrates of CYP3A4, P-gp and OATP with ciclosporin may 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 extexilate 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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies have shown reproductive toxicity in rats and rabbits.

Experience with Sandimmun in pregnant women is limited. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks).

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. However, there are no adequate and well-controlled studies in pregnant women and therefore Sandimmun 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 Sandimmun formulations should also be taken into account in pregnant women (see section 4.4).

Breast-feeding

Ciclosporin passes into breast milk. The ethanol content of the Sandimmun formulations should also be taken into account in women who are breast-feeding (see section 4.4). 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 breast-feeding or to abstain from using the medicinal drug, taking into account the importance of the medicinal product to the mother.

Fertility
There is limited data on the effect of Sandimmun on human fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No data exist on the effects of Sandimmun on the ability to drive and use machines.

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 1) 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 1: 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
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	Muscle weakness, myopathy
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.

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).

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

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

Absorption
Following oral administration of Sandimmun peak blood concentrations are reached within 1 to 6 hours. The absolute oral bioavailability following administration of Sandimmun is 20 to 50%. The absorption of ciclosporin is variable and may be influenced by intake of food. About 37% increase in AUC Cmax was observed when Sandimmun was administered with high-fat meal. Within the therapeutic dose range the peak plasma concentration and the area under the plasma concentration/time curve are proportional to the dose; for whole blood, however, the relationship is non-linear. Sandimmun oral solution and soft gelatin capsules are bioequivalent. The inter- and intra-subject variability ranges between 18 to 74%.

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 elimination half-life of ciclosporin, depending on the assay applied and 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. The 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 Sandimmun 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 Sandimmun Neoral and Sandimmun in paediatrics are comparable to those observed in adults.

5.3 Preclinical safety data

Ciclosporin gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg/day and rabbits up to 30 mg/kg/day orally). At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day orally), ciclosporin was embryo- and foetotoxic as indicated by increased prenatal and postnatal mortality, and reduced foetal weight together with related skeletal retardations.

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. Pregnant rats which received 12 mg/kg/day of ciclosporin intravenously (twice the recommended human intravenous dose) had foetuses with an increased incidence of ventricular septal defect. These findings have not been demonstrated in other species and their relevance for humans is unknown. No impairment in fertility was demonstrated in studies 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
Maize oil interesterified
Maize oil refined

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

The oral solution should not be refrigerated. It may be stored at room temperature not exceeding 30°C. A slight precipitate that may occur during storage does not affect the efficacy and safety of the drug. Once the bottle has been opened, the content must be used within 2 months.

6.5 Nature and contents of container

50 ml amber glass bottles with an aluminium cap and rubber stopper. A dispenser set is also provided.

[To be completed nationally]

6.6 Special precautions for disposal

Sandimmun oral solution is provided with two syringes for measuring the doses. The 1-ml syringe is used to measure doses less than or equal to 1 ml (each graduation of 0.05 ml corresponds to 5 mg of ciclosporin). The 4-ml syringe is used to measure doses greater than 1 ml and up to 4 ml (each graduation of 0.1 ml corresponds to 10 mg of ciclosporin).

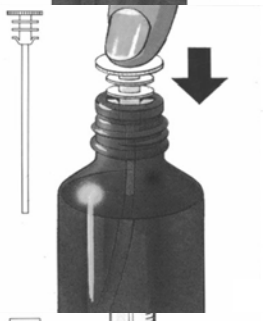
Initial use of Sandimmun oral solution

1. Raise the flap in the centre of the metal sealing ring.

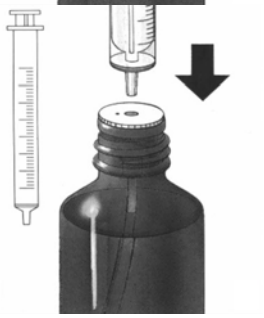
2. Tear off the sealing ring completely.

3. Remove the black stopper and throw it away.

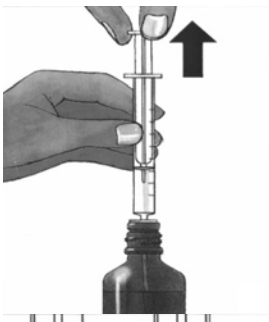
4. Push the tube unit with the white stopper firmly into the neck of the bottle.



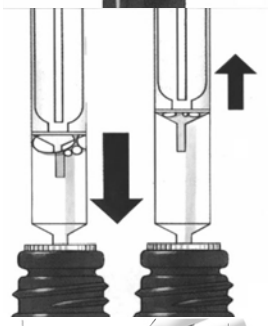
5. Choose the syringe depending on the prescribed volume. For volume less than 1 ml or equal to 1 ml, use the 1-ml syringe. For volume greater than 1 ml, use the 4-ml syringe. Insert the nozzle of the syringe into the white stopper.



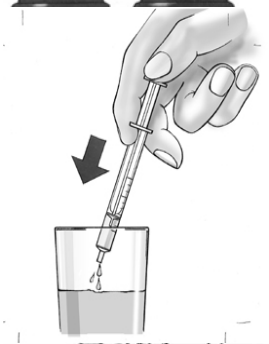
6. Draw up the prescribed volume of solution (position the lower part of the plunger ring in front of the graduation corresponding to the prescribed volume).



7. Expel any large bubbles by depressing and withdrawing the plunger a few times before removing the syringe containing the prescribed dose from bottle. The presence of a few tiny bubbles is of no importance and will not affect the dose in any way.



8. Push the medicine out of the syringe into a small glass with some liquid (not grapefruit juice). Avoid any contact between the syringe and the liquid in the glass. The medicine can be mixed just before it is taken. Stir and drink the entire mixture right away. Once mixed it should be taken immediately after preparation.



9. After use, wipe the syringe on the outside only with a dry tissue and replace it in its cover. The white stopper and tube should remain in the bottle. Close the bottle with the cap provided.

Subsequent use
Commence at point 5.

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

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

1. NAME OF THE MEDICINAL PRODUCT

Sandimmun and associated names (see Annex I) 50 mg/ml concentrate for solution for infusion
[See Annex I – To be completed nationally]

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).
Polyethoxylated 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.

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.

The daily doses of Sandimmun should be given in two divided doses equally distributed throughout the day. It is recommended that Sandimmun be administered on a consistent schedule with regard to time of day and in relation to meals.

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

Treatment with Sandimmun should be initiated within 12 hours before surgery at a dose of 10 to 15 mg/kg given in 2 divided doses. 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 Sandimmun 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.

If Sandimmun concentrate for solution for infusion is used, the recommended dose is approximately one-third of the corresponding Sandimmun oral dose, and it is recommend that patients be switched to oral therapy as soon as possible.

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 at daily 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 Sandimmun 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 Sandimmun, 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.

Polyethoxylated castor oil and anaphylactoid reactions
Sandimmun concentrate for solution for infusion contains polyethoxylated 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 polyethoxylated castor 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-glycoprotein (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).

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

Ciclosporin is an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein 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.

Special excipients: Polyoxyl 40 hydrogenated castor oil
Sandimmun contains polyoxyl 40 hydrogenated castor oil, which may cause stomach upsets and diarrhoea.

Special excipients: Ethanol
Sandimmun contains around 12% vol. ethanol. A 500 mg dose of Sandimmun contains 500 mg ethanol, equivalent to nearly 15 ml beer or 5 ml wine. This may be harmful in alcoholic patients and should be taken into account in pregnant or breast-feeding women, in patients presenting with liver disease or epilepsy, or if the patients is a child.

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.

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-glycoprotein 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-glycoprotein are expected to decrease ciclosporin levels. Examples of drugs that decrease ciclosporin levels are:
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-glycoprotein may lead to increased levels of cyclosporine. 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 antibiotics: 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%.

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).

Effects of ciclosporin on other drugs
Ciclosporin is an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein (P-gp) and organic anion transporter proteins (OATP). Co-administration of drugs that are substrates of CYP3A4, P-gp and OATP with ciclosporin may 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 extexilate 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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies have shown reproductive toxicity in rats and rabbits.

Experience with Sandimmun in pregnant women is limited. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks).

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. However, there are no adequate and well-controlled studies in pregnant women and therefore Sandimmun 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 Sandimmun formulations should also be taken into account in pregnant women (see section 4.4).

Breast-feeding
Ciclosporin passes into breast milk. The ethanol content of the Sandimmun formulations should also be taken into account in women who are breast-feeding (see section 4.4). 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 breast-feeding or to abstain from using the medicinal drug, taking into account the importance of the medicinal product to the mother.

Fertility
There is limited data on the effect of Sandimmun on human fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No data exist on the effects of Sandimmun on the ability to drive and use machines.

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 1) 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 1: 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
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	Muscle weakness, myopathy
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.

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).

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

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 Sandimmun 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 Sandimmun Neoral and Sandimmun in paediatrics are comparable to those observed in adults.

5.3 Preclinical safety data

Ciclosporin gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg/day and rabbits up to 30 mg/kg/day orally). At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day orally), ciclosporin was embryo- and foetotoxic as indicated by increased prenatal and postnatal mortality, and reduced foetal weight together with related skeletal retardations.

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. Pregnant rats which received 12 mg/kg/day of ciclosporin intravenously (twice the recommended human intravenous dose) had foetuses with an increased incidence of ventricular septal defect. These findings have not been

demonstrated in other species and their relevance for humans is unknown. No impairment in fertility was demonstrated in studies 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/polyethoxylated castor oil

6.2 Incompatibilities

Sandimmun concentrate for solution for infusion contains macrogolglycerol ricinoleate/polyethoxylated castor oil, which can cause phathalate 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

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package. Once an ampoule has been opened, the contents should be used immediately. Following dilution, the solution should be used immediately. If it is not used immediately, the conditions and duration of storage are the responsibility of the user and storage should not be longer than 24 hours at 2 to 8°C, unless dilution has been carried out under controlled and validated aseptic conditions.

6.5 Nature and contents of container

Uncoloured glass (type I) ampoule.
[To be completed nationally]

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

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}.

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGINGANDTHE IMMEDIATE PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Sandimmun and associated names (see Annex I) 25 mg soft capsules
Sandimmun and associated names (see Annex I) 50 mg soft capsules
Sandimmun and associated names (see Annex I) 100 mg soft capsules

[See Annex I - To be completed nationally]

Ciclosporin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Ciclosporin

[To be completed nationally]

3. LIST OF EXCIPIENTS

Contains ethanol (see leaflet for further information).

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, soft

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

[To be completed nationally]

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

[To be completed nationally]

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[To be completed nationally]

8. EXPIRY DATE

[To be completed nationally]

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
{tel}
{fax}
{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sandimmun and associated names (see Annex I) 25 mg soft capsules
Sandimmun and associated names (see Annex I) 50 mg soft capsules
Sandimmun and associated names (see Annex I) 100 mg soft capsules

[See Annex I - To be completed nationally]

Ciclosporin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name}

3. EXPIRY DATE

[To be completed nationally]

4. BATCH NUMBER

[To be completed nationally]

5. OTHER

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Sandimmun and associated names (see Annex I) 100 mg/ml oral solution

[See Annex I - To be completed nationally]

Ciclosporin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 mg ciclosporin

3. LIST OF EXCIPIENTS

Contains ethanol (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution containing 100 mg ciclosporin per mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

Read the package leaflet before use.

[To be completed nationally]

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

[To be completed nationally]

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[To be completed nationally]

8. EXPIRY DATE

[To be completed nationally]

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
{tel}
{fax}
{e-mail}

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Sandimmun and associated names (see Annex I) 50 mg/ml concentrate for solution for infusion
[See Annex I - To be completed nationally]

Ciclosporin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ampoule contains 50 mg/mL ciclosporin

3. LIST OF EXCIPIENTS

Also contains: Ethanol anhydrous, macrogolglycerol ricinoleate/polyethoxylated castor oil

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion containing 50 mg ciclosporin per mL.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous administration

Read the package leaflet before use.

[To be completed nationally]

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

[To be completed nationally]

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[To be completed nationally]

8. EXPIRY DATE

[To be completed nationally]

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sandimmun and associated names (see Annex I) 50 mg/ml concentrate for solution for infusion

[See Annex I - To be completed nationally]

Ciclosporin
Intravenous use

2. METHOD OF ADMINISTRATION

[To be completed nationally]

3. EXPIRY DATE

[To be completed nationally]

4. BATCH NUMBER

[To be completed nationally]

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

[To be completed nationally]

PACKAGE LEAFLET

Package leaflet: Information for the patient

Sandimmun 25 mg soft capsules
Sandimmun 50 mg soft capsules
Sandimmun 100 mg soft capsules

ciclosporin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Sandimmun is and what it is used for

What Sandimmun is
The name of your medicine is Sandimmun. It contains the active substance ciclosporin. This belongs to a group of medicines known as immunosuppressive agents. These medicines are used to lower the body's immune reactions.

What Sandimmun is used for and how Sandimmun works
- **If you have had an organ transplant, bone marrow and stem cell transplantation**, the function of Sandimmun is to control your body's immune system. Sandimmun prevents rejection of transplanted organs by blocking the development of certain cells which would normally attack the transplanted tissue.
- **If you have an autoimmune disease**, in which your body's immune response attacks your body's own cells, Sandimmun stops this immune reaction. Such diseases include eye problems which threaten your vision (endogenous uveitis, including Behçet's uveitis), severe cases of certain skin diseases (atopic dermatitis, or eczema and psoriasis), severe rheumatoid arthritis and a kidney disease called nephrotic syndrome.

2. What you need to know before you take Sandimmun

If you are taking Sandimmun following a transplant it will only be prescribed for you by a doctor with experience in transplants and/or autoimmune diseases.

The advice in this leaflet may vary depending on whether you are taking the medicine for a transplant or for an autoimmune disease.

Follow all your doctor's instructions carefully. They may differ from the general information contained in this leaflet.

Do not take Sandimmun:
- if you are allergic to ciclosporin or any of the other ingredients of this medicine (listed in section 6).
- with products containing *Hypericum perforatum* (St John´s Wort).
- with products containing *dabigatran etexilate* (used to avoid blood clots after surgery) *or bosentan and aliskiren* (used to reduce high blood pressure).

Do not take Sandimmun and **tell your doctor** if the above applies to you. If you are not sure, talk to your doctor before taking Sandimmun.

Warnings and precautions
Before and during treatment with Sandimmun, tell your doctor straight away:
- if you have any signs of infection, such as fever or a sore throat. Sandimmun suppresses the immune system and may also affect your body's ability to fight against infection.
- if you have liver problems.
- if you have kidney problems. Your doctor will carry out regular blood tests and may change your dose if necessary.
- if you develop high blood pressure. Your doctor will check your blood pressure regularly and may give you a medicine to lower blood pressure if necessary.
- if you have low levels of magnesium in your body. Your doctor may give you magnesium supplements to take, especially just after your operation if you have had a transplant.
- if you have high levels of potassium in your blood.
- if you have gout.
- if you need to have a vaccination.

If any of the above applies to you before or during treatment with Sandimmun, tell your doctor straight away.

Sunlight and sun protection
Sandimmun suppresses your immune system. This increases your risk of developing cancers, particularly of the skin and lymphoid system. You should limit your exposure to sunlight and UV light by:
- Wearing appropriate protective clothing.
- Often applying a sunscreen with a high protection factor.

Talk to your doctor before taking Sandimmun:
- if you have or have had alcohol-related problems.
- if you have epilepsy.
- if you have any liver problems.
- if you are pregnant.
- if you are breast-feeding.
- if this medicine is being prescribed for a child.

If any of the above apply to you (or you are not sure), tell your doctor before taking Sandimmun. This is because this medicine contains alcohol (see section below "Sandimmun contains ethanol").

Monitoring during your treatment with Sandimmun
Your doctor will check:
- the **levels of ciclosporin in your blood,** especially if you have had a transplant,
- your **blood pressure** before the start of your treatment and regularly during treatment,
- how well your **liver and kidneys** are working,
- your **blood lipids (fats)**.

If you have any questions about how Sandimmun works or why this medicine has been prescribed for you, ask your doctor.

In addition if you are taking Sandimmun for a non-transplant disease (intermediary or posterior uveitis and Behçet's uveitis, atopic dermatitis, severe rheumatoid arthritis or nephrotic syndrome), do not take Sandimmun:

- if you have kidney problems (except for nephrotic syndrome).
- if you have an infection which is not under control with medication.
- if you have any type of cancer.
- if you have high blood pressure (hypertension) which is not under control with medication. If you get high blood pressure during treatment and it cannot be controlled, Sandimmun should be stopped by your doctor.

Do not take Sandimmun if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Sandimmun.

If you are being treated for Behçet`s uveitis, your doctor will monitor you particularly carefully if you have neurological symptoms (for example: increased forgetfulness, personality changes noticed over time, psychiatric or mood disorders, burning sensation in limbs, decreased sensation in limbs, tingling sensation in limbs, weakness of limbs, walking disturbances, headache with or without nausea and vomiting, vision disturbances including restricted movement of eyeball).

Your doctor will closely monitor you if you are elderly and are being treated for psoriasis or atopic dermatitis. If you have been prescribed Sandimmun to treat your psoriasis or atopic dermatitis, you must not be exposed to any UVB-rays or phototherapy during treatment.

Children and adolescents
Sandimmun should not be given to children for a non-transplant disease, except for treatment of nephrotic syndrome.

Elderly population (65 years of age and older)
There is limited experience with Sandimmun in elderly patients. Your doctor should monitor how well your kidneys work. If you are over 65 and have psoriasis or atopic dermatitis, you should only be treated with Sandimmun if your condition is particularly severe.

Other medicines and Sandimmun
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular tell your doctor or pharmacist if you are taking any of the following medicines before or during Sandimmun treatment:

- Medicines that may affect your potassium levels. These include medicines which contain potassium, potassium supplements, water tablets (diuretics) called potassium-sparing diuretics and some medicines which lower your blood pressure.
- Methotrexate. This is used to treat tumours, severe psoriasis and severe rheumatoid arthritis.
- Medicines which may increase or decrease the level of ciclosporin (the active substance of Sandimmun) in your blood. Your doctor might check the level of ciclosporin in your blood when starting or stopping treatment with other medicines.
    - Medicines which may increase the level of ciclosporin in your blood include: antibiotics (such as erythromycin or azythromycin), anti-fungals (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 your 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),

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).

- Medicines which may affect your 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 your 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).
- Nifedipine. This is used to treat high blood pressure and heart pain. You might get swollen gums that might grow over your teeth if you are taking nifedipine during your treatment with ciclosporin.
- Digoxin (used to treat heart problems), medicines which lower cholesterol (HMG-CoA reductase inhibitors also called statins), prednisolone, etoposide (used to treat cancer), repaglinide (oral anti-diabetic medicine), immunosuppressives (everolimus, sirolimus), ambrisentan and specific anti-cancer medicines called anthracyclines (such as doxorubicin).

If any of the above applies to you (or you are not sure), talk to your doctor or pharmacist before taking Sandimmun.

Sandimmun with food and drink
Do not take Sandimmun with grapefruit or grapefruit juice. This is because these can affect how Sandimmun works.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking this medicine. Your doctor will discuss with you the potential risks of taking Sandimmun during pregnancy.

- **Tell your doctor if you are pregnant or intend to become pregnant.** Experience with Sandimmun in pregnancy is limited. In general, Sandimmun should not be taken during pregnancy. If it is necessary for you to take this medicine, your doctor will discuss with you the benefits and potential risks of taking it during pregnancy.
- **Tell your doctor if you are breast-feeding.** Breast-feeding is not recommended during treatment with Sandimmun. This is because ciclosporin, the active substance, passes into breast milk. This may affect your baby.

Driving and using machines
Sandimmun contains alcohol. This may affect your ability to drive and use machines.

Sandimmun contains ethanol
Sandimmun contains approximately 12.0 vol. % ethanol (alcohol), which corresponds to up to 500 mg per dose used in transplant patients. This is equivalent to nearly 15 ml beer or 5 ml wine per dose.

Alcohol may be harmful if you have alcohol-related problems, epilepsy, brain injury, liver problems or if you are pregnant or breast-feeding. It may also be harmful if this medicine is given to children.

Sandimmun contains castor oil
Sandimmun contains castor oil, which may cause stomach discomfort and diarrhoea.

Sandimmun contains sorbitol
If you have an intolerance to some sugars, inform your doctor before taking this medicine.

3. How to take Sandimmun

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.
Do not take more than the recommended dose.

The dose of this medicine will be carefully adjusted to your individual needs by your doctor. Too much of the medicine can affect your kidneys. You will have regular blood tests and visits to the hospital, especially after a transplant. This will give you the chance to talk to your doctor about your treatment and talk about any problems you may be having.

How much Sandimmun to take
Your doctor will work out the correct dose of Sandimmun for you. This depends on your body weight and what you are taking the medicine for. Your doctor will also tell you how often to take your medicine.

- **In adults:**
  Organ, bone marrow and stem cell transplantation
  - The total dose each day is usually between 2 mg and 15 mg per kilogram body weight. This is divided in two doses.
  - Usually, higher doses are used before and just after your transplant. Lower doses are used once your transplanted organ or bone marrow has stabilised.
  - Your doctor will adjust your dose to one that is ideal for you. To do this, your doctor may need to do some blood tests.

  Endogenous uveitis
  - The total dose each day is usually between 5 mg and 7 mg per kilogram body weight. This is divided in two doses.

  Nephrotic syndrome
  - The total dose each day for adults is usually 5 mg per kilogram body weight. This is divided in two doses. In patients with kidney problems, the first dose taken each day should not be more than 2.5 mg per kilogram body weight.

  Severe rheumatoid arthritis
  - The total dose each day is usually between 3 mg per kilogram of your body weight and 5 mg per kilogram body weight. This is divided in two doses.

  Psoriasis and atopic dermatitis
  - The total dose each day is usually between 2.5 mg per kilogram of your body weight and 5 mg per kilogram body weight. This is divided in two doses.
- **In children:**
  Nephrotic syndrome
  - The total dose each day for children is usually 6 mg per kilogram body weight. This is divided in two doses. In patients with kidney problems, the first dose taken each day should not be more than 2.5 mg per kilogram body weight.

Follow your doctor's instructions exactly and never change the dose yourself, even if you feel well.

If your doctor switches you from one oral formulation of ciclosporin to another
After you change from one oral formulation of ciclosporin to another:
- Your doctor will monitor you more closely for a short time.
- You may have some side effects. If this happens, tell your doctor or pharmacist. Your dose may need to be changed. Never change your dose yourself, unless a doctor has told you to.

When to take Sandimmun
Take Sandimmun **at the same time every day**. This is very important if you have had a transplant.

How to take Sandimmun
Your daily doses should always be taken in 2 divided doses.
Remove the capsules from the blister. Swallow the capsules whole with water.

How long to take Sandimmun

Your doctor will tell you how long you need to take Sandimmun for. This depends on whether you are taking it after a transplant or for the treatment of a severe skin condition, rheumatoid arthritis, uveitis or nephrotic syndrome. For severe rash, the treatment usually lasts for 8 weeks.

Keep taking Sandimmun for as long as your doctor tells you.

If you have questions about how long to take Sandimmun, talk to your doctor or your pharmacist.

If you take more Sandimmun than you should
If you accidentally take too much of your medicine, tell your doctor immediately or go to your nearest hospital emergency unit. You may need medical attention.

If you forget to take Sandimmun
- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose. Then go on as before.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Sandimmun
Do not stop taking Sandimmun unless your doctor tells you to.

Keep taking Sandimmun even if you feel well. Stopping your treatment with Sandimmun may increase the risk of your transplanted organ being rejected.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious
Tell your doctor straight away if you notice any of the following serious side effects:
- Like other medicines that act on the immune system, ciclosporin may influence your body's ability to fight against infection and may cause tumours or other cancers, particularly of the skin. Signs of infection might be fever or sore throat.
- Changes in your 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.
- 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.
- Swelling at the back of the eye. This may be associated with blurred vision. It may also affect your sight because of the higher pressure inside your head (benign intracranial hypertension).
- Liver problems and damage with or without yellow skin and eyes, nausea, loss of appetite and dark urine.
- Kidney problems which may greatly reduce the amount of urine you produce.
- Low level of red blood cells or platelets. The signs include pale skin, feeling tired, being breathless, having dark urine (this is a sign of the breakdown of red blood cells), bruising or bleeding with no obvious reasons, feeling confused, feeling disorientated, being less alert and having kidney problems.

Other side effects include:

Very common side effects: *These side effects may affect more than 1 in 10 people.*

- Kidney problems.
- High blood pressure.
- Headache.
- Shaking of your body which you cannot control.
- Excessive growth of body and facial hair.
- High level of lipids in your blood.

If any of these affects you severely, **tell your doctor**.

Common side effects: *These side effects may affect between 1 and 10 in every 100 people.*

- Fits (seizures).
- Liver problems.
- High level of sugar in your blood.
- Tiredness.
- Loss of appetite.
- Nausea (feeling sick), vomiting, abdominal pain, constipation, diarrhoea.
- Excessive hair growth.
- Acne, hot flushes.
- Fever.
- Low level of white blood cells.
- Feeling numb or tingling.
- Pain in your muscles, muscle spasm.
- Stomach ulcer.
- Gum tissue overgrowing and covering your teeth.
- High level of uric acid or patassium in your blood, low levels of magnesium in your blood.

If any of these affects you severely, **tell your doctor**.

Uncommon side effects: *These side effects may affect between 1 and 10 in every 1,000 people.*

- Symptoms of brain disorders including sudden fits, mental confusion, sleeplessness, disorientation, disturbance of vision, unconsciousness, sense of weakness in the limbs, impaired movements.
- Rash.
- General swelling.
- Weight gain.
- Low level of red blood cells, low level of platelets in your blood which could increase the risk of bleeding.

If any of these affects you severely, **tell your doctor**.

Rare side effects: *These side effects may affect between 1 and 10 in every 10,000 people.*

- Nerve problems with numbness or tingling in fingers and toes.
- Inflammation of the pancreas with severe upper stomach pain.
- Muscle weakness, loss of muscle strength, pain in muscles of the legs or hands or anywhere in the body.
- Destruction of red blood cells, involving kidney problems with symptoms such as swelling of the face, stomach, hands and/or feet, decreased urination, breathing difficulty, chest pain, fits, unconsciousness.
- Changes in menstrual cycle, breast enlargement in men.

If any of these affects you severely, **tell your doctor**.

Very rare side effects: *These side effects may affect between 1 and 10 in every 100,000 people.*

- Swelling at the back of the eye which may be associated with an increase in pressure inside the head and eyesight disturbances.

If this affects you severely, **tell your doctor**.

Other side effects with frequency not known: Frequency cannot be estimated from the available data.

- 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.
- Bleeding underneath the skin or purple skin patched, sudden bleeding with no apparent cause.
- Migraine or severe headache often with feeling and being sick (nausea, vomiting) and being sensitive to light.

If any of these affects you severely, **tell your doctor**.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Additional side effects in children and adolescents
There are no additional side effects to be expected in children and adolescents compared to adults.

5. How to store Sandimmun

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the package.
- Do not store your capsules in a hot place (maximum temperature 30°C).
- Leave your capsules in the foil. Only remove them when it is time to take your medicine.
- When a blister is opened, a characteristic smell is noticeable. This is normal and does not mean that there is anything wrong with the capsules.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Sandimmun contains

- The active substance is ciclosporin. Each capsule contains 25 mg ciclosporin.
- The other ingredients are:
  - Capsule contents: ethanol anhydrous, maize oil interesterified, maize oil refined.
  - Capsule shell: Iron oxide red (E172), titanium dioxide (E 171), glycerol 85%, sorbitol syrup special, gelatin.
- The active substance is ciclosporin. Each capsule contains 50 mg ciclosporin.
- The other ingredients are:
  - Capsule contents: ethanol anhydrous, maize oil interesterified, maize oil refined.
  - Capsule shell: Iron oxide yellow (E172), titanium dioxide (E171), glycerol 85%, sorbitol syrup special, gelatin.
- The active substance is ciclosporin. Each capsule contains 100 mg ciclosporin.
- The other ingredients are:
  - Capsule content: ethanol anhydrous, maize oil interesterified, maize oil refined.
  - Capsule shell: Iron oxide red (E172), titanium dioxide (E 171), glycerol 85%, sorbitol syrup special, gelatin.

What Sandimmun looks like and contents of the pack

Sandimmun 25 mg soft capsules are pink and oval.
Sandimmun 50 mg soft capsules are corn yellow and oblong.
Sandimmun 100 mg soft capsules are dusty rose and oblong.

Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

{Name of the Member State} {Name of the medicinal product}
{Name of the Member State} {Name of the medicinal product}

This leaflet was last revised in {MM/YYYY} {month YYYY}.

[To be completed nationally]

Package leaflet: Information for the patient

Sandimmun 100 mg/ml oral solution

ciclosporin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Sandimmun is and what it is used for

What Sandimmun is
The name of your medicine is Sandimmun. It contains the active substance ciclosporin. This belongs to a group of medicines known as immunosuppressive agents. These medicines are used to lower the body's immune reactions.

What Sandimmun is used for and how Sandimmun works
- **If you have had an organ transplant, bone marrow and stem cell transplantation**, the function of Sandimmun is to control your body's immune system. Sandimmun prevents rejection of transplanted organs by blocking the development of certain cells which would normally attack the transplanted tissue.
- **If you have an autoimmune disease**, in which your body's immune response attacks your body's own cells, Sandimmun stops this immune reaction. Such diseases include eye problems which threaten your vision (endogenous uveitis, including Behçet's uveitis), severe cases of certain skin diseases (atopic dermatitis, or eczema and psoriasis), severe rheumatoid arthritis and a kidney disease called nephrotic syndrome.

2. What you need to know before you take Sandimmun

If you are taking Sandimmun following a transplant it will only be prescribed for you by a doctor with experience in transplants and/or autoimmune diseases.

The advice in this leaflet may vary depending on whether you are taking the medicine for a transplant or for an autoimmune disease.

Follow all your doctor's instructions carefully. They may differ from the general information contained in this leaflet.

Do not take Sandimmun:

- if you are allergic to ciclosporin or any of the other ingredients of this medicine (listed in section 6).
- with products containing *Hypericum perforatum* (St John´s Wort).
- with products containing *dabigatran etexilate* (used to avoid blood clots after surgery) *or bosentan and aliskiren* (used to reduce high blood pressure).

Do not take Sandimmun and **tell your doctor** if the above applies to you. If you are not sure, talk to your doctor before taking Sandimmun.

Warnings and precautions
Before and during treatment with Sandimmun, tell your doctor straight away:
- if you have any signs of infection, such as fever or a sore throat. Sandimmun suppresses the immune system and may also affect your body's ability to fight against infection.
- if you have liver problems.
- if you have kidney problems. Your doctor will carry out regular blood tests and may change your dose if necessary.
- if you develop high blood pressure. Your doctor will check your blood pressure regularly and may give you a medicine to lower blood pressure if necessary.
- if you have low levels of magnesium in your body. Your doctor may give you magnesium supplements to take, especially just after your operation if you have had a transplant.
- if you have high levels of potassium in your blood.
- if you have gout.
- if you need to have a vaccination.

If any of the above applies to you before or during treatment with Sandimmun, tell your doctor straight away.

Sunlight and sun protection
Sandimmun suppresses your immune system. This increases your risk of developing cancers, particularly of the skin and lymphoid system. You should limit your exposure to sunlight and UV light by:
- Wearing appropriate protective clothing.
- Often applying a sunscreen with a high protection factor.

Talk to your doctor before taking Sandimmun:
- if you have or have had alcohol-related problems.
- if you have epilepsy.
- if you have any liver problems.
- if you are pregnant.
- if you are breast-feeding.
- if this medicine is being prescribed for a child.

If any of the above apply to you (or you are not sure), tell your doctor before taking Sandimmun. This is because this medicine contains alcohol (see section below "Sandimmun contains ethanol").

Monitoring during your treatment with Sandimmun
Your doctor will check:
- the **levels of ciclosporin in your blood,** especially if you have had a transplant,
- your **blood pressure** before the start of your treatment and regularly during treatment,
- how well your **liver and kidneys** are working,
- your **blood lipids (fats)**.

If you have any questions about how Sandimmun works or why this medicine has been prescribed for you, ask your doctor.

In addition if you are taking Sandimmun for a non-transplant disease (intermediary or posterior uveitis and Behçet's uveitis, atopic dermatitis, severe rheumatoid arthritis or nephrotic syndrome), do not take Sandimmun:

- if you have kidney problems (except for nephrotic syndrome).
- if you have an infection which is not under control with medication.
- if you have any type of cancer.
- if you have high blood pressure (hypertension) which is not under control with medication. If you get high blood pressure during treatment and it cannot be controlled, Sandimmun should be stopped by your doctor.

Do not take Sandimmun if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Sandimmun.

If you are being treated for Behçet`s uveitis, your doctor will monitor you particularly carefully if you have neurological symptoms (for example: increased forgetfulness, personality changes noticed over time, psychiatric or mood disorders, burning sensation in limbs, decreased sensation in limbs, tingling sensation in limbs, weakness of limbs, walking disturbances, headache with or without nausea and vomiting, vision disturbances including restricted movement of eyeball).

Your doctor will closely monitor you if you are elderly and are being treated for psoriasis or atopic dermatitis. If you have been prescribed Sandimmun to treat your psoriasis or atopic dermatitis, you must not be exposed to any UVB-rays or phototherapy during treatment.

Children and adolescents
Sandimmun should not be given to children for a non-transplant disease, except for treatment of nephrotic syndrome.

Elderly population (65 years of age and older)
There is limited experience with Sandimmun in elderly patients. Your doctor should monitor how well your kidneys work. If you are over 65 and have psoriasis or atopic dermatitis, you should only be treated with Sandimmun if your condition is particularly severe.

Other medicines and Sandimmun
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular tell your doctor or pharmacist if you are taking any of the following medicines before or during Sandimmun treatment:

- Medicines that may affect your potassium levels. These include medicines which contain potassium, potassium supplements, water tablets (diuretics) called potassium-sparing diuretics and some medicines which lower your blood pressure.
- Methotrexate. This is used to treat tumours, severe psoriasis and severe rheumatoid arthritis.
- Medicines which may increase or decrease the level of ciclosporin (the active substance of Sandimmun) in your blood. Your doctor might check the level of ciclosporin in your blood when starting or stopping treatment with other medicines.
  - Medicines which may increase the level of ciclosporin in your blood include: antibiotics (such as erythromycin or azythromycin), anti-fungals (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 your 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), 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).
- Medicines which may affect your 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 your 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).
- Nifedipine. This is used to treat high blood pressure and heart pain. You might get swollen gums that might grow over your teeth if you are taking nifedipine during your treatment with ciclosporin.
- Digoxin (used to treat heart problems), medicines which lower cholesterol (HMG-CoA reductase inhibitors also called statins), prednisolone, etoposide (used to treat cancer), repaglinide (oral anti-diabetic medicine), immunosuppressives (everolimus, sirolimus), ambrisentan and specific anti-cancer medicines called anthracyclines (such as doxorubicin).

If any of the above applies to you (or you are not sure), talk to your doctor or pharmacist before taking Sandimmun.

Sandimmun with food and drink
Do not take Sandimmun with grapefruit or grapefruit juice. This is because these can affect how Sandimmun works.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking this medicine. Your doctor will discuss with you the potential risks of taking Sandimmun during pregnancy.
- **Tell your doctor if you are pregnant or intend to become pregnant.** Experience with Sandimmun in pregnancy is limited. In general, Sandimmun should not be taken during pregnancy. If it is necessary for you to take this medicine, your doctor will discuss with you the benefits and potential risks of taking it during pregnancy.
- **Tell your doctor if you are breast-feeding.** Breast-feeding is not recommended during treatment with Sandimmun. This is because ciclosporin, the active substance, passes into breast milk. This may affect your baby.

Driving and using machines
Sandimmun contains alcohol. This may affect your ability to drive and use machines.

Sandimmun contains ethanol
Sandimmun contains approximately 12.0 vol. % ethanol (alcohol), which corresponds to up to 500 mg per dose used in transplant patients. This is equivalent to nearly 15 ml beer or 5 ml wine per dose.

Alcohol may be harmful if you have alcohol-related problems, epilepsy, brain injury, liver problems or if you are pregnant or breast-feeding. It may also be harmful if this medicine is given to children.

Sandimmun contains castor oil
Sandimmun contains castor oil, which may cause stomach discomfort and diarrhoea.

3. How to take Sandimmun

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.
Do not take more than the recommended dose.

The dose of this medicine will be carefully adjusted to your individual needs by your doctor. Too much of the medicine can affect your kidneys. You will have regular blood tests and visits to the hospital, especially after a transplant. This will give you the chance to talk to your doctor about your treatment and talk about any problems you may be having.

How much Sandimmun to take
Your doctor will work out the correct dose of Sandimmun for you. This depends on your body weight and what you are taking the medicine for. Your doctor will also tell you how often to take your medicine.

- **In adults:**
  Organ, bone marrow and stem cell transplantation
  - The total dose each day is usually between 2 mg and 15 mg per kilogram body weight. This is divided in two doses.
  - Usually, higher doses are used before and just after your transplant. Lower doses are used once your transplanted organ or bone marrow has stabilised.
  - Your doctor will adjust your dose to one that is ideal for you. To do this, your doctor may need to do some blood tests.

  Endogenous uveitis
  - The total dose each day is usually between 5 mg and 7 mg per kilogram body weight. This is divided in two doses.

  Nephrotic syndrome
  - The total dose each day for adults is usually 5 mg per kilogram body weight. This is divided in two doses. In patients with kidney problems, the first dose taken each day should not be more than 2.5 mg per kilogram body weight.

  Severe rheumatoid arthritis
  - The total dose each day is usually between 3 mg per kilogram of your body weight and 5 mg per kilogram body weight. This is divided in two doses.

  Psoriasis and atopic dermatitis
  - The total dose each day is usually between 2.5 mg per kilogram of your body weight and 5 mg per kilogram body weight. This is divided in two doses.
- **In children:**
  Nephrotic syndrome
  - The total dose each day for children is usually 6 mg per kilogram body weight. This is divided in two doses. In patients with kidney problems, the first dose taken each day should not be more than 2.5 mg per kilogram body weight.

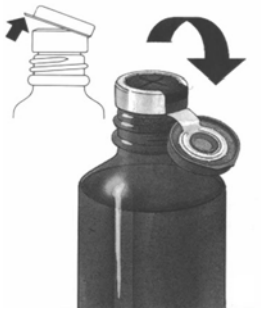
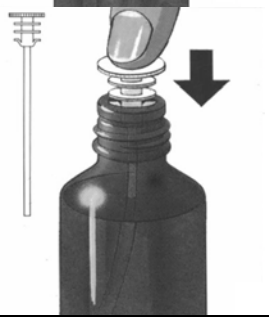
Follow your doctor's instructions exactly and never change the dose yourself, even if you feel well.

If your doctor switches you from one oral formulation of ciclosporin to another
After you change from one oral formulation of ciclosporin to another:
- Your doctor will monitor you more closely for a short time.
- You may have some side effects. If this happens, tell your doctor or pharmacist. Your dose may need to be changed. Never change your dose yourself, unless a doctor has told you to.

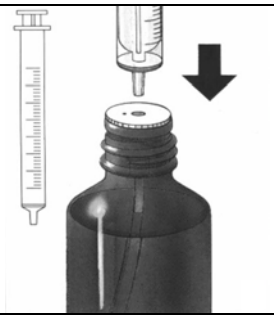
When to take Sandimmun
Take Sandimmun **at the same time every day**. This is very important if you have had a transplant.

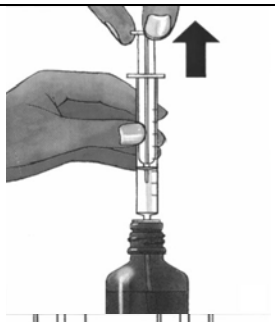
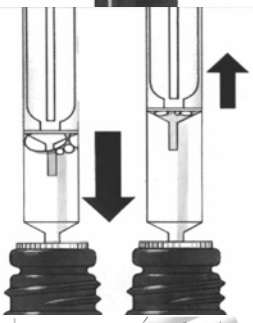
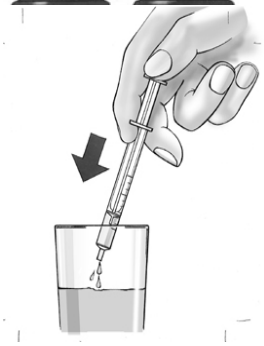
How to take Sandimmun
Your daily doses should always be taken in 2 divided doses.
- For initial use, follow steps 1 to 9.
- For subsequent use, follow steps 5 to 9.

Starting a new bottle of Sandimmun oral solution

1.	Lift the flap in the centre of the metal sealing ring.	
2.	Tear off the sealing ring completely.	
3.	Take off the black stopper and throw it away.	
4.	Push the tube unit with the white stopper firmly into the neck of the bottle.	

Measuring your dose

5.	Choose the syringe depending on how much medicine you need to measure: - For 1 ml or less of medicine, use the 1 ml syringe. - For more than 1 ml of medicine, use the 4 ml syringe. Push the nozzle of the syringe into the white stopper.	

6.	Pull up the plunger until you have drawn up the correct amount of medicine. - The lower part of the plunger ring needs to be in front of the mark on the syringe which shows the amount of medicine.	
7.	Push down and pull up the plunger a few times. - This will get rid of any large air bubbles. It does not matter if there are a few tiny bubbles in the syringe. This will not affect the dose in any way. Ensure that the correct amount of medicine is in the syringe. Then, take the syringe out of the bottle	
8.	Push the medicine out of the syringe into a small glass (not plastic) containing liquids, preferably cold chocolate drink, milk, fruit juice or cola - Make sure that the syringe does not touch the liquid in the glass. - Stir and drink the whole contents of the glass straight away.	
9.	After use, wipe the syringe on the outside only with a dry tissue. - Then, put the syringe back in its cover. - Leave the white stopper and tube in the bottle. - Close the bottle with the cap provided.	

How long to take Sandimmun
Your doctor will tell you how long you need to take Sandimmun for. This depends on whether you are taking it after a transplant or for the treatment of a severe skin condition, rheumatoid arthritis, uveitis or nephrotic syndrome. For severe rash, the treatment usually lasts for 8 weeks.

Keep taking Sandimmun for as long as your doctor tells you.

If you have questions about how long to take Sandimmun, talk to your doctor or your pharmacist.

If you take more Sandimmun than you should
If you accidentally take too much of your medicine, tell your doctor immediately or go to your nearest hospital emergency unit. You may need medical attention.

If you forget to take Sandimmun
- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose. Then go on as before.

- Do not take a double dose to make up for a forgotten dose.

If you stop taking Sandimmun
Do not stop taking Sandimmun unless your doctor tells you to.

Keep taking Sandimmun even if you feel well. Stopping your treatment with Sandimmun may increase the risk of your transplanted organ being rejected.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious
Tell your doctor straight away if you notice any of the following serious side effects:
- Like other medicines that act on the immune system, ciclosporin may influence your body's ability to fight against infection and may cause tumours or other cancers, particularly of the skin. Signs of infection might be fever or sore throat.
- Changes in your 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.
- 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.
- Swelling at the back of the eye. This may be associated with blurred vision. It may also affect your sight because of the higher pressure inside your head (benign intracranial hypertension).
- Liver problems and damage with or without yellow skin and eyes, nausea, loss of appetite and dark urine.
- Kidney problems which may greatly reduce the amount of urine you produce.
- Low level of red blood cells or platelets. The signs include pale skin, feeling tired, being breathless, having dark urine (this is a sign of the breakdown of red blood cells), bruising or bleeding with no obvious reasons, feeling confused, feeling disorientated, being less alert and having kidney problems.

Other side effects include:

Very common side effects: *These side effects may affect more than 1 in 10 people.*
- Kidney problems.
- High blood pressure.
- Headache.
- Shaking of your body which you cannot control.
- Excessive growth of body and facial hair.
- High level of lipids in your blood.

If any of these affects you severely, **tell your doctor**.

Common side effects: *These side effects may affect between 1 and 10 in every 100 people.*
- Fits (seizures).
- Liver problems.
- High level of sugar in your blood.
- Tiredness.
- Loss of appetite.

- Nausea (feeling sick), vomiting, abdominal pain, constipation, diarrhoea.
- Excessive hair growth.
- Acne, hot flushes.
- Fever.
- Low level of white blood cells.
- Feeling numb or tingling.
- Pain in your muscles, muscle spasm.
- Stomach ulcer.
- Gum tissue overgrowing and covering your teeth.
- High level of uric acid or patassium in your blood, low levels of magnesium in your blood.

If any of these affects you severely, **tell your doctor**.

Uncommon side effects: *These side effects may affect between 1 and 10 in every 1,000 people.*
- Symptoms of brain disorders including sudden fits, mental confusion, sleeplessness, disorientation, disturbance of vision, unconsciousness, sense of weakness in the limbs, impaired movements.
- Rash.
- General swelling.
- Weight gain.
- Low level of red blood cells, low level of platelets in your blood which could increase the risk of bleeding.

If any of these affects you severely, **tell your doctor**.

Rare side effects: *These side effects may affect between 1 and 10 in every 10,000 people.*
- Nerve problems with numbness or tingling in fingers and toes.
- Inflammation of the pancreas with severe upper stomach pain.
- Muscle weakness, loss of muscle strength, pain in muscles of the legs or hands or anywhere in the body.
- Destruction of red blood cells, involving kidney problems with symptoms such as swelling of the face, stomach, hands and/or feet, decreased urination, breathing difficulty, chest pain, fits, unconsciousness.
- Changes in menstrual cycle, breast enlargement in men.

If any of these affects you severely, **tell your doctor**.

Very rare side effects: *These side effects may affect between 1 and 10 in every 100,000 people.*
- Swelling at the back of the eye which may be associated with an increase in pressure inside the head and eyesight disturbances.

If this affects you severely, **tell your doctor**.

Other side effects with frequency not known: Frequency cannot be estimated from the available data.
- 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.
- Bleeding underneath the skin or purple skin patched, sudden bleeding with no apparent cause.
- Migraine or severe headache often with feeling and being sick (nausea, vomiting) and being sensitive to light.

If any of these affects you severely, **tell your doctor**.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Additional side effects in children and adolescents
There are no additional side effects to be expected in children and adolescents compared to adults.

5. How to store Sandimmun

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the package.
- Store at room temperature (15°C to 30°C).
- Do not store in the refrigerator.
- If the medicine is put in the refrigerator by mistake, let it reach room temperature before using it again. Flakes or small bits (sediments) in the medicine do not affect how the medicine works or how safe it is to use. The dose can still be measured correctly with the syringe.
- The content of the bottle is stable for 2 months after opening. After 2 months, you should use a new bottle.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Sandimmun contains

- The active substance is ciclosporin. One ml oral solution contains 100 mg ciclosporin.
- The other ingredients are ethanol anhydrous, maize oil interesterified, maize oil refined.

What Sandimmun looks like and contents of the pack

Sandimmun comes in the form of an oral solution. It is a clear, yellow to yellow-brownish liquid with a small amount of very fine sediment.
It is available in a 50 ml glass bottle, with two syringes for measuring the dose.

- The 1 ml syringe is used to measure doses of 1 ml or smaller. Each mark on the syringe is 0.05 ml. This contains 5 mg of ciclosporin.
- The 4 ml syringe is used to measure doses bigger than 1 ml and up to 4 ml. Each mark on the syringe is 0.1 ml. This contains 10 mg of ciclosporin.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

{Name of the Member State} {Name of the medicinal product}
{Name of the Member State} {Name of the medicinal product}

This leaflet was last revised in {MM/YYYY} {month YYYY}.

[To be completed nationally]

Package leaflet: Information for the patient

Sandimmun 50 mg/ml concentrate for solution for infusion

ciclosporin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Sandimmun is and what it is used for

What Sandimmun is
The name of your medicine is Sandimmun. It contains the active substance ciclosporin. The concentrate is used to prepare a solution which is administered by intravenous infusion. This belongs to a group of medicines known as immunosuppressive agents. These medicines are used to lower the body's immune reactions.

What Sandimmun is used for and how it works
Sandimmun is used to control the body's immune system following an organ transplant, including bone marrow and stem cell transplantation. It prevents rejection of transplanted organs by blocking the development of certain cells which would normally attack the transplanted tissue.

2. What you need to know before Sandimmun is used

Sandimmun will only be prescribed for you by a doctor with experience in transplants.

Follow all your doctor's instructions carefully. They may differ from the general information contained in this leaflet.

Do not use Sandimmun:
- if you are allergic to ciclosporin or any of the other ingredients of this medicine (listed in section 6; also see section "Sandimmun contains castor oil and ethanol").
- with products containing *Hypericum perforatum* (St John´s Wort).
- with products containing *dabigatran etexilate* (used to avoid blood clots after surgery) *or bosentan and aliskiren* (used to reduce high blood pressure).

Do not use Sandimmun and **tell your doctor** if the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Sandimmun.

Warnings and precautions
Before and during treatment with Sandimmun, tell your doctor straight away:
- if you have any signs of infection, such as fever or a sore throat. Sandimmun suppresses the immune system and may also affect your body's ability to fight against infection.
- if you have liver problems.
- if you have kidney problems. Your doctor will carry out regular blood tests and may change your dose if necessary.
- if you develop high blood pressure. Your doctor will check your blood pressure regularly and may give you a medicine to lower blood pressure if necessary.
- if you have low levels of magnesium in your body. Your doctor may give you magnesium supplements to take, especially just after your transplant operation.
- if you have high levels of potassium in your blood.
- if you have gout.
- if you need to have a vaccination.

If any of the above applies to you before or during treatment with Sandimmun, tell your doctor straight away.

Sunlight and sun protection
Sandimmun suppresses your immune system. This increases your risk of developing cancers, particularly of the skin and lymphoid system. You should limit your exposure to sunlight and UV light by:
- Wearing appropriate protective clothing.
- Often applying a sunscreen with a high protection factor.

Talk to your doctor before taking Sandimmun:
- if you have or have had alcohol related problems.
- if you have epilepsy.
- if you have any liver problems.
- if you are pregnant.
- if you are breast-feeding.
- if this medicine is being prescribed for a child.

If any of the above applies to you (or you are not sure), tell your doctor before taking Sandimmun. This is because this medicine contains alcohol (see section below "Sandimmun conatins castor oil and ethanol").

Monitoring during your treatment with Sandimmun
Your doctor will check:
- the **levels of ciclosporin in your blood,** especially if you have had a transplant,
- your **blood pressure** before the start of your treatment and regularly during treatment,
- how well your **liver and kidneys** are working,
- your **blood lipids (fats)**.

If you have any questions about how Sandimmun works or why this medicine has been prescribed for you, ask your doctor.

Children and adolescents
There is limited experience with Sandimmun in children.

Elderly population (65 years of age and older)
There is limited experience with Sandimmun in elderly patients. Your doctor should monitor how well your kidneys work.

Other medicines and Sandimmun
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines before or during Sandimmun treatment:

- Medicines that may affect your potassium levels. These include medicines which contain potassium, potassium supplements, water tablets (diuretics) called potassium-sparing diuretics, and some medicines which lower your blood pressure.
- Methotrexate. This is used to treat tumours, severe psoriasis and severe rheumatoid arthritis.
- Medicines which may increase or decrease the level of ciclosporin (the active substance of Sandimmun) in your blood. Your doctor might check the level of ciclosporin in your blood when starting or stopping treatment with other medicines.
    - Medicines which may increase the level of ciclosporin in your blood include: antibiotics (such as erythromycin or azythromycin), anti-fungals (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 your blood include: barbiturates (used to help you to sleep), some anti-convulsant medicines (such as carbamazepine or phenytoine), octreotide (used to treat acromegaly or neuroendorcrine tumours in the gut), 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).
- Medicines which may affect your 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 your stomach (acid secretion inhibitors of the H_2-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).
- Nifedipine. This is used to treat high blood pressure and heart pain. You might get swollen gums that might grow over your teeth if you are taking nifedipine during your treatment with ciclosporin.
- Digoxin (used to treat heart problems), medicines which lower cholesterol (HMG-CoA reductase inhibitors also called statins), prednisolone, etoposide (used to treat cancer), repaglinide (an anti-diabetic medicine), immunosuppressives (everolimus, sirolimus), ambrisentan and specific anti-cancer medicines called anthracyclines (such as doxorubicin).

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Sandimmun.

Sandimmun with food and drink

Do not take Sandimmun with grapefruit or grapefruit juice. This is because these can affect how Sandimmun works.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking this medicine. Your doctor will discuss with you the potential risks of taking Sandimmun during pregnancy.

- **Tell your doctor if you are pregnant or intend to become pregnant.** Experience with Sandimmun in pregnancy is limited. In general, Sandimmun should not be taken during pregnancy. If it is necessary for you to take this medicine, your doctor will discuss with you the benefits and potential risks of taking it during pregnancy.
- **Tell your doctor if you are breast-feeding.** Breast-feeding is not recommended during treatment with Sandimmun. This is because ciclosporin, the active substance, passes into breast milk. This may affect your baby.

Driving and using machines
Sandimmun contains alcohol. This may affect your ability to drive and use machines.

Sandimmun contains castor oil and ethanol
Sandimmun concentrate for solution for infusion contains castor oil which may cause severe allergic reactions.

Sandimmun concentrate for solution for infusion contains approximately 34.4 v/v ethanol (alcohol). A 100 mg dose of Sandimmun contains 556 mg ethanol. This is equivalent to nearly 15 ml beer or 5 ml wine.

Alcohol may be harmful if you have alcohol-related problems, epilepsy, brain injury, liver problems or if you are pregnant or breast-feeding. It may also be harmful if this medicine is given to children

3. How Sandimmun is used

Carefully follow all the instructions given to you by your doctor. Check with your doctor if you are not sure.

How much Sandimmun you will be given
Your doctor will work out the correct dose of Sandimmun for you. This depends on your body weight and what you are being given the medicine for.

- The total dose each day is usually between 3 to 5 mg per kilogram of your weight. This is divided into two doses.
- Usually, higher doses are used before and just after your transplant. Lower doses are used once your transplanted organ or bone marrow has stabilised.
- Your doctor will adjust your dose to one that is ideal for you. To do this, your doctor may need to do some blood tests.

How Sandimmun will be used
The medicine will be diluted before use with saline or 5% glucose and then given to you by slow infusion.

How long Sandimmun will be used
You will be switched to ciclosporin in the form of capsules or oral solution (both of which are taken by mouth) as soon as possible.

If you have been given more Sandimmun than you should
Too much of the medicine can affect your kidneys. You will have regular blood tests and visits to the hospital. This will give you the chance to talk to your doctor about your treatment and talk about any problems you may be having.

If you think you have been given too much Sandimmun, tell your doctor immediately.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious.
Tell your doctor straight away if you notice any of the following serious side effects:

- Like other medicines that act on the immune system, ciclosporin may influence your body's ability to fight against infection and may cause tumours or other cancers, particularly of the skin. Signs of infection might be fever or sore throat.
- Changes in your 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.
- 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.
- Swelling at the back of the eye. This may be associated with blurred vision. It may also affect your sight because of the higher pressure inside your head (benign intracranial hypertension).
- Liver problems and damage with or without yellow skin and eyes, nausea, loss of appetite and dark urine.
- Kidney problems, which may greatly reduce the amount of urine you produce.
- Low level of red blood cells or platelets. The signs include pale skin, feeling tired, being breathless, having dark urine (this is a sign of the breakdown of red blood cells), bruising or bleeding with no obvious reasons, feeling confused, feeling disorientated, being less alert and having kidney problems.

Other side effects include:

Very common side effects: *These side effects may affect more than 1 in 10 people.*

- Kidney problems.
- High blood pressure.
- Headache.
- Shaking of your body which you cannot control.
- Excessive growth of body and facial hair.
- High level of lipids in your blood.

If any of these affects you severely, **tell your doctor**.

Common side effects: *These side effects may affect between 1 and 10 in every 100 people.*

- Fits (seizures).
- Liver problems.
- High level of sugar in your blood.
- Tiredness,
- Loss of appetite.
- Nausea (feeling sick), vomiting, abdominal pain, constipation, diarrhoea.
- Excessive hair growth.
- Acne, hot flushes.
- Fever.
- Low level of white blood cells.
- Feeling numb or tingling.
- Pain in your muscles, muscle spasm.
- Stomach ulcer.
- Gum tissue overgrowing and covering your teeth.
- High level of uric acid or potassium in your blood, low levels of magnesium in your blood.

If any of these affects you severely, **tell your doctor**.

Uncommon side effects: *These side effects may affect between 1 and 10 in every 1,000 people.*

- Symptoms of brain disorders including sudden fits, mental confusion, sleeplessness, disorientation, disturbance of vision, unconsciousness, sense of weakness in the limbs, impaired movements.

- Rash.
- General swelling.
- Weight gain.
- Low level of red blood cells, low level of platelets in your blood which could increase the risk of bleeding.

If any of these affects you severely, **tell your doctor**.

Rare side effects: *These side effects may affect between 1 and 10 in every 10,000 people.*
- Nerve problems with numbness or tingling in fingers and toes.
- Inflammation of the pancreas with severe upper stomach pain.
- Muscle weakness, loss of muscle strength, pain in muscles of the legs or hands or anywhere in the body.
- Destruction of red blood cells, involving kidney problems with symptoms such as swelling of the face, stomach, hands and/or feet, decreased urination, breathing difficulty, chest pain, fits, unconsciousness.
- Changes in menstrual cycle, enlargement in men.

If any of these affects you severely, **tell your doctor**.

Very rare side effects: *These side effects may affect between 1 and 10 in every 100,000 people.*
- Swelling at the back of the eye which may be associated with an increase in pressure inside the head and eyesight disturbances.

If this affects you severely, **tell your doctor**.

Other side effects with frequency not known: Frequency cannot be estimated from the available data.
- 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.
- Bleeding underneath the skin or purple skin patched, sudden bleeding with no apparent cause.
- Migraine or severe headache often with feeling and being sick (nausea, vomiting) and being sensitive to light.

If any of these affects you severely, **tell your doctor**.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Additional side effects in children and adolescents
There are no additional side effects to be expected in children and adolescents compared to adults.

5. How to store Sandimmun

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the package.
- Do not throw away any medicines via wastewater or household waste. These measures will help to protect the environment.

6. Contents of the pack and other information

What Sandimmun contains
- The active substance is ciclosporin. One ml of the concentrate for solution for infusion contains 50 mg ciclosporin.
- The other ingredients are: ethanol anhydrous, macrogolglycerol ricinolate/polyethoxynolated castor oil.

What Sandimmun looks like and contents of the pack
Sandimmun concentrate for solution for infusion is supplied in ampoules containing 1 ml or 5 ml concentrate. The concentrate is a clear brown/yellow oily liquid. It is used by your doctor or nurse to prepare a solution which will be given to you by slow intravenous infusion.

Not all pack sizes may be available.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

{Name and address}
{tel}
{fax}
{e-mail}

This medicinal product is authorised in the Member States of the EEA under the following names:

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{Name of the Member State}{Name of the medicinal product}

This leaflet was last revised in {MM/YYYY} {month YYYY}.

[To be completed nationally]