Sandimmun Neoral®

Sandimmun®

Immunosuppressive agents, calcineurin inhibitors

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

Sandimmun Neoral soft-gelatin capsules.

25 mg: blue-grey oval shaped gelatin capsule, soft, imprinted with "NVR 25mg" in red

100 mg: blue-grey oblong shaped gelatin capsule, soft, imprinted with "NVR 100mg" in red

Sandimmun Neoral oral solution: clear, faintly yellow to browning yellow solution for oral administration. The formulation of Sandimmun Neoral is a microemulsion preconcentrate.

Sandimmun concentrate for solution for infusion: clear, brown-yellow, oleaginous concentrate to be diluted before parenteral administration.

Active substance

Each capsule contains 25 or 100 mg of ciclosporin.

The oral solution contains 100 mg of ciclosporin per mL. Each bottle of 50 mL contains 5000 mg of ciclosporin.

Sandimmun Neoral is a pharmaceutical form of the active ingredient ciclosporin based on the microemulsion principle, which reduces the variability of pharmacokinetic parameters and provides dose linearity of ciclosporin exposure with a more consistent absorption profile and less influence from concomitant food intake. The Sandimmun Neoral formulation is a microemulsion preconcentrate, which in pharmacokinetic and clinical studies has demonstrated that the correlation between trough concentration and exposure to ciclosporin is much stronger when ciclosporin is given as Sandimmun Neoral than when it is given as Sandimmun. The formation of the microemulsion itself takes place in the presence of water, either in the form of a beverage or in the form of the gastric fluid.

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

Certain dosage strengths and dosage forms may not be available in all countries.

Excipients

Soft gelatin capsules

Capsule content: alpha–tocopherol, ethanol anhydrous, propylene glycol, corn oil–mono–di–triglycerides, macrogolglycerol hydroxystearate (Ph.Eur)/ polyoxyl 40 hydrogenated castor oil (NF). Sandimmun Neoral soft gelatin capsules contain 11.8% v/v ethanol (9.4% w/v) (see section WARNINGS AND PRECAUTIONS).

Capsule shell: Iron oxide black (E 172) (25- and 100-mg capsules), titanium dioxide (E 171), glycerol 85%, propylene glycol, gelatin.

Imprint: carminic acid (E 120).

Oral solution

Alpha–tocopherol, ethanol anhydrous, propylene glycol, corn oil-mono–di–triglycerides, macrogolglycerol hydroxystearate (Ph.Eur)/polyoxyl 40 hydrogenated castor oil (USP). Sandimmun Neoral oral solution contains 12% v/v ethanol (9.5% w/v) (see section WARNINGS AND PRECAUTIONS).

Sandimmun concentrate for solution for infusion

Ethanol anhydrous, macrogolglycerol ricinoleate (Ph.Eur)/polyoxyl 35 castor oil (NF) (see section WARNINGS AND PRECAUTIONS). Sandimmun concentrate for solution for infusion contains 34.4% v/v ethanol (27.8% w/v).

Pharmaceutical formulations may vary between countries.

INDICATIONS

Transplantation indications

Solid organ transplantation

Prevention of graft rejection following kidney, liver, heart, combined heart-lung, lung or pancreas allogeneic transplantations.

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

Bone marrow transplantation

Prevention of graft rejection following bone marrow transplantation.

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

Non-transplantation indications

Endogenous uveitis

Active sight-threatening intermediate or posterior uveitis of non-infectious aetiology in patients where conventional therapy fails, or causes unacceptable side effects.

Behçet uveitis with repeated inflammatory attacks involving the retina.

Nephrotic syndrome

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

Sandimmun Neoral can be used to induce remissions and to maintain them. 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 ineffective or inappropriate.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

The daily doses of Sandimmun Neoral should always be given in 2 divided doses.

Because of considerable inter- and intra-individual variations in absorption and elimination and the possibility of pharmacokinetic drug interactions (see section INTERACTIONS), doses should be titrated individually according to clinical response and tolerability.

In *transplant patients,* routine monitoring of ciclosporin trough blood levels is required to avoid adverse effects due to high levels and to prevent organ rejection due to low levels (see section WARNINGS AND PRECAUTIONS).

In patients treated for *non-transplant indications*, monitoring of ciclosporin blood levels is of limited value except in the case of unexpected treatment failure or relapse, where it may be appropriate to establish the possibility of very low levels caused by non-compliance, impaired gastrointestinal absorption, or pharmacokinetic interactions (see section WARNINGS AND PRECAUTIONS).

General target population

Transplantation

Solid organ transplantation

Treatment with Sandimmun Neoral or 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 before being gradually reduced in accordance with blood levels until a maintenance dose of about 2 to 6 mg/kg given in 2 divided doses is reached.

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

If the Sandimmun concentrate for solution for infusion is used, the recommended dose is approximately one-third of the appropriate Sandimmun Neoral dose, and it is recommended that patients be put on oral therapy as soon as possible.

Bone marrow transplantation

The initial dose should be given on the day before transplantation. In most cases, Sandimmun intravenous (i.v.) infusion is preferred for this purpose; the recommended i.v. dose is 3 to 5

mg/kg per 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 Neoral at a daily dose 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 Neoral is used to initiate therapy, the recommended daily dose is 12.5 to 15 mg/kg given in 2 divided doses, starting on the day before transplantation.

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

In some patients, GVHD occurs after discontinuation of ciclosporin treatment, but usually responds favorably 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 ciclosporin should be used to treat mild, chronic GVHD.

Non-transplantation

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

- Before initiation of treatment a reliable baseline level of serum creatinine should be established by at least two measurements, and renal function must be assessed regularly throughout therapy to allow dosage adjustment (see section WARNINGS AND PRECAUTIONS).
- The only accepted route of administration is by mouth (the concentrate for intravenous infusion must not be used), and the daily dose should be given in two divided doses.
- 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 Neoral should be discontinued.

Endogenous uveitis

For *inducing remission*, initially 5 mg/kg per 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 per 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 Neoral alone does not control the situation sufficiently.

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

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:

- 5 mg/kg for adults and

- 6 mg/kg for children

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

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

If no improvement has been observed after 3 months' treatment, Sandimmun Neoral therapy should be discontinued.

The doses need to be adjusted individually according to efficacy (proteinuria) and safety (primarily serum creatinine), but should not exceed 5 mg/kg per day in adults and 6 mg/kg per 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 per 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 Neoral therapy may be required.

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

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

Psoriasis

Due to the variability of this condition, treatment must be individualized. For *inducing remission*, the recommended initial dose is 2.5 mg/kg per 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 per day, or in whom the effective dose is not compatible with the established safety guidelines (see section WARNINGS AND PRECAUTIONS).

Initial doses of 5 mg/kg per day are justified in patients whose condition requires rapid improvement. Once satisfactory response is achieved, Sandimmun Neoral may be discontinued and subsequent relapse managed with re-introduction of Sandimmun Neoral 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 per day.

Special populations

Renal impairment

All indications

Ciclosporin undergoes minimal renal elimination and its pharmacokinetics is not affected by renal impairment (see section CLINICAL PHARMACOLOGY). However, due to its nephrotoxic potential (see section ADVERSE DRUG REACTIONS), a careful monitoring of the renal function is recommended (see section WARNINGS AND PRECAUTIONS - subsection All indications)

Non-transplant indications

Patients with impaired renal function, except nephrotic syndrome patients, should not receive ciclosporin (see section WARNING AND PRECAUTIONS - subsection additional precautions in non-transplant indications). In nephrotic syndrome patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg per day.

Hepatic impairment

Ciclosporin is extensively metabolized by the liver. The terminal half-life varied between 6.3 hours in healthy volunteers to 20.4 hours in severe liver disease patients (see section CLINICAL PHARMACOLOGY). Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see section WARNINGS AND PRECAUTIONS and also section CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

Experience with ciclosporin in children is still limited. Clinical studies have included children from 1 year of age using standard ciclosporin dosage with no particular problems. In several studies, pediatric patients required and tolerated higher doses of ciclosporin per kg body weight than those used in adults. Sandimmun Neoral use in children for non-transplant indications other than nephrotic syndrome cannot be recommended (see section WARNINGS AND PRECAUTIONS - subsection additional precautions in non-transplant indications).

Geriatric patients (65 years of age or above)

Experience with ciclosporin in the elderly is limited, but no particular problems have been reported following the use of the drug at the recommended dose.

In rheumatoid arthritis clinical trials with oral ciclosporin, 17.5% of patients were aged 65 or older. These patients 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.

Clinical studies of ciclosporin in transplant and psoriasis patients did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experiences have not identified differences in response between the elderly and younger patients. In general, 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 other drug therapy.

Conversion from oral Sandimmun to Sandimmun Neoral

The available data indicate that after a 1:1 conversion from Sandimmun to Sandimmun Neoral, the trough concentrations of ciclosporin in whole blood are comparable. In many patients, however, higher peak concentrations (C_{max}) and an increased exposure to the drug (AUC) may occur. In a small percentage of patients these changes are more marked and may be of clinical significance. Their magnitude depends largely on the individual variance in the absorption of ciclosporin from the originally used Sandimmun, which is known to be highly variable in its bioavailability. Patients with variable trough levels or very high doses of Sandimmun may be poor or inconsistent absorbers of ciclosporin (e.g. patients with cystic fibrosis, liver transplant patients with cholestasis or poor bile secretion, children or some kidney transplant recipients) who may, on conversion to Sandimmun Neoral, become good absorbers. Therefore, in this population, the increase in bioavailability of ciclosporin following a 1:1 conversion from Sandimmun to Sandimmun Neoral might be greater than usually observed. The dose of Sandimmun Neoral should therefore be down titrated individually according to their target trough level range.

It needs to be emphasized that the absorption of ciclosporin from Sandimmun Neoral is less variable and the correlation between ciclosporin trough concentrations and exposure (in terms of AUC) is much stronger than with Sandimmun. This makes ciclosporin blood trough concentrations a more robust and reliable parameter for therapeutic drug monitoring.

Since the conversion from Sandimmun to Sandimmun Neoral may result in an increased drug exposure, the following rules must be observed:

In *transplant patients* Sandimmun Neoral should be started with the same daily dose as was previously used with Sandimmun. Ciclosporin trough concentrations in whole blood should be monitored initially within 4 to 7 days after the conversion to Sandimmun Neoral. In addition, clinical safety parameters such as serum creatinine and blood pressure are to be monitored during the first 2 months after the conversion. If the ciclosporin trough blood levels are beyond the therapeutic range, and/or worsening of the clinical safety parameters occur, the dosage must be adjusted accordingly.

In *patients treated for non-transplant indications*, Sandimmun Neoral should be started with the same daily dose as was used with Sandimmun. Two, 4 and 8 weeks after the conversion, serum creatinine levels and blood pressure should be monitored. If serum creatinine levels or blood pressure significantly exceed the pre-conversion levels or if serum creatinine levels increase to more than 30% above creatinine levels prior to Sandimmun therapy at more than one measurement, the dose should be reduced (see also ‘Additional precautions’ in section WARNINGS AND PRECAUTIONS). In case of unexpected toxicity or inefficacy of ciclosporin, blood trough levels should also be monitored.

Conversion between oral ciclosporin formulations

Switching from one oral ciclosporin formulation to another should be made with caution and under physician supervision. The introduction of the new formulation must be made with monitoring of blood levels of ciclosporin to ensure that pre-conversion levels are attained.

Method of administration

Oral administration

Sandimmun Neoral capsules should be swallowed whole.

Sandimmun Neoral oral solution should be diluted with, preferably, orange or apple juice; however, other drinks such as soft drinks can be used according to individual taste. Immediately before taking the oral solution, it should be stirred well. Owing to its possible interference with the cytochrome P450-dependent enzyme system, grapefruit juice should be avoided for dilution (see section INTERACTIONS). The syringe should not come in contact with the diluent. If the syringe is to be cleaned, do not rinse it but wipe the outside with a dry tissue (see section INSTRUCTIONS FOR USE AND HANDLING).

Intravenous administration

The types of container suitable for the infusion solution are mentioned in section INSTRUCTIONS FOR USE AND HANDLING.

Because of the risk of anaphylaxis (see section WARNINGS AND PRECAUTIONS), the use of the Sandimmun concentrate for solution for infusion should be reserved for organ transplant patients who are unable to take the drug orally (e.g., shortly after surgery) or in whom the absorption of the oral forms might be impaired during episodes of gastrointestinal disorders. In such cases, it is recommended to change to oral administration as soon as feasible. Another well-established use of the concentrate for solution for infusion consists in the initial treatment of patients with 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 i.v. infusion over approximately 2 to 6 hours.

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

CONTRAINDICATIONS

Hypersensitivity to ciclosporin or to any of the excipients of Sandimmun Neoral.

Hypersensitivity to ciclosporin or to any of the excipients of Sandimmun concentrate for solution for infusion including hypersensitivity to polyoxyl castor oil.

WARNINGS AND PRECAUTIONS

All indications

Medical supervision

Sandimmun Neoral and Sandimmun concentrate for solution for infusion 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 the drug should be managed in facilities with adequate laboratory and supportive medical

resources. The physician responsible for maintenance therapy should receive complete information for the follow-up of the patient.

Polyoxyl castor oil in the i.v. formulation and anaphylactoid reactions

Sandimmun concentrate for solution for infusion contains polyoxyl castor oil (see section DESCRIPTION AND COMPOSITION), which following i.v. administration has been reported to cause anaphylactoid reactions. These reactions can consist of flushing of the face and upper thorax, and non-cardiogenic pulmonary oedema, with acute respiratory distress, dyspnoea, wheezing and blood pressure changes and tachycardia. Special caution is therefore necessary in patients who have previously received, by i.v. injection or infusion, preparations containing polyoxyl castor oil (e.g. a preparation containing Cremophor® EL), 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 at the bedside. Prophylactic administration of an antihistaminic (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. Hence a treatment regimen containing multiple immunosuppressants (including ciclosporin) should be used with caution as this could lead to lymphoproliferative disorders and solid organ tumours, some with reported fatalities (see section ADVERSE DRUG REACTIONS).

In view of the potential risk of skin malignancy, patients on Sandimmun Neoral should be warned to avoid excess ultraviolet light exposure.

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 (see section ADVERSE DRUG REACTIONS).

Acute and chronic nephrotoxicity

A frequent and potentially serious complication, an increase in serum creatinine and urea, may occur during the first few weeks of ciclosporin therapy. These functional changes are dose-dependent and reversible, usually responding to dose reduction. During long-term treatment,

some patients may develop structural changes in the kidney (e.g. arteriolar hyalinosis, tubular atrophy and interstitial fibrosis) which, in renal transplant patients, must be differentiated from changes due to chronic rejection (see section ADVERSE DRUG REACTIONS). Close monitoring of parameters that assess renal function is required. Abnormal values may necessitate dose reduction (see section DOSAGE AND ADMINISTRATION and section CLINICAL PHARMACOLOGY).

Hepatotoxicity and liver injury

Ciclosporin may also cause dose-dependent, reversible increases in serum bilirubin and in liver enzymes (see section ADVERSE DRUG REACTIONS). There have been solicited and spontaneous postmarketing 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 ADVERSE DRUG REACTIONS). Close monitoring of parameters that assess hepatic function is required. Abnormal values may necessitate dose reduction (see section DOSAGE REGIMEN AND ADMINISTRATION and section CLINICAL PHARMACOLOGY).

Geriatric patients (65 years of age or above)

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

Monitoring ciclosporin levels in transplant patients

When ciclosporin is used in transplant patients, routine monitoring of ciclosporin blood levels is an important safety measure (see section DOSAGE AND ADMINISTRATION).For monitoring ciclosporin levels in whole blood, a specific monoclonal antibody (measurement of parent drug) is preferred; a HPLC method, which also measures the parent drug, 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 nonspecific monoclonal antibody should be performed, to ensure a dosage that provides adequate immunosuppression.

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 (see section DOSAGE REGIMEN AND ADMINISTRATION).

Hypertension

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

Blood lipids increased

Since ciclosporin 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 (see section ADVERSE DRUG REACTIONS).

Hyperkalemia

Ciclosporin enhances the risk of hyperkalemia, especially in patients with renal dysfunction (see section ADVERSE DRUG REACTIONS). Caution is also required when ciclosporin is co-administered with potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) and potassium containing drugs as well as in patients on a potassium rich diet (see section INTERACTIONS). Control of potassium levels in these situations is advisable.

Hypomagnesemia

Ciclosporin enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplant period (see section ADVERSE DRUG REACTIONS). 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.

Hyperuricemia

Caution is required in treating patients with hyperuricemia (see section ADVERSE DRUG REACTIONS).

Live-attenuated vaccines

During treatment with ciclosporin, vaccination may be less effective; the use of live-attenuated vaccines should be avoided (see section INTERACTIONS).

Interactions

Caution should be observed while co-administering lercanidipine with ciclosporin (see section INTERACTIONS).

Ciclosporin may increase blood levels of concomitant medications that are substrates for the multidrug efflux transporter P-glycoprotein (P-gp) or the organic anion transporter proteins (OATP) such as aliskiren, dabigatran or bosentan. Co-administration of ciclosporin with aliskiren is not recommended. Co-administration of ciclosporin together with dabigatran or bosentan should be avoided. These recommendations are based upon the potential clinical impact of these interactions (see section INTERACTIONS).

Special excipients: Ethanol

The ethanol content (see section DESCRIPTION AND COMPOSITION) should be taken into account when given to pregnant or breast feeding women, in patients presenting with liver disease or epilepsy, in alcoholic patients, or if Sandimmun Neoral or Sandimmun concentrate for solution for infusion is being given to a child.

Driving and using machines

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

Additional precautions in non-transplant indications

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

Additional precautions in endogenous uveitis

Since Sandimmun Neoral can impair renal function, it is necessary to assess renal function frequently, and if serum creatinine remains increased to more than 30% above baseline at more than one measurement, to reduce the dosage of Sandimmun Neoral by 25 to 50%. If the increase from baseline exceeds 50%, further reduction should be considered. These recommendations apply even if the patient's values still lie within the laboratory's normal range.

Sandimmun Neoral should be administered with caution in patients with neurological Behcet’s syndrome. The neurological status of patients with neurological Behcet’s syndrome should be carefully monitored.

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

Additional precautions in nephrotic syndrome

Since Sandimmun Neoral can impair renal function, it is necessary to assess renal function frequently, and if the serum creatinine remains increased to more than 30% above baseline at more than one measurement, to reduce the dosage of Sandimmun Neoral by 25 to 50%. If the increase from baseline exceeds 50%, further reduction should be considered. Patients with abnormal baseline renal function should initially be treated with 2.5 mg/kg per day and must be monitored very carefully.

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

Since Sandimmun Neoral can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals for the first 3 months of therapy and thereafter once

a month. After 6 months of therapy, serum creatinine needs to be measured 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 Neoral dose is increased, or concomitant treatment with a non-steroidal anti-inflammatory drug is initiated or its dosage increased (see section INTERACTIONS).

If the serum creatinine remains increased to more than 30% above baseline at more than one measurement, the dosage of Sandimmun Neoral should be reduced. If the serum creatinine increases by more than 50%, a dosage reduction by 50% is mandatory. These recommendations apply even if the patient's values still lie within the laboratory's normal range. If dose reduction is not successful in reducing levels within one month, Sandimmun Neoral treatment should be discontinued.

Discontinuation of the drug may also become necessary if hypertension developing during Sandimmun Neoral therapy cannot be controlled by appropriate antihypertensive therapy (see section INTERACTIONS).

As with other long-term immunosuppressive treatments (including ciclosporin), an increased risk of lymphoproliferative disorders must be borne in mind. Special caution should be observed if Sandimmun Neoral is used in combination with methotrexate (see section INTERACTIONS).

Additional precautions in psoriasis

Since Sandimmun Neoral can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals for the first 3 months of therapy. Thereafter, if creatinine remains stable, measurements should be made at monthly intervals. If the serum creatinine increases and remains increased to more than 30% above baseline at more than one measurement, the dosage of Sandimmun Neoral must be reduced by 25 to 50%. If the increase from baseline exceeds 50%, further reduction should be considered. These recommendations apply even if the patient's creatinine values still lie within the laboratory's normal range. If dose reduction is not successful in reducing creatinine levels within one month, Sandimmun Neoral treatment should be discontinued.

Discontinuation of Sandimmun Neoral therapy is also recommended if hypertension developing during Sandimmun Neoral treatment cannot be controlled with appropriate therapy (see section INTERACTIONS).

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 Neoral 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 Neoral treatment is started. Patients with malignant or pre-malignant alterations of the skin should be treated with Sandimmun Neoral only after appropriate treatment of such lesions, and if no other option for successful therapy exists.

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

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

ADVERSE DRUG REACTIONS

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 i.v. administration (see section WARNINGS AND PRECAUTIONS).

Patients receiving immunosuppressive therapies, including ciclosporin and ciclosporin-containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic) (see section WARNINGS AND PRECAUTIONS). Both generalized and localized 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 leukoencephalopathy (PML). Serious and/or fatal outcomes have been reported.

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 WARNINGS AND PRECAUTIONS). 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), including isolated reports.

Table 1 Adverse drug reactions from clinical trials

Blood and lymphatic system disorders	
Common	Leucopenia
Metabolism and nutrition disorders	
Very common	Anorexia; hyperglycaemia
Nervous system disorders	

Very common	Tremor; headache
Common	Convulsions; paraesthesia
Vascular disorders	
Very common	Hypertension (see section WARNINGS AND PRECAUTIONS)
Common	Flushing
Gastrointestinal disorders	
Very Common	Nausea; vomiting; abdominal discomfort; diarrhoea; gingival hyperplasia
Common	Peptic ulcer
Hepatobiliary disorders	
Common	Hepatotoxicity (see section WARNINGS AND PRECAUTIONS)
Skin and subcutaneous tissue disorders	
Very common	Hirsutism
Common	Acne; rash
Renal and urinary disorders	
Very common	Renal dysfunction (see section WARNINGS AND PRECAUTIONS)
Reproductive system and breast disorders	
Rare	Menstrual disturbances
General disorders and administration site conditions	
Common	Pyrexia; oedema

Adverse drug reactions from post-marketing experience (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Sandimmun Neoral or Sandimmun via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each organ class, ADRs are presented below in Table 2 in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Blood and lymphatic system disorders
Thrombotic microangiopathy, haemolytic uraemic syndrome; thrombotic thrombocytopenic purpura; anaemia; thrombocytopenia
Metabolism and nutrition disorders
Hyperlipidaemia; hyperuricaemia; hyperkalaemia; hypomagnesaemia.
Nervous system disorders
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, cerebellar ataxia; optic disc oedema including papilloedema, with possible visual impairment secondary to benign intracranial hypertension; peripheral neuropathy; migraine
Gastrointestinal disorders
Pancreatitis acute
Hepatobiliary disorders
Hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure with some fatal outcomes (see section WARNINGS AND PRECAUTIONS)
Skin and subcutaneous tissue disorders

Hypertrichosis
Musculoskeletal and connective tissue disorders
Myopathy; muscle spasm; myalgia; muscular weakness; pain of lower extremities
Reproductive system and breast disorders
Gynaecomastia
General disorders and administration site conditions
Fatigue; weight increase

Description of selected adverse drug reactions

Hepatotoxicity and liver injury

There have been solicited and spontaneous post-marketing 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 WARNINGS AND PRECAUTIONS)

Acute and chronic nephrotoxicity

Patients receiving calcineurin inhibitors (CNIs) 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 ciclosporin. Cases of acute nephrotoxicity reported disorders of ion homeostasis, such as hyperkalaemia, hypomagnesaemia, and hyperuricaemia which developed in the majority of the cases within the first month of treatment. Cases reporting chronic morphological changes included arteriolar hyalinosis, tubular atrophy and interstitial fibrosis, (see section WARNINGS AND PRECAUTIONS).

Pain of lower extremities

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

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.

Interactions resulting in a concomitant use not being recommended

During treatment with ciclosporin, vaccination may be less effective, the use of **live-attenuated vaccines** should be avoided (see section WARNINGS AND PRECAUTIONS).

Interactions to be considered

Caution is required for concomitant use of **potassium sparing drugs** (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) or

potassium containing drugs since they may lead to significant increases in serum potassium (see section WARNINGS AND PRECAUTIONS).

Following concomitant administration of ciclosporin and **lercanidipine**, the AUC of lercanidipine was increased threefold and the AUC of ciclosporin was increased 21%. Therefore caution is recommended when co-administering ciclosporin together with lercanidipine (see section WARNINGS AND PRECAUTIONS).

Care should be taken when using ciclosporin together with **methotrexate** in rheumatoid arthritis patients due to the risk of nephrotoxic synergy (see section WARNINGS AND PRECAUTIONS).

Interactions increasing or decreasing ciclosporin levels to be considered

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 a substrate of P-gp, hence inhibitors or inducers of P-gp may alter the concentrations of ciclosporin.

If the concomitant use of drugs known to interact with ciclosporin cannot be avoided, the following basic recommendations should be observed:

- In *transplant patients:* frequent measurement of ciclosporin levels and, if necessary, ciclosporin dosage adjustment are required, particularly during the introduction or withdrawal of the co-administered drug.
- In *non-transplant patients:* the value of ciclosporin blood level monitoring is questionable, as in these patients the relationship between blood level and clinical effects is less well established. If drugs 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.

Interactions decreasing ciclosporin levels

Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, sulfadimidine i.v., rifampicin, octreotide, probucol, orlistat, *Hypericum perforatum* (St. John's wort), ticlopidine, sulfinpyrazone, terbinafine, bosentan.

Interactions increasing ciclosporin levels

Macrolide antibiotics (e.g. erythromycin, azithromycin and clarithromycin); ketoconazole, fluconazole, itraconazole, voriconazole; diltiazem, nicardipine, verapamil; metoclopramide; oral contraceptives; danazol; methylprednisolone (high dose); allopurinol; amiodarone; cholic acid and derivatives; protease inhibitors; imatinib; colchicine; nefazodone.

Other relevant interactions

Drug-food/drink interactions

The concomitant intake of **grapefruit juice** has been reported to increase the bioavailability of ciclosporin (see section DOSAGE REGIMEN AND ADMINISTRATION).

Interactions resulting in a potential increased nephrotoxicity

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

Care should be taken when using ciclosporin together with other drugs that exhibit nephrotoxic synergy such as: aminoglycosides (incl. gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); non-steroidal anti-inflammatory drugs (incl. diclofenac, naproxen, sulindac); melphalan, histamine H_2-receptor-antagonists (e.g. cimetidine, ranitidine); methotrexate (see above subsection interactions resulting in a concomitant use not being recommended)

Concomitant use with tacrolimus should be avoided due to increased potential for nephrotoxicity.

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 non-steroidal anti-inflammatory drugs with a low first-pass effect (e.g. acetylsalicylic acid) are given together with ciclosporin, no increase in their bioavailability is to be expected. Non-steroidal anti-inflammatory drugs known to undergo strong first-pass metabolism (e.g. diclofenac) should be given at doses lower than those that would be used in patients not receiving ciclosporin.

In graft recipients there have been isolated reports of considerable but reversible impairment of kidney function (with corresponding increase in serum creatinine) following concomitant administration of fibric acid derivatives (e.g. bezafibrate, fenofibrate). Kidney function must therefore be closely monitored in these patients. In the event of significant impairment of kidney function the co-medication should be withdrawn.

Interaction resulting in an increased rate of gingival hyperplasia

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 nifedipine should be avoided in patients in whom gingival hyperplasia develops as a side effect of ciclosporin (see section ADVERSE DRUG REACTIONS).

Interactions resulting in an increase of other drug levels

Ciclosporin is also an inhibitor of CYP3A4 and of the multidrug efflux transporter P-gp and may increase plasma levels of co-medications that are substrates of this enzyme and/or transporter.

Ciclosporin may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins), etoposide, aliskiren, bosentan or dabigatran.

Severe digitalis toxicity has been seen within days of starting ciclosporin in several patients taking digoxin. There are also reports on the potential of ciclosporin to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. If digoxin or colchicine is used concurrently with ciclosporin, close clinical observation is

required in order to enable early detection of toxic manifestations of digoxin or colchicine, followed by reduction of dosage or its withdrawal.

Literature and post-marketing cases of myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of ciclosporin with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely, fluvastatin. When concurrently administered with ciclosporin, the dosage of these statins should be reduced according to 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.

If digoxin, colchicine or HMG-CoA reductase inhibitors (statins) are used concurrently with ciclosporin, close clinical observation is required in order to enable early detection of toxic manifestations of the drugs, followed by reduction of its dosage or its withdrawal.

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.

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

Co-administration of bosentan and ciclosporin in healthy volunteers resulted in an approximately 2-fold increase in bosentan exposure and a 35% decrease in ciclosporin exposure (see above subsection drug interactions decreasing ciclosporin levels and section WARNINGS AND PRECAUTIONS).

Following concomitant administration of ciclosporin and aliskiren, the Cmax of aliskiren was increased by approximately 2.5 fold and the AUC by approximately 5 fold. However, the pharmacokinetic profile of ciclosporin was not significantly altered (see section WARNINGS AND PRECAUTIONS).

Concomitant administration of dabigatran and ciclosporin leads to increased plasma level of dabigatran due to the P-gp inhibitory activity of ciclosporin (see section WARNINGS AND PRECAUTIONS). Dabigatran has a narrow therapeutic index and an increase in plasma level may be associated with an increased risk of bleeding.

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 significant increased exposure in 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.

Interactions resulting in decrease of other drug levels

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

The coadministration of a single dose of ciclosporin (200 mg or 600 mg) with a single dose of eltrombopag (50 mg) decreased plasma eltrombopag AUCinf by 18% to 24% and Cmax by 25% to 39%.

Eltrombopag dose adjustment is permitted during the course of the treatment based on the patient's platelet count. Platelet count should be monitored at least weekly for 2 to 3 weeks when eltrombopag is co-administered with ciclosporin. Eltrombopag dose may need to be increased based on these platelet counts.

PREGNANCY , LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There are no adequate or well-controlled clinical studies in pregnant women using ciclosporin. There is a moderate amount of data on the use of ciclosporin in pregnant patients from post-marketing experience, including published literature. Pregnant women receiving immunosuppressive therapies after transplantation, including ciclosporin and ciclosporin-containing regimens, are at risk of premature delivery (<37 weeks). The data have not demonstrated a higher incidence of miscarriages, major birth defects, or maternal events as compared to the rates seen in the general population (see HUMAN DATA).

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

Sandimmun Neoral should not be used during pregnancy unless the expected benefit to the mother outweighs the potential risk to the fetus. The ethanol content should also be taken into account in pregnant women (see section WARNINGS AND PRECAUTIONS).

Data

Human data

Published data from National Transplantation Pregnancy Registry (NTPR), described pregnancy outcomes in female kidney (482), liver (97), and heart (43) transplant recipients receiving ciclosporin. The data indicated successful pregnancies with a live birth rate of 76% and 76.9%, and 64% in kidney, liver, and heart transplant recipients, respectively. Premature delivery (<37 weeks) was reported in 52%, 35%, and 35% of kidney, liver, and heart transplant recipients, respectively.

The rates of miscarriages and major birth defects were reported to be comparable to the rates observed in the general population. A potential direct effect of ciclosporin on maternal hypertension, preeclampsia, infections, or diabetes could not be excluded given the limitations inherent to registries and postmarketing safety reporting.

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

Animal data

Three EFD studies (two oral and one intravenous) are available in rats. In oral EFD studies, pregnant rats were administered with ciclosporin either at doses of 10, 17, 30, 100 and 300

mg/kg/day or 4, 10 and 25 mg/kg/day from gestation day (GD) 6 to 15 or from GD 7 to 17, respectively. Maternal toxicity characterized by mortality, clinical signs of toxicity and impaired body weight gain were observed at 30 mg/kg/day and above. Ciclosporin was embryo- and fetotoxic as indicated by increased embryonic mortality and reduced fetal weight together with skeletal retardations in rats at 25 mg/kg/day and above. In addition, ventricular septal defect was observed at 25 mg/kg/day in fetuses. The no observed effect level (NOEL) for both dams and fetus was 17 mg/kg/day (below the MRHD based on BSA) after oral administration. In the other oral study, the NOEL for dams and fetuses were 10 and 4 mg/kg/day (below the MRHD based on BSA), respectively. In the IV EFD study, rats were administered with 3, 6 and 12 mg/kg/day of ciclosporin from GD 7 to 17. An increase in post implantation loss was observed at 12 mg/kg/day; ventricular septal defect was observed at 6 mg/kg/day and above in fetuses. The NOEL for dams and fetus were 6 and 3 mg/kg/day (below the MRHD based on BSA), respectively, after IV administration.

In rabbits, ciclosporin was orally administered at dose levels of 10, 30, 100 or 300 mg/kg/day from GD 6 to 18. At 100 mg/kg/day and above, reduction in body weight gain of dams and at 300 mg/kg/day abortions were observed. Maternal toxicity, embryo-fetotoxicity as indicated by increased pre- and postnatal mortality, reduced fetal weight together with skeletal retardations were observed at 100 mg/kg/day and above. The NOEL for dams and fetuses was 30 mg/kg/day (below the MRHD based on BSA).

In two published research studies, pregnant rabbits exposed to ciclosporin (10 mg/kg/day subcutaneously) during gestation demonstrated maternal toxicity (reduced body weight gain) and kidney changes in pups and adults (reduced numbers of nephrons, renal hypertrophy, systemic hypertension, and progressive renal insufficiency). An increase in fetal resorptions and a decrease in live pups and pup body weight were observed.

In a peri-and postnatal development study in rats, pregnant rats were orally administered with ciclosporin (5, 15 or 45 mg/kg/day) from GD 15 until end of lactation. At 45 mg/kg/day (below the MRHD based on BSA), increased pre and postnatal mortality of offspring and reduced body weight gain of surviving pups were observed. Ciclosporin up to 15 mg/kg/day (below the MRHD based on BSA) had no effect on pregnancy, pre and postnatal development of offspring [83].

Lactation

Risk summary

Ciclosporin is transferred into breast milk. Mothers receiving treatment with Sandimmun Neoral should not breast-feed. Because of the potential of Sandimmun Neoral to cause serious adverse drug reactions in breastfed 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 benefit of breast-feeding for the newborn/infant and the importance of the medicinal product to the mother.

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

The ethanol content of the Sandimmun Neoral formulations should also be taken into account (see section WARNINGS AND PRECAUTIONS).

Females and males of reproductive potential

Females

There are no special recommendations for women of child-bearing potential.

Fertility

There is limited data on the effect of ciclosporin on human fertility. No impairment in fertility was demonstrated in male and female rats up to 5mg/kg/day (below MRHD based on BSA) (see Section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

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 i.v. 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 dialyzable to any great extent, nor is it well cleared by charcoal hemoperfusion.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA) / Pharmacodynamics (PD)

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 hemopoiesis and has no effect on the function of phagocytic cells. Patients treated with ciclosporin are less prone to infection than those receiving other immunosuppressive therapy.

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 Sandimmun Neoral therapy have also been shown in a variety of conditions that are known, or may be considered to be of autoimmune origin.

Pharmacokinetics (PK)

When Sandimmun Neoral is given, it provides improved dose linearity in ciclosporin exposure (AUC_B), a more consistent absorption profile, and less influence from concomitant food intake and from diurnal rhythm than does Sandimmun. These properties combined yield a lower within-patient variability in pharmacokinetics of ciclosporin, and a stronger correlation between trough concentration and total exposure (AUC_B). As a consequence of these additional advantages, the time schedule of Sandimmun Neoral administration need no longer take that of meals into account. In addition, Sandimmun Neoral produces a more uniform exposure to ciclosporin throughout the day, and from day to day on a maintenance regimen.

Sandimmun Neoral soft gelatin capsules and Sandimmun Neoral oral solution are bioequivalent. The data available indicate that following a 1:1 conversion from Sandimmun to Sandimmun Neoral, trough concentrations in whole blood are comparable, thereby remaining in the desired therapeutic trough level range. Compared to Sandimmun (with which peak blood concentrations are achieved within 1 to 6 hours), Sandimmun Neoral is more quickly absorbed (resulting in a 1 hour earlier mean t_{max} and a 59% higher mean $C_{max)}$, and exhibits, on average, a 29% higher bioavailability.

Ciclosporin is distributed largely outside the blood volume. 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.

Ciclosporin is extensively biotransformed to approximately 15 metabolites. There is no single major metabolic pathway. Elimination is primarily biliary, with only 6% of the oral dose excreted in the urine; only 0.1% is excreted in the urine as unchanged drug.

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 (see section DOSAGE REGIMEN AND ADMINISTRATION and section WARNINGS AND PRECAUTIONS).

Special population

Renal impairment

In a study performed in patients with terminal renal failure, following an intravenous infusion of 3.5 mg/kg over 4 hours mean peak blood levels of 1,800 ng/mL (range 1,536 to 2,331 ng/mL) resulted. The mean volume of distribution (Vdss) was 3.49 L/kg and systemic clearance (CL) was 0.369 L/hr/kg. This systemic CL (0.369 L/hr/kg) was approximately two thirds of the mean systemic CL (0.56 L/hr/kg) in patients with normally functioning kidneys. Renal impairment had no significant effect on the elimination of ciclosporin.

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).

CLINICAL STUDIES

Transplantation indications

Solid organ transplantation

The efficacy of ciclosporin has been demonstrated in 13 global studies which evaluated the success transplantation rate using ciclosporin versus other immunosuppressive agents. Clinical trials have been performed in various regions (Europe, Australia and North America). Some of these trials included the evaluation of different solid organs including kidney, liver, heart, combined heart-lung, lung or pancreas allogenic transplantation. In the clinical trials performed, the ciclosporin dose used in transplanted patients ranged from 10 to 25 mg/kg per day as initial treatment dose and ranged from 6 to 8 mg/kg per day as maintenance dose (see section DOSAGE REGIMEN AND ADMINISTRATION).

Clinical studies are displayed in below Tables 3 to 7.

Kidney and pancreas transplantation

Table 3 presents clinical studies that were mainly performed in kidney transplanted patients and Table 4 presents clinical studies performed only in kidney transplanted patients. Table 3 also includes pancreas-transplanted patients. The included studies in these tables confirm that ciclosporin used in combination with steroids is an effective treatment in renal transplantation. The one year graft survival was significantly improved in these ciclosporin-treated patients over control therapy.

Table 3 Solid organ transplant - European Clinical Studies and Australian clinical study

Study Number/ Country	Study Characteristics	Organ (N)
Study # 1 Cambridge, UK	Single center CsA vs. Historical AZA+CS	Kidney (63) Liver (7) Pancreas (10) Including Kidney/Pancreas (7) Kidney/Liver (1) Pancreas/Liver (1)
Study #2 Australia	Single center, randomized CsA vs. AZA+CS+ALG	Kidney (29 total; 14 Ciclosporin)
Study #3 European Multicenter Trial	Multicenter randomized CsA vs	Kidney (232 total; 117 Ciclosporin)

Study Number/ Country	Study Characteristics	Organ (N)
	AZA+Pred	
Study #4 Sweden	Single center; CsA (4 patients) CsA + Pred (16) vs. Historical control	Kidney (20)
Study # 5 Finland	Multicenter CsA vs. AZA+MP vs. CsA IV+ MP	Kidney (9) (32) (32)

UK: United Kingdom; CsA: ciclosporin; AZA: azathioprine; CS: corticosteroids; ALG: anti lymphocyte globulin; Pred: prednisone; MP: methylprednisolone; IV: intravenous; N: Number of patients,

Table 4 Solid organ transplant - North American clinical studies

Study Number Country	Study characteristics	Organ (N)
Study # 2 USA	Group I: CsA[a]+ TDD Group II: CsA[b] Group III: CsA[c] All patients received CS	Kidney Group I: 12 Group II: 20 Group III: 34
Study # 5 USA	CsA +low dose pred vs. AZA+ ATG	Kidney (98 total; 47 CsA)
Study #7 USA	CsA + CS+ diuretics vs. AZA+ CS+ diuretics	Kidney (27 total; 14 CsA)
Study #15 USA	Open, randomized CsA+pred vs. AZA+pred	Kidney (41 total; 21 CsA)
Canadian Multicenter	Randomized, CsA vs. AZA + CS	Kidney (209 ; 103 CsA)

TDD: thoracic duct drainage; CsA: ciclosporin; CS: corticosteroids; Pred: prednisone; ATG: anti-thymocyte globulin; AZA: azathioprine; [a]: CsA administered as a single dose on the day of transplant and subsequently; [b]: CsA administered 2-30 days prior to transplant, without TDD; [c]: CsA administered as a single dose on the day of the transplant and subsequently without TDD

In addition to the above clinical studies performed in kidney-transplanted patients, two studies were performed for safety and tolerability assessment of the Sandimmun Neoral formulation. These 2 studies (Table 5) where Sandimmun was converted to Sandimmun Neoral in 1:1 protocols have shown based on stable steady-state trough concentration, that comparable doses of Sandimmun Neoral to Sandimmun, led to higher C_{max} and AUC values with Sandimmun Neoral compared to Sandimmun.

Table 5 Safety and tolerability studies in renal transplantation

Study Number	Title, design	Number of patients
OLM 102	Randomized, double blind, controlled, parallel, multicenter study on the safety and tolerability of SIM Neoral in STABLE renal transplant recipients after a 1:1 switch from SIM, compared to patients maintained on SIM. Pharmacokinetic profile	Total: 466 (373 switched to SIM Neoral) 45 patients
OLM 103	Randomized, controlled, double blind study on safety and tolerability of SIM Neoral in DE NOVO renal transplant	Total 86 patients (45 to SIM Neoral)

SIM: Sandimmun; SIM Neoral: Sandimmun Neoral

Liver transplantation

In the liver transplantation (see Table 6), the clinical studies demonstrated that one year patient survival rate was higher in the ciclosporin group than historical controls that were under previous immunosuppressive regimens.

Most of the thirteen deaths were attributed to surgical complications, acute infections (usually developing in the immediate period after transplantation, and possibly caused by organ procurement and preservation procedure), or recurrence of the original disease.

The episodes of acute rejection were generally controlled by increased steroid administration whereas several episodes of nephrotoxicity were noted which resolved on dosage reduction of ciclosporin. The clinical studies demonstrated that ciclosporin and steroid therapy offers considerable advantage over standard therapy using azithromycin and steroids.

Table 6 Solid organ transplant- Liver studies

Study Number Country	Design	Organ (N)	Patient/ graft survival
Study #4 USA	Single arm CsA+CS vs. Historical Control With TDD	Liver (14)	71% (CsA) 32% (Historical control)
Study #14 USA	Single arm CsA +CS vs.	Liver 26 (17 adults, 9 children)	64% versus 32% (Historical control)

Study Number Country	Design	Organ (N)	Patient/ graft survival
	Historical control		

CsA: ciclosporin; CS: corticosteroids; TDD: thoracic duct drainage

Heart and Heart-lung transplantation

In heart transplantation, the clinical studies demonstrated that one year and 18 months patient survival rates were significantly higher in the ciclosporin-treated patients than in the control-group patients. Ten of the 28 patients enrolled in heart transplantation had no rejection episodes following transplantation.

In heart-lung transplantation, the one year survival rate was 67% in the ciclosporin-treated patients.

In both heart and heart-lung transplantation, episodes of suspected hepatotoxicity and nephrotoxicity were controlled by dosage reduction of ciclosporin. Serious lung infections were observed and the majority was successfully treated.

Results of the clinical trials performed in heart and heart-lung transplanted patients are summarized in Table 7 below.

Table 7 Solid organ transplantation- Heart and Heart/Lung Studies

Study Number Country	Design	Organ (N)	1 Year Patient survival (%)
Study # 9	CsA+Pred+ ATG	Heart (28)	76% vs. 62%
USA	vs.		
	Historical (AZA+CS+ATG)	Heart/Lung (6)	67%
Study #99	Pilot	Heart (12)	67%
USA	CsA + Pred		

CsA: ciclosporin; Pred: prednisone; ATG: anti thymocyte globulin; AZA: azathioprine.

Bone marrow transplantation

The efficacy of Sandimmun has been demonstrated in bone marrow transplant (BMT) recipients in eight studies carried out in Europe and US with a total of 227 patients. Seven trials were conducted for the prevention of graft-versus host disease (GVHD), one trial for the treatment of acute GVHD. Five European centers (EU 1-5) and one U.S. center (US #6) conducted "open" non-randomized trials for the prevention of GVHD. One randomized trial (US #3) was conducted for the prevention of GVHD and one randomized trial (US #11) was conducted for the treatment of acute GVHD. Six patients in US #6 received ciclosporin in an effort to reverse established acute, severe (Grade III-IV) GVHD. These patients had not been previously treated with ciclosporin and the GVHD was resistant to other therapies. Results from these studies were compared to methotrexate (MTX) therapy in the prevention of GVHD trials (historical controls in the open trials) and to steroid therapy in the treatment of GVHD trial. These studies contained 227 patients: 204 patients were BMT recipients treated for prophylaxis of GVHD, and 23 patients treated for established GVHD. There were a total of 20 HLA mismatched patients in these studies.

The dosage of ciclosporin varied in the different studies. For prevention of GVHD the usual dosage was 12.5 mg/kg/day. However, several European centers started higher (20-25 mg/kg/day) during the first few days then tapered to 12.5 mg/kg/day. Most centers held the dose constant and tapered after several months, usually discontinuing after 4-6 months. The dosage of ciclosporin used for treatment of GVHD was approximately 15 mg/kg/day. This was tapered over time and discontinued at about 6 months. Ciclosporin was given mostly once or twice daily, but at one center, three times daily. In most studies, if the I.V. formulation of ciclosporin was used, it was given at about 1/3 the oral dose.

Efficacy results from the European studies demonstrated a reduction of severity and perhaps frequency of GVHD, with one-year survival for all Ciclosporin patients with matched grafts approximately 70%. For historical controls treated with MTX the figure was only 52% for one-year survival. Death associated with GVHD was only 10/132 patients (8%), much lower that what was previously found with MTX in matched grafts (fatal in >25% cases). The efficacy results from the US studies support the European efficacy results, and demonstrate that Ciclosporin is at least as efficacious as and probably superior to MTX therapy in the prevention of GVHD in BMT, with a significantly faster time to engraftment and a relative risk of approximately 50% of developing GVHD greater than Grades II or III (p=N.S.). US Study #6 also demonstrated that ciclosporin reversed established acute severe (Grade III-IV) GVHD in patients not previously treated with ciclosporin and resistant to other therapies.

Non-transplantation indications

Endogenous uveitis including Behcet’s uveitis

The efficacy of ciclosporin was demonstrated in 11 open uncontrolled studies from Europe, the U.S., Japan, Africa and Asia, including 242 patients suffering from endogenous uveitis, in most of whom conventional therapy failed or caused unacceptable adverse events. In 4 controlled masked studies from Israel, Japan, the Netherlands and the U.S., 202 patients were randomly assigned to receive ciclosporin (97 patients) or conventional therapy - prednisolone, chlorambucil, colchicine - (92 patients) or placebo (13 patients). Of the 339 patients treated with ciclosporin, 161 were diagnosed with Behçet's uveitis and the remaining 178 predominantly with intermediate or posterior uveitis of non-infectious etiology. Males patients were 201 and females were 138; the mean age was 35.8 years. Most patients receiving ciclosporin had an initial loading dose of 5 to 10 mg/kg/day followed by a dose reduction according to ocular inflammatory activity and tolerability. Improvement of visual acuity from baseline was the primary endpoint most commonly used in the clinical program, and the incidence of ocular attacks was used for Behçet's uveitis. Over 60% of patients treated with ciclosporin had improvement in visual acuity from baseline as measured at 3 and 6 months after the initiation of ciclosporin therapy. The initial limiting factor for improvement in the majority of the remaining 40% being irreversible changes that developed during the disease process before the initiation of ciclosporin therapy. The incidence of ocular attacks in patients with Behçet's uveitis was significantly reduced (p=0.001) in patients treated with ciclosporin compared to patients treated with colchicine.

Nephrotic syndrome

The efficacy of Sandimmun has been demonstrated in four randomized controlled and 5 uncontrolled studies. The clinical results from these nine clinical studies were analyzed using a pooling of data from all studies (controlled and uncontrolled).

Two double-blind placebo controlled multicenter studies (9,515 and 9,516) and a multicenter study to comparing Ciclosporin with cyclophosphamide in steroid-resistant patients (9,508) had to be stopped prematurely because of a lack of suitable patients consenting to receive placebo or a cytostatic agent.

A retrospective collection of data from patients treated with ciclosporin was performed in a trial entitled OL 03.

Adults and pediatric patients included in the studies were mainly steroid resistant or steroid dependent patients or patients with signs of steroid toxicity needing alternate treatment.

The controlled studies included 47 patients amongst which 43 were pediatric patients (defined as patients up to 16 years of age). These patients were presenting with focal segmental glomerulosclerosis (FSGS), Minimal change nephropathy (MCN) and Membranous glomerulonephritis (MG) and were steroid dependent and steroid resistant. Additionally, 24 adult patients with IgA nephropathy (an entity that may present with nephrotic syndrome, particularly common in patients with Asian origin) were studied as well. The studies compared ciclosporin either with cyclophosphamide (OL9511), chlorambucil (OL9505), placebo (OL9509) or “no treatment” or palliative care (OL9510).

The uncontrolled trials studied 361 adult patients and 178 pediatric patients (aged 1 to 17 years of age) with FSGS, MCN and MG nephrotic syndrome and were steroid dependent or steroid resistant. In addition, 9 adult and 27 pediatric patients with frequently relapsing forms of FSGS and MCN nephrotic syndrome were studied.

Of the 9 studies described in this document, seven included pediatric patients between 1 to 17 years of age. One controlled study (OL9505) and one uncontrolled study (OL9504) were performed exclusively in the pediatric population. A total of 398 children (319 treated with ciclosporin) were included in these studies.

The efficacy and safety results from the studies including pediatrics were similar to those in the adult population. Most of the steroid dependent patients achieved complete remission. The elimination of ciclosporin is influenced by the age of the patients. Pediatric patients clear the drug more rapidly than adults on a body weight basis. Therefore pediatric patients require higher doses of ciclosporin per kilogram of body weight to achieve blood concentrations of the drug similar to those observed in adults patients (see section DOSAGE REGIMEN AND ADMINISTRATION).

Rheumatoid arthritis

The efficacy of Sandimmun Neoral in the treatment of severe rheumatoid arthritis was evaluated in 5 clinical studies involving a total of 728 ciclosporin-treated patients and 273 placebo-treated patients.

A summary of the results is presented for the “responder” rates per treatment group, with a responder being defined as a patient having completed the trial with a 20% improvement in the tender and the swollen joint counts and a 20% improvement in 2 of 4 of investigator global, patient global, disability, and erythrocyte sedimentation rates (ESR) for the Studies 651 and 652 and 3 of 5 of investigator global, patient global, disability, visual analog pain, and ESR for Studies 2008, 654, and 302.

Study 651 enrolled 264 patients with active rheumatoid arthritis with at least 20 involved joints, who had failed at least one major RA drug, using a 3:3:2 randomization to one of the following

three groups: (1) ciclosporin dosed at 2.5 to 5 mg/kg/day, (2) methotrexate at 7.5 to 15 mg/week, or (3) placebo. Treatment duration was 24 weeks. The mean ciclosporin dose at the last visit was 3.1 mg/kg/day. See Figure 1

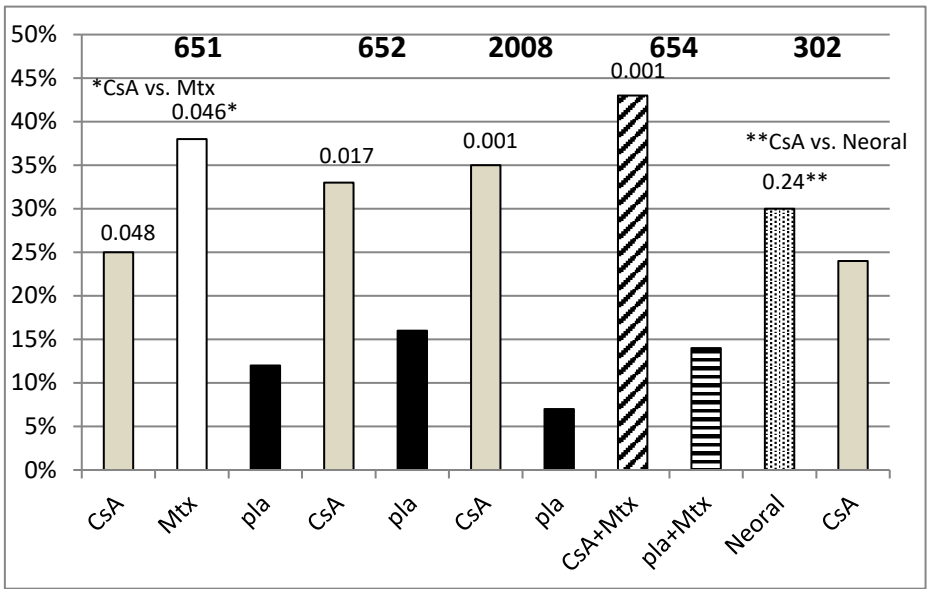
Study 652 enrolled 250 patients with active RA with > 6 active painful or tender joints who had failed at least one major RA drug. Patients were randomized using a 3:3:2 randomization to 1 of 3 treatment arms: (1) 1.5-5 mg/kg/day of ciclosporin, (2) 2.5-5 mg/kg/day of ciclosporin, and (3) placebo. Treatment duration was 16 weeks. The mean ciclosporin dose for group 2 at the last visit was 2.92 mg/kg/day. See Figure 1.

Study 2008 enrolled 144 patients with active RA and >6 active joints who had unsuccessful treatment courses of aspirin and gold or Penicillamine. Patients were randomized to 1 of 2 treatments groups (1) ciclosporin 2.5-5 mg/kg/day with adjustments after the first month to achieve a target trough level and (2) placebo. Treatment duration was 24 weeks. The mean ciclosporin dose at the last visit was 3.63 mg/kg/day. See Figure 1.

Study 654 enrolled 148 patients who remained with active joint counts of 6 or more despite treatment with maximally tolerated methotrexate doses for at least three months. Patients continued to take their current dose of methotrexate and were randomized to receive, in addition, one of the following medications: (1) ciclosporin 2.5 mg/kg/day with dose increases of 0.5 mg/kg/day at weeks 2 and 4 if there was no evidence of toxicity and further increases of 0.5 mg/kg/day at weeks 8 and 16 if a <30% decrease in active joint count occurred without any significant toxicity; dose decreases could be made at any time for toxicity or (2) placebo. Treatment duration was 24 weeks. The mean ciclosporin dose at the last visit was 2.8 mg /kg/day (range: 1.3 to 4.1). See Figure 1.

Study 302 enrolled 299 patients with severe active RA, 99% of whom were unresponsive or intolerant to at least one prior major RA drug. Patients were randomized to 1 of 2 treatment groups (1) Neoral and (2) ciclosporin, both of which were started at 2.5 mg/kg/day and increased after 4 weeks for inefficacy in increments of 0.5 mg/kg/day to a maximum of 5 mg/kg/day and decreased at any time for toxicity. Treatment duration was 24 weeks. The mean ciclosporin dose at the last visit was 2.91 mg/kg/day (range: 0.72 to 5.17) for Neoral and 3.27 mg/kg/day (range: 0.73 to 5.68) for ciclosporin. See Figure 1.

Figure 1 Efficacy of ciclosporin in the treatment of severe rheumatoid arthritis in 5 clinical studies (651, 652, 2008, 654 and 302)



*CsA: ciclosporin, Mtx: methotrexate, Pla: Placebo

Psoriasis

The efficacy of ciclosporin has been demonstrated in 1,270 patients with severe psoriasis in 13 clinical studies. Three main double blind placebo controlled trial enrolling overall 296 patients, of whom 199 treated with ciclosporin and 97 with placebo, have been conducted over a 12-16 week treatment period (Study US299, US501 and US502); smaller placebo controlled studies including overall 105 patients, of whom 53 treated with ciclosporin and 52 treated with placebo (Study OL8002, OL8003, OL8006 and CyA40) supported the short term use. Two larger studies (Study OL8013 and OL8014) including 405 patient of whom 192 treated with ciclosporin and 38 with etretinate, provided information on long term efficacy, safety and tolerability of different ciclosporin dosing. The two formulation of ciclosporin were directly compared in a multicenter randomized double blind study including 309 patients (Study OLP302), supported by a smaller PK study including 39 patients (Study N101) and by an investigational study (Study OL8095) in which the microemulsion formulation was given intermittently to 41 patients.

Patients treated in the clinical programme were adult patients with severe psoriasis in whom conventional therapy was ineffective or inappropriate. A number of different primary measures of efficacy were used in the clinical studies i.e. the overall and global evaluation scores assessed by the investigators, the time to relapse, the evaluation of the body surface area (BSA), the evaluation of the psoriasis area and severity index (PASI score).

The results of a pooled analysis of the 3 main double blind placebo controlled trials (Study US299, US501 and US502) showed a reduction at least of 75% in PASI in a range from 76% of the patients treated with a starting dose of 3 mg/kg/day to 100% of the patients treated with a starting dose of 7.5 mg/kg/day, being 83% in patients treated with 5 mg/kg/day. The highest percentage of patients in the placebo group was 4%.The results of the pooled analysis of a pooled analysis of other trials (Study 8002, 8003, 8006, CyA-40, 8013 and 8014) showed a reduction at least of 75% in PASI in 55% of the patients treated with a starting dose of 2.5

mg/kg/day to 87% of the patients treated with a starting dose of 5 mg/kg/day. Reduction of at least 75% in PASI was observed in 72% of the 152 patients treated with Sandimmun Neoral and in 62% of the 156 patients treated with Sandimmun (Study OLP302); in both arms the starting dose was 2.5 mg/kg/day.

NON-CLINICAL SAFETY DATA

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.

Ciclosporin has not been found mutagenic/genotoxic in the Ames test, the v79–hgprt test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone marrow, the mouse dominant lethal assay, and the DNA repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by ciclosporin using human lymphocytes *in vitro* gave indication of a positive effect (i.e. induction of SCE) at high concentrations in this system.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies during ciclosporin treatment is higher than in the normal, healthy population, but similar to that in patients receiving other immunosuppressive therapies. It has been reported that reduction or discontinuance of immunosuppression may cause the lesions to regress.

In a fertility study in rats, increased perinatal mortality and impaired postnatal development of F1 pups were observed at 15 mg/kg/day (below the MRHD based on BSA). No adverse effects on fertility and reproduction were observed up to 5 mg/kg/day (below the MRHD based on BSA) in male and female rats.

For reproductive toxicity, see Section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

SHELF LIFE

Soft gelatin capsules: 2 years.

Oral solution: 3 years.

Sandimmun concentrate for i.v. infusion: 4 years.

PACK SIZE

Sandimmun Neoral Capsules 10 mg, 25 mg and 100 mg:

Available in a box of 5 x 10 PA/AL/PVC blisters.

Sandimmun Neoral oral solution:

Available in a brown 50 ml bottle.

Sandimmun concentrate for solution for infusion:

Available in a box of 10 ampoules.

STORAGE

See folding box.

Sandimmun Neoral capsules may be stored below 30°C.

Sandimmun Neoral capsules should be left in the blister pack until required for use. 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.

Sandimmun Neoral oral solution should be stored below 30°C, but not below 20°C for more than 1 month, as it contains oily components of natural origin which tend to solidify at low temperatures. A jelly-like formation may occur below 20°C, which is however reversible at temperatures up to 30°C. Minor flakes or slight sediment may still be observed. These phenomena do not affect the efficacy and safety of the product and the dosing by means of the pipette remains accurate. After opening, Sandimmun Neoral oral solution should be used within 2 months.

Sandimmun concentrated for infusion should be stored below 30°C.

Sandimmun Neoral & Sandimmun should not be used after the date marked “EXP” on the pack.

Sandiummun Neoral & Sandimmun must be kept out of reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

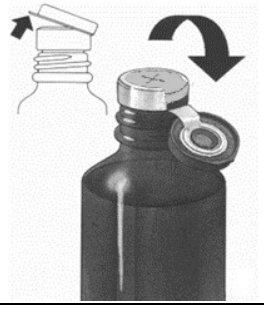
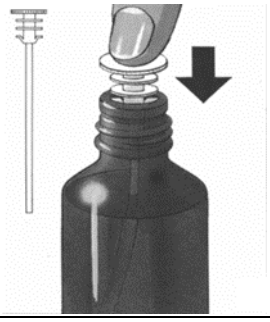
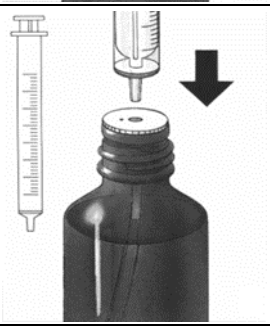
Instructions for use and handling of Sandimmun concentrate for solution for infusion

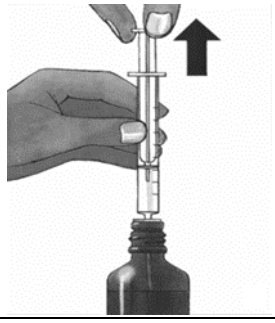
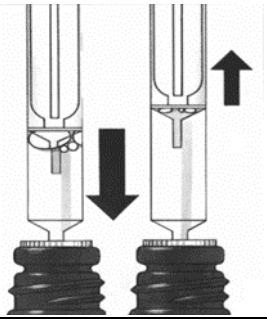
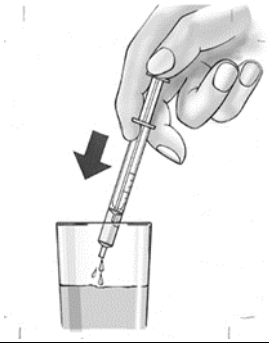
Sandimmun concentrate for solution for infusion contains polyoxyl castor oil, which can cause phthalate stripping from PVC. If available, glass containers should be used for infusion. Plastic bottles should be used only if they conform to the requirements for ’Sterile plastic containers for human blood and blood components’ respectively to ‘Empty sterile containers of plasticized poly(vinyl chloride) for human blood and blood components’ of the current European Pharmacopoeia. Containers and stoppers should be free of silicone oil and fatty substances.

Instructions for use and handling of Sandimmun Neoral solution

Sandimmun Neoral 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 Neoral oral solution

1.	Raise flap in center of the metal sealing ring.	
2.	Tear off the sealing ring completely.	
3.	Remove the grey 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 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 plunger a few times before removing syringe containing 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, but no 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 syringe on outside only with a dry tissue and replace in its cover. White stopper and tube should remain in bottle. Close bottle with cap provided.	

Subsequent use

Commence at point 5.

Special precautions for disposal

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

Product Registration Holder:

Novartis Corporation (Malaysia) Sdn. Bhd.

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47400 Petaling Jaya, Selangor

Malaysian Package Leaflet

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® = registered trademark

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