PRODUCT MONOGRAPH

PrNEORAL®
(cyclosporine capsules)
(cyclosporine oral solution)
for microemulsion

AND

PrSANDIMMUNE® I.V.
(cyclosporine for injection)

NEORAL® (solution, 100 mg/mL)

NEORAL® (soft gelatin capsules, 10, 25, 50 and 100 mg)

SANDIMMUNE® I.V. (50 mg/mL for injection)

Immunosuppressant

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Soft Gelatin Capsules 10 mg, 25 mg, 50 mg and 100 mg	Ethanol (9.4% w/v) v/v 11.8%, maize oil, hydrogenated castor oil *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.*
Oral	Oral Solution 100 mg/mL	Ethanol (9.5% w/v) v/v 12%, maize oil, hydrogenated castor oil*For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.*
Intravenous	50 mg/mL concentrate for infusion	Ethanol (27.8% w/v) v/v 34.4% Polyoxyethylated castor oil *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.*

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe NEORAL® and SANDIMMUNE® I.V. (cyclosporine). Patients receiving the drug should be managed in centres staffed with professionals experienced in transplantation and the use of immunosuppressants and equipped with adequate laboratory facilities to monitor cyclosporine levels. The ability to measure cyclosporine blood levels facilitates the management of the patient. The radioimmunoassay (RIA) method has been used most often in clinical trials.

For long-term follow-up, the attending physician should receive complete information from

the transplant centre on the patient, to include: recommended NEORAL® dosage, target trough levels of cyclosporine and, frequency of determination of these levels. The attending physician should consult with the transplant centre when making dose adjustments to ensure that toxicity is minimized while maintaining adequate immunosuppression. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.

Psoriasis/Rheumatoid Arthritis/Nephrotic Syndrome: Careful monitoring of NEORAL® treated patients is mandatory. NEORAL® should only be prescribed for psoriasis, rheumatoid arthritis or nephrotic syndrome by physicians experienced with its use.

Psoriasis patients previously treated with PUVA and to a lesser extent, methotrexate, or other immunosuppressive agents, UVB, coal tar, or radiation therapy, are at an increased risk of developing skin malignancies when taking cyclosporine."

INDICATIONS AND CLINICAL USE

Solid Organ Transplantation
NEORAL® capsules and oral solution and SANDIMMUNE® I.V. (cyclosporine) are indicated in the prevention of graft rejection following solid organ transplantation and in the treatment of transplant rejection in patients previously receiving other immunosuppressive agents.

Bone Marrow Transplantation
NEORAL® capsules and oral solution and SANDIMMUNE® I.V. (cyclosporine) are indicated in the prevention of graft rejection following bone marrow transplantation and the prevention or treatment of graft-versus-host disease (GVHD).

Psoriasis
NEORAL® capsules and oral solution (cyclosporine) are indicated for the treatment of severe psoriasis in patients for whom conventional therapy is ineffective or inappropriate.

Rheumatoid Arthritis
NEORAL® capsules and oral solution (cyclosporine) are also indicated for the treatment of severe active rheumatoid arthritis in patients for whom classical slow-acting antirheumatic agents are inappropriate or ineffective.

Nephrotic Syndrome
NEORAL® capsules and oral solution (cyclosporine) are indicated in adults and children for steroid dependent and steroid resistant nephrotic syndrome due to glomerular diseases such as minimal change nephropathy; focal and segmental glomerulosclerosis, or membranous glomerulonephritis. NEORAL® can be used to induce remissions and to maintain them. It can also be used for maintenance of steroid induced remissions, allowing withdrawal of, or reduction

in the dosage of steroids.

CONTRAINDICATIONS

- Patients who are hypersensitive to cyclosporine or any of its excipients. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

- NEORAL® is also contraindicated in the treatment of psoriasis and rheumatoid arthritis patients under the following circumstances: abnormal renal function; uncontrolled hypertension; malignancy (except non-melanoma skin cancer); uncontrolled infection; primary or secondary immunodeficiency excluding autoimmune disease.

- Co-administration of cyclosporine together with bosentan is contraindicated.

WARNINGS AND PRECAUTIONS

General

Medical supervision
NEORAL® capsules and oral solution and SANDIMMUNE® I.V. (cyclosporine) should be prescribed only by physicians who are experienced in immunosuppressive therapy and management of transplant patients and can provide adequate follow-up, including regular full physical examination, measurement of blood pressure and control of laboratory safety parameters. Patients receiving the drug should be managed in facilities with adequate laboratory and supportive medical resources.

For All Patients
Appropriate patient and laboratory monitoring is essential to prevent, reverse or minimize the following adverse events: nephrotoxicity; hypertension; the development of malignancies and lymphoproliferative disorders; increased risk of infections; hepatotoxicity; lipoprotein abnormalities; neurotoxicity.

Cyclosporine absorption has significant inter-and intra-patient variability. Cyclosporine whole blood concentrations as well as the effectiveness and the adverse events related to cyclosporine should be appropriately monitored in all patients, particularly in de novo patients undergoing any change in their treatment regimen, to ensure maximum safety and optimal clinical outcome.

Polyethoxylated castor oil in the i.v. formulation and anaphylactoid reactions
The concentrate for solution for infusion contains polyoxyethylated castor oil which has been reported to cause anaphylactoid reactions. Patients receiving SANDIMMUNE® I.V. should be observed continuously for at least 30 minutes following the start of the infusion and at frequent intervals thereafter (see also **MONITORING AND LABORATORY TESTS**, **TRANSPLANT**

PATIENT MANAGEMENT).

Non transplant indications

Patients with impaired renal function (except in nephrotic syndrome patients with a permissible degree of renal impairment), abnormal liver function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy should not receive NEORAL®. The risks inherent in treatment with cyclosporine have to be justified for the non-transplant patients.

Psoriasis

NEORAL® should only be prescribed for psoriatic patients by physicians experienced with its use. All patients to be treated with NEORAL® for psoriasis must have a pre-treatment physical examination to include blood pressure, renal function and careful examination for tumours, particularly of the skin, to establish accurate baseline values and clinical status.

Skin lesions not typical of psoriasis should be biopsied to exclude skin cancers, mycosis fungoides or other pre-malignant conditions.

Rheumatoid Arthritis

Discontinuation of the drug is recommended if hypertension developing during NEORAL® therapy cannot be controlled with appropriate antihypertensive therapy. As with other long-term immunosuppressive treatments, an increased risk of lymphoproliferative disorders must be borne in mind.

Nephrotic Syndrome

NEORAL® should only be prescribed by physicians experienced with its use. All patients to be treated with NEORAL® for nephrotic syndrome must have a pre-treatment physical examination to include blood pressure, renal function (see **DOSAGE AND ADMINISTRATION**) and screening for malignancies.

Carcinogenesis and Mutagenesis

Malignancy and lymphoproliferative disorders have developed, but their incidence and distribution are similar to those in patients on conventional immuno-suppressive therapy.
In psoriatic patients on cyclosporine therapy, development of malignancies (in particular of the skin) has been reported. Patients with psoriasis previously treated with PUVA and to a lesser extent, methotrexate or other immunosuppressive agents, UVB are at an increased risk of developing skin malignancies when taking NEORAL®. Skin lesions, not typical of psoriasis, but suspected to be malignant or premalignant should be biopsied before starting cyclosporine treatment. Patients with malignant or premalignant alterations of the skin should be treated with cyclosporine only after appropriate treatment of such lesions and if no other option for successful therapy exists. Cyclosporine should be discontinued if malignancy occurs.

In view of the potential risk of skin malignancy, patients on NEORAL® or SANDIMMUNE®

I.V., should be warned to avoid excess ultraviolet light exposure. In view of the potential risk of skin malignancy, patients on NEORAL® or SANDIMMUNE® I.V., should be warned to avoid excess unprotected sun exposure and should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy. Malignancy and lymphoproliferative disorders have developed, but their incidence and distribution are similar to those in patients on conventional immuno-suppressive therapy. In psoriatic patients on cyclosporine therapy, development of malignancies (in particular of the skin) has been reported.

Cardiovascular

Hypertension

Patients receiving cyclosporine may develop hypertension, and regular monitoring of blood pressure is required. Caution is advised in choosing an agent to treat this hypertension. Preference should be given to an antihypertensive agent that does not interfere with the pharmacokinetics of cyclosporine, e.g. isradipine. Diuretics are not recommended (see **DRUG INTERACTIONS**).

In addition, in psoriasis patients; beta-blockers are not generally recommended due to their propensity to exacerbate psoriasis. Only calcium channel blockers which do not interfere with cyclosporine pharmacokinetics are recommended (see **DRUG INTERACTIONS**).

Endocrine and Metabolism

Lipoprotein Abnormalities

Many transplant patients have hyperlipidemia and cyclosporine may contribute to the genesis of this problem. It is advisable to perform lipid determination before treatment and after the first month of therapy. If lipids are increased, restriction of dietary fat should be considered. (If the risk benefit ratio warrants, a reduction of NEORAL® capsules and oral solution (cyclosporine) dose may also be considered.) Caution is advised in the co-administration of NEORAL® or SANDIMMUNE® I.V. and the HMG-CoA reductase inhibitor, lovastatin due to the risk of myocyte necrosis. The potential for interaction with other drugs in this class should be considered (see **DRUG INTERACTIONS**, **ADVERSE REACTIONS** and **REFERENCES**).

Hyperkalemia/Hyperuricemia/Hypomagnesemia

Cyclosporine enhances the risk of hyperkalemia, especially in patients with renal dysfunction (see **ADVERSE REACTIONS**). Caution is also required when cyclosporine is co-administered with 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 **DRUG INTERACTIONS**). Control of potassium levels in these situations is advisable.

Caution is required in treating patients with hyperuricemia. (see **DRUG INTERACTIONS** and **ADVERSE REACTIONS**)

Cyclosporine enhances the clearance of magnesium. This can lead to symptomatic hypomagnesemia, especially in the peri-transplant period (see ~~ADVERSE REACTIONS~~

ADVERSE REACTIONS). Control of serum magnesium levels is therefore recommended in the peri-transplant period, particularly in the presence of neurological symptoms/signs. If considered necessary, magnesium supplementation should be given.

Hepatic/Biliary/Pancreatic

Hepatotoxicity
Cyclosporine may also cause dose-dependent, reversible increases in serum bilirubin and in liver enzymes (see **ADVERSE 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 cyclosporine. 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 **ADVERSE REACTIONS**).

Close monitoring of parameters that assess hepatic function is required. Abnormal values may necessitate dose reduction (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Immune

Infection/Immunization
Like other immunosuppressants, cyclosporine, 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) has been observed in patients receiving cyclosporine. 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 outcome**s** have been reported**.** Effective pre-emptive and therapeutic strategies should be employed particularly in patients on multiple long-term immunosuppressive therapy.

Vaccination may be less effective and the use of live attenuated vaccines should be avoided.

Neurologic

Cyclosporine is neurotoxic and has the potential to induce tremor, convulsions and paresthesia in post-transplant recipients. More complex neurological abnormalities including motor spinal cord, cerebellar syndromes, and encephalopathy have been reported in post-transplant patients. In many cases, changes in the white matter of the brain have been detected. Dose reduction or discontinuation should be considered in patients with severe cyclosporine-associated

neurotoxicity.

Renal

Cyclosporine may cause increases in serum creatinine and urea levels, even at recommended doses as a result of reduced glomerular filtration rate (GFR). The mechanism leading to these increases is not fully understood. These functional changes are dose dependent and reversible, and usually respond to dose reduction. Although less frequent, some patients may develop structural changes in the kidney (e.g. arteriolar hyalinosis, tubular atrophy and interstitial fibrosis) during long term treatment. Although these renal changes are less common, they may be irreversible. Therefore, dose reduction or discontinuation should be considered in these patients.

In renal transplant patients, structural changes in the kidney must be differentiated from organ rejection.

Close monitoring of parameters that assess renal function is required. Abnormal values may necessitate dose reduction.

In elderly patients (> 65 years of age), renal function should be monitored more closely. Kidney changes occur both structurally and functionally with aging leading to a natural decrease of renal function. Cyclosporine whole blood concentrations should be closely monitored in this patient group to ensure maximum safety and optimal clinical outcome.

In patients who are treated with cyclosporine for non-transplant indications, the risk of renal structural changes is greater if the serum creatinine level increases more than 30% from the patient's own baseline value. Thus regular measurements of serum creatinine levels must be made (see also **MONITORING AND LABORATORY TESTS, PSORIASIS/ RHEUMATOID ARTHRITIS/ NEPHROTIC SYNDROME PATIENT MANAGEMENT**).

Special Excipients: Ethanol

The ethanol content (see **SUMMARY PRODUCT INFORMATION**) should be taken into account when given to pregnant or breast feeding women and children, to patients with liver disease or epilepsy, and to patients with alcohol-dependence.

Special Populations

Women of child-bearing potential:

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

Pregnant Women:

Animal studies have shown reproductive toxicity in rats and rabbits (see **DETAILED**

PHARMACOLOGY).

Cyclosporine is not teratogenic in animals, but was shown to be both embryo- and feto-toxic in rats and rabbits at 2 to 5 times the human dose.

To date, information has been received on 514 pregnancies with exposure to SANDIMMUNE®. In most patients, the indication for cyclosporine therapy was organ transplantation.

Pregnant women receiving immunosuppressive therapies after transplantation, including cyclosporine and cyclosporine-containing regimens, are at risk of premature delivery (<37 weeks).

Most patients who became pregnant continued cyclosporine therapy throughout pregnancy, usually in combination with other immunosuppressive drugs and further medication.

Fetal loss occurred in 9.1% of the patients, which is within the range found in a normal population. In 4.9% of the patients, the pregnancy was interrupted, either for medical considerations or at the wish of the patient.

The course of pregnancy was often complicated by disorders specific to pregnancy, in particular in renal transplant patients, or by disorders relating to the underlying disease. A large proportion of the pregnancies ended in preterm delivery. Accordingly, the main problems seen in the neonates relate to prematurity, best exemplified by the short median gestation duration of 35.7 weeks in the 439 pregnancies completed, and the low median birth weight, 2291 g, of the 446 babies delivered, including 10 twins.

It appears that premature delivery and the delivery of infants small for their age occur more often in patients who have undergone a renal transplantation.

Out of 102 babies born to mothers treated with SANDIMMUNE®, five were born with malformations. It is not clear what role cyclosporine has played in the complications of pregnancy.

Males treated with cyclosporine have fathered normal children.

In pregnant transplant recipients who are being treated with immunosupressants the risks of premature births is increased.

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

However there are no adequate data in pregnant women and, therefore, NEORAL® or SANDIMMUNE® I.V. should not be used during pregnancy unless the expected benefit to the mother outweighs the potential risk to the foetus. The ethanol content should also be taken into

account in pregnant women (see **WARNINGS AND PRECAUTIONS**).

Nursing Women:

Cyclosporine passes into breast milk. Mothers receiving treatment with NEORAL® or SANDIMMUNE® I.V. should not breast feed. The ethanol content of NEORAL® should also be taken into account (see **WARNINGS AND PRECAUTIONS**). Because of the potential of 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 importance of the medicinal product to the mother.

Fertility

There is a limited data on the effect of NEORAL® on human fertility. No impairment in fertility was demonstrated in studies in male and female rats (see **DETAILED PHARMACOLOGY**).

Renal impairment

All indications
Cyclosporine undergoes minimal renal elimination and its pharmacokinetics is not affected by renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY**). However, due to its nephrotoxic potential (see **ADVERSE REACTIONS**), a careful monitoring of the renal function is recommended (see **WARNINGS AND PRECAUTIONS**, **ALL INDICATIONS**).

Non-transplant indications
Patients with impaired renal function, except nephrotic syndrome patients, should not receive cyclosporine (see **WARNINGS AND PRECAUTIONS**, **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

Cyclosporine 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 **ACTION AND CLINICAL PHARMACOLOGY**). Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACLOGY**).

Pediatrics:

NEORAL® is not recommended in children of non-transplant indications other than nephrotic syndrome. Pediatric patients have similar adverse drug reaction profiles as those in the adults (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

Clinical studies in patients with nephrotic syndrome have included children from one year of age using standard cyclosporine dosage. In several studies, pediatric patients required higher doses of cyclosporine per kg body weight than those used in adults.

Geriatrics (> 65 years of age):

Experience with cyclosporine in the elderly is limited, but no particular problems have been reported following the use of the drug at the recommended dose. However, factors sometimes associated with aging, in particular impaired renal function, necessitate careful supervision and may necessitate dosage adjustment.

In rheumatoid arthritis clinical trials with cyclosporine, 17.5% of patients were age 65 or older. These patients were more likely to develop systolic hypertension on therapy, and more likely to show serum creatinine rises $\geq$ 50% above the baseline after 3-4 months of therapy**.**

Clinical studies of NEORAL® 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.

Monitoring and Laboratory Tests

Transplant Patient Management

Clinical

The concentrate for solution for infusion contains polyoxyethylated castor oil which has been reported to cause anaphylactoid reactions. These reactions can consist of flushing of the face and upper thorax, and non-cardiogenic pulmonary edema with acute respiratory distress, dyspnea, 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 polyoxyethylated castor oil, or in patients with an allergic predisposition. Thus, patients receiving SANDIMMUNE® I.V. should be observed continuously for at least the first 30 minutes following 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 antihistamine (H1 + H2 blocker) prior to SANDIMMUNE® I.V. has also been successfully employed to reduce the severity and prevent the occurrence of anaphylactoid reactions. The oral forms of NEORAL® (cyclosporine) do not contain polyoxyethylated castor oil.

Laboratory

Accurate and regular monitoring of cyclosporine blood levels in conjunction with other laboratory and clinical parameters is regarded as an essential aid to maintain the trough concentrations within the relatively narrow therapeutic window between efficacy and toxicity.

During the immediate post-operative period, levels should be monitored every 2-3 days.

Monitoring schedules should continue until the patient's clinical condition and NEORAL® or SANDIMMUNE® I.V. dosage are stable. Following discharge from hospital, cyclosporine levels are determined at each clinic visit, which is usually twice weekly for the first two months, weekly until four months and monthly thereafter for the first year.

The reported therapeutic range for 12 hour trough levels from whole blood which appear to minimize side effects and rejection episodes are between 100-400 ng/mL as measured by the RIA method using specific monoclonal antibody (see **DOSAGE AND ADMINISTRATION**).

Two methods are available for the specific assay of cyclosporine parent compound: radioimmunoassay (RIA) and high-performance liquid chromatography (HPLC). Comparative findings for the analysis of blood samples by both the RIA method (based on specific monoclonal antibody) and the HPLC method has established that the specific antibody gives a selective measure of the cyclosporine parent compound without significant interference from drug metabolites. Therefore, 12 hour trough levels of the cyclosporine parent compound should routinely be measured using the radioimmunoassay (RIA) kit for cyclosporine based on the specific monoclonal antibody.

Because there is a temperature and time-dependent uptake of cyclosporine by erythrocytes, the concentration of cyclosporine in plasma separated at room temperature and 37°C will differ substantially, the latter being higher. For this reason, it is not recommended to use plasma or serum as the matrix of choice. However, if plasma or serum is used a standard separation protocol (time and temperature) should be followed.

Whole blood is the matrix of choice. Specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anticoagulant. Heparin anticoagulation is not recommended because of the tendency to form clots on storage. Samples which are not to be analyzed immediately should be stored in a refrigerator (4°C) and assayed within 7 days; if the samples are to be kept longer they should be deep frozen (-20°C) for up to 6 months.

Psoriasis / Rheumatoid Arthritis / Nephrotic Syndrome Patient Management

Prior to Initiation of NEORAL® Therapy

Clinical

Before treatment, the patient should undergo a history and physical examination with investigations as warranted. An initial blood pressure reading should be made on at least two

occasions within 2 weeks to establish a baseline. As NEORAL® is immunosuppressive, a search should be made for tumours of all kinds, particularly of the skin. Any persistent previously undiagnosed skin lesion should be biopsied for a confirmed diagnosis prior to starting therapy. Female patients should have an examination of the cervix within the first 6 months of therapy, and periodically thereafter, to exclude malignancy.

Laboratory
Prior to therapy, a 12-hour fasting serum creatinine should be measured on at least three occasions within 2 weeks to give an accurate baseline value. A baseline creatinine clearance is also suggested, if possible.

It is recommended that initial investigations should include urinalysis, complete blood count, liver function tests, serum uric acid and serum potassium.

Follow-up during NEORAL® Therapy

Clinical
Regular clinical examinations are necessary during treatment with NEORAL®. Follow-up assessment of blood pressure should be performed every 2 weeks during the initial 3 months and every month thereafter.

Should hypertension occur, in the majority of patients, elevated blood pressure can be adequately controlled by dose reduction. Should antihypertensive therapy be necessary, diuretics are not recommended. In addition, in psoriasis patients, beta-blockers are not generally recommended due to their propensity to exacerbate psoriasis. Only calcium channel blockers which do not interfere with NEORAL® pharmacokinetics are recommended (see **DRUG INTERACTIONS**). If hypertension is uncontrolled with antihypertensive treatment, NEORAL® should be discontinued. When NEORAL® is discontinued, blood pressure returns to normal within 3 months. Development of malignancies has been reported in patients when treated with cyclosporine. In patients with nephrotic syndrome treated with immunosuppressants (including cyclosporine) the occurrence of malignancies (including Hodgkin's lymphoma) has occasionally been reported. Careful physical examination should thus be made for malignancies, notably of skin, oral mucosa, major lymph nodes. Psoriatic patients should avoid direct sun exposure as this will increase the risk of skin cancer.

Laboratory

a) Psoriasis and rheumatoid arthritis

A complete blood count including, differential WBC, platelet counts, liver function tests, urinalysis, serum potassium, uric acid should be measured periodically during treatment with NEORAL®. Serum creatinine should be measured every 2 weeks for the initial 3 months (see **DOSAGE AND ADMINISTRATION**). Thereafter, if creatinine levels remain stable, measurements should be made every 2 months in patients who are receiving up to 2.5 mg/kg/day and every 4 weeks in patients who are receiving higher doses. If creatinine increased from the

baseline, dose reduction or discontinuation should be considered.

More frequent checks are necessary when the NEORAL® dose is increased or concomitant treatment with a non-steroidal anti-inflammatory drug is initiated or the dosage is increased. The same precaution applies to the introduction of any drug known to increase cyclosporine blood levels.

Routine measurements of cyclosporine blood levels are not necessary because of their poor predictive value, but may be useful in special cases where drug interactions or altered bioavailability are suspected.

b) Nephrotic syndrome

Since cyclosporine can impair renal function, it is necessary to assess renal function frequently and, if the serum creatinine remains increased by more than 30% above baseline at more than one measurement the dosage of NEORAL® must be reduced by 25 to 50%. If the creatinine increase greater than 30% occurs, further dose reduction or discontinuation should be considered. In some patients it may be difficult to detect cyclosporine-induced renal dysfunction because of changes in renal function related to the nephrotic syndrome itself. This may explain why, in rare cases, cyclosporine- associated structural kidney alterations have been observed without changes in serum creatinine. Therefore, renal biopsy should be considered for patients with steroid-dependent minimal change nephropathy in whom cyclosporine therapy has been maintained for more than one year.

Periodic monitoring of cyclosporine trough levels is recommended.

Drug Interactions

Caution should be exercised in patients receiving drug treatment with:

- Nephrotoxic Drugs
- Cytotoxic Drugs
- Immunosuppressants or radiation (including PUVA or UVB)
- Drugs affecting metabolism/absorption of cyclosporine
- Lercanidipine
- Methotrexate
- Substrates of P-glycoprotein (Pgp) such as aliskiren

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

ADVERSE REACTIONS

Adverse drug reactions from clinical trials are listed by MedDRA system organ classes. 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.

Adverse Drug Reaction Overview

Despite the increase in C_{max} and AUC seen in patients who are treated with NEORAL® capsules and oral solution (cyclosporine), a similar safety profile to the conventional formulation of cyclosporine (SANDIMMUNE® capsules and oral solution) has been observed. Studies have reported no significant difference between the two formulations in terms of renal safety, risk of adverse events, or laboratory parameters (eg blood pressure, creatinine clearance, serum levels of urea, creatinine, potassium, cholesterol, triglycerides). Furthermore, there is no indication of a correlation between peak cyclosporine concentration (C_{max}) and changes in renal function.

The following adverse reactions observed with SANDIMMUNE® are also likely to occur with NEORAL®.

The principal adverse reactions observed in clinical trials and associated with the administration of cyclosporine include renal dysfunction, tremor, hirsutism, hypertension, diarrhea, anorexia, nausea and vomiting.

Many side effects associated with cyclosporine 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 **WARNINGS AND PRECAUTIONS).**

Infections and Infestations

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

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Patients receiving immunosuppressive therapies, including cyclosporine and cyclosporine-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 **WARNINGS AND PRECAUTIONS**).

Blood and Lymphatic System disorders: Common: Leucopenia; Uncommon: anemia (in 1 patient only <1%), thrombocytopenia (in 5 patients i.e., 2%), thrombotic thrombocytopenic purpura reported as purpura 2 patients (<1%) in the pooled data of bone marrow transplantation and GvHD trials.

Cardiovascular disorders: Very common: hypertension (particularly in heart transplant patients); Common: flushing.

Gastrointestinal tract disorders: Very common*:* nausea, vomiting, abdominal discomfort, diarrhea, gingival hyperplasia; Common: peptic ulcer. Rare: Pancreatitis acute (in 1 patient only <1%).

General disorders and administration site conditions: Common: pyrexia, edema; Uncommon: weight increase (in 1 patient only <1%).

Hepatobiliary disorders: Uncommon: hepatoxicity (in 3 patients only <1%)

Metabolism and nutrition disorders: Very common: anorexia**,** hyperglycemia

Musculoskeletal and connective tissue disorders: Uncommon: muscle cramps (in 1 patient only <1%) myalgia (reported as muscle pain in 2 patients (<1%)

Nervous system disorders:

Very common: tremor, headache

Common: convulsions, paresthesia

Renal and Urinary disorders: Very common: renal dysfunction (see **WARNINGS AND PRECAUTIONS**).

Reproductive System and breast disorders: Rare: Menstrual disturbances, Uncommon: Gynecomastia reported in US CyA liver and kidney transplant studies as 2 patients and 4 patients respectively.

Skin and subcutaneous tissue disorders: Very common: hirsutism; Common: acne.

Especially in liver transplant patients, signs of encephalopathy, vision and movement disturbances, and impaired consciousness are described. Whether these alterations are caused by cyclosporine, the underlying disease or other conditions remains to be established.

In rare instances, thrombocytopenia, in some patients associated with micro-angiopathic hemolytic anemia and renal failure (hemolytic uremic syndrome), has been observed.

Malignancies and lymphoproliferative disorders have developed, but their incidence and distribution are similar to those in patients on conventional immunosuppressive therapy.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Transplantation

The following events occurred in patients involved in two clinical trials with NEORAL®. The first column reports on a study in which stable renal transplant patients were switched to NEORAL®; in the second, de novo renal transplant patients were treated with NEORAL®.

Adverse Event	1. Stable renal transplant patients (N=372)	2. New renal transplant patients (N=45)
Gingival hyperplasia	29 (7.8%)	3 (6.7%)
Hypertrichosis	24 (6.5%)	17 (37.8%)
Edema	32 (8.6%)	14 (31.1%)
Tremor	31 (8.3%)	19 (42.2%)
Loss of muscle strength	3 (0.8%)	8 (17.8%)
Changes in vegetative functions	24 (6.5%)	8 (17.8%)
Nausea, vomiting, epigastrical pain	30 (8.1%)	7 (15.6%)
Headache	37 (10.0%)	10 (22.2%)
Paresthesia	16 (4.3%)	5 (11.1%)
Heat Sensations	28 (7.5%)	5 (11.1%)
Others	62 (16.7%)	11 (27.5%)

Psoriasis

In clinical trials, the most frequent side effects associated with the use of cyclosporine in psoriasis were renal dysfunction, hypertension, gastrointestinal disorders, hypertrichosis, paresthesia, headache, influenza-like symptoms, upper-respiratory tract infections, gum hyperplasia, fatigue, hyperuricemia, hypomagnesemia and increase in plasma liquids.

The following events (excluding renal dysfunction, hypertension and malignancies) occurred in 3% or greater of 631 psoriatic patients involved in clinical trials:

Body System Adverse Event	%
Skin and Appendages Hypertrichosis	 14.6
Central and Peripheral Nervous System Paresthesia Headache	 11.4 9.4
Gastrointestinal Tract Nausea Gingival overgrowth Gastrointestinal disorder	 4.8 4.6 3.3
General Disorders Fatigue	 4.0
E.N.T. and Respiratory Tract Influenza-like symptoms Upper respiratory tract infection	 5.5 4.6

In psoriasis in 1,439 patients treated with SANDIMMUNE® the following were reported: 21 cases of skin cancer, 17 cases of solid malignant tumours and 6 cases of lymphoproliferative disorders (2 lymphomas).

There is an increased risk of malignancies, particularly skin cancer in psoriasis patients especially when the psoriasis has been previously treated with carcinogens, such as PUVA treatment.

Rheumatoid Arthritis

In clinical trials, the most frequent side effects associated with the use of cyclosporine in rheumatoid arthritis were hypertrichosis; hypertension; nausea; abdominal pain; paresthesia; headache and gum disorders.

Body System Adverse Event	**SANDIMMUNE® Patients** Initial Dose < 6 mg/kg/d (n=378) (%)	**Placebo-Treated Patients** (n=176) (%)
Skin Appendages		
Alopecia	3.4	2.3
Hypertrichosis	33.9	5.1
Rash	3.4	6.3
Central and Peripheral		
Cramps	4.0	0.6
Dizziness	4.5	4.5
Headache	15.6	9.7
Paresthesia	15.9	6.3
Tremor	13.5	3.4
Autonomic Nervous		
Flushing	5.0	1.7
Gastro-Intestinal		
Abdominal pain	18.8	10.2
Diarrhea	6.1	6.3
Dyspepsia	9.5	5.7
Gum Disorders	11.6	0.6
Nausea	27.2	13.6
Vomiting	8.2	2.3
Body as a Whole		
Fatigue	4.2	4.0
Fever	3.2	2.3
Edema	4.8	2.8
Resistance Change		
Pharyngitis	3.2	2.3

Nephrotic Syndrome

In clinical trials, the most frequent side effects associated with the use of cyclosporine in nephrotic syndrome were: renal dysfunction, hypertrichosis, gingival hyperplasia, hypertension, tremor and paresthesia, and gastrointestinal symptoms.

The following events occurred in 3% or greater of nephrotic syndrome patients involved in clinical trials

Body System Adverse Event	SANDIMMUNE® Patients (n=270) (%)
Skin/Appendages	
Hypertrichosis	31.5%
Hypotrichosis	3.0%
Musculo-Skeletal	
Muscle Contraction	4.1%
Central and Peripheral Nervous System	
Paresthesia	12.2%
Headache	5.6%
Tremor	5.6%
Psychiatric Disorders	
Weakness	4.8%
Gastro-Intestinal	
Gingival Hyperplasia	27.0%
Nausea	4.4%
Gastric Pain	3.7%
Diarrhea	3.3%
Abdominal Pain	3.1%
Liver and Biliary System	
Liver Enzyme Increase	3.3%
Metabolic and Nutritional	
Hypomagnesemia	5.2%
Cardiovascular	
Hypertension	13.7%
Urinary System	
Renal Dysfunction	7.0%

In nephrotic syndrome of 660 patients treated with SANDIMMUNE®, malignancies occurred in 5 patients (3 carcinomas, 2 Hodgkin's lymphomas).

Post-Marketing Adverse Drug Reactions

The following adverse drug reactions have been derived from post-marketing experience with NEORAL® or SANDIMMUNE® 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 order of decreasing seriousness.

Blood and Lymphatic System disorders: Thrombotic microangiopathy, haemolytic uremic syndrome

Metabolism and nutrition disorders: hyperlipidemia, hyperuricemia, hyperkalemia, hypomagnesemia.

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 edema including papilledema, with possible visual impairment secondary to benign intracranial hypertension, peripheral neuropathy, migraine.

Hepatobiliary disorders: Liver injury including cholestasis, jaundice, hepatitis and liver failure with some fatal outcome (see **WARNINGS AND PRECAUTIONS**).

Skin and subcutaneous tissue disorders: Hypertrichosis.

Musculoskeletal and connective tissue disorders: Myopathy, muscular weakness, as well as muscle pain, myositis, and rhabdomyolysis (with concomitant administration of cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin, and rarely fluvastatin (see **DRUG-DRUG INTERACTIONS**), pain of lower extremities (including as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS) as described in the literature).

General disorders and administration site conditions: Fatigue

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 cyclosporine. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and comedications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see **WARNINGS AND PRECAUTIONS**).

Acute and chronic nephrotoxicity

Patients receiving calcineurin inhibitors (CNIs) therapies, including cyclosporine and cyclosporine-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 NEORAL®. Cases of acute nephrotoxicity reported disorders of ion homeostasis, such as

hyperkalemia, hypomagnesemia, hyperuricemia 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 **WARNINGS AND PRECAUTIONS**).

DRUG INTERACTIONS

Overview

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

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

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

- In transplant patients: frequent measurements of cyclosporine levels and, if necessary, cyclosporine dosage adjustment are required, particularly during the introduction or withdrawal of the co-administered drug.
- In non-transplant patients: the value of cyclosporine 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 cyclosporine levels are given concomitantly, frequent assessment of renal function and careful monitoring for cyclosporine-related side effects may be more appropriate than blood level measurement.

Cyclosporine is also an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein and may increase plasma levels of comedications that are substrates of this enzyme and/or transporter.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drug therapy should be discontinued where possible. As nonsteroidal anti- inflammatory drugs alone can have an adverse effect on renal function, addition of these drugs to NEORAL® or SANDIMMUNE® I.V. therapy or an increase in their dosage should be accompanied by particular close monitoring of renal function.

Infection/Immunization

During treatment with cyclosporine, vaccination may be less effective; the use of live-attenuated vaccines should be avoided.

HMG-CoA Reductase Inhibitors

In transplant patients who received the HMG-CoA reductase inhibitor lovastatin in combination

with cyclosporine and other immunosuppressive drugs, there have been reports of severe rhabdomyolysis that precipitated acute renal failure. The potential for NEORAL® or SANDIMMUNE® I.V. to interact with drugs in this class should be considered.

Cyclosporine 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 cyclosporine in several patients taking digoxin. There are also reports on the potential of cyclosporine 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 cyclosporine, 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 cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely, fluvastatin. When concurrently administered with cyclosporine, 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 cyclosporine, 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 sirolimus in combination with full-dose cyclosporine for microemulsion. This effect is often reversible with cyclosporine dose reduction. Sirolimus had only a minor influence on cyclosporine pharmacokinetics. Co-administration of cyclosporine significantly increases blood levels of sirolimus.

The concomitant use of these drugs with NEORAL® capsules and oral solution or SANDIMMUNE® I.V. (cyclosporine) should be carefully considered.

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 comedication should be withdrawn.

Prednisolone and methylprednisolone

It has been noted that cyclosporine reduces the clearance of prednisolone and conversely, high

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

dose therapy with methylprednisolone can increase the blood concentration of cyclosporine.

Potassium sparing drugs and potassium containing drugs
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 **WARNINGS AND PRECAUTIONS**).

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

Co-administration of bosentan and cyclosporine in healthy volunteers resulted in an approximately 2-fold increase in bosentan exposure and a 35% decrease in cyclosporine exposure (see **WARNINGS AND PRECAUTIONS**).

Following concomitant administration of cyclosporine 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 cyclosporine was not significantly altered (see **WARNINGS AND PRECAUTIONS**).

Concomitant administration of dabigatran and cyclosporine leads to increased plasma level of dabigatran due to the P-gp inhibitory activity of cyclosporine (see **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 cyclosporine in healthy volunteers resulted in an approximately 2-fold increase in ambrisentan exposure while the cyclosporine 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 cyclosporine.

Lercanidipine

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

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential

interactions due to the expected magnitude and seriousness of the interaction.

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.

Summary of Drug Interactions

	Drugs Increasing the Serum Concentration of Cyclosporine	**Drugs Decreasing the Serum Concentration of Cyclosporine**	**Drugs Causing additive nephrotoxicity**
Substantiated Interactions	Allopurinol Amiodarone Calcium-channel blockers – Diltiazem – Verapamil – Nicardipine Colchicine Cholic acid and derivatives Corticosteroids Danazol Fluconazole Imatinib Imipenem Itraconazole Ketoconazole Macrolide antibiotics (erythromycin, azithromycin and clarithromycin) Lercanidipine Metoclopramide Methylprednisolone Norethisterone or danazol Oral contraceptives Protease inhibitors Voriconazole Nefazodone	Barbiturates Bosentan Carbamazepine *Hypericum perforatum* (St. John's wort) Metamizole Nafcillin Octreotide Orlistat Oxcarbazepine Phenytoin or phenobarbitone Probucol Rifampicin i.v. Sulfadimine i.v. and trimethoprim i.v. Sulfinpyrazone Terbinafine Ticlopidine	Aminoglycosides (incl. Gentamycin, tobramycin) Amphotericin # Ciprofloxacin Colchicine Cotrimoxazole or Trimethoprim (+ sulfamethoxazole) Melphalan Methotrexate* Vancomycin

	Drugs Increasing the Serum Concentration of Cyclosporine	Drugs Decreasing the Serum Concentration of Cyclosporine	Drugs Causing additive nephrotoxicity
Suspected or potential Interactions	AcyclovirAndrogenic steroids Cephalosporins Furosemide H2-antagonists Thiazide diuretics Warfarin	Anticonvulsants	Histamine H2 receptor antagonist (e.g. cimetidine, ranitidine) Nonsteroidal anti-inflammatory drugs (e.g. diclofenac, naproxen, sulindac) Tacrolimus

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

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

The concomitant use of diclofenac and cyclosporine has been found to result in a significant increase in the bioavailability of diclofenac, with the possible consequence of renal function impairment which shows reversible after discontinuation of both the medications in a 24 week study. 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 cyclosporine, 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 cyclosporine.

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 evnt of significant impairment of kidney function the co-medication should be withdrawn.

If combined administration is unavoidable, careful monitoring of blood cyclosporine concentration and appropriate modification of NEORAL® or SANDIMMUNE® I.V. dosage are essential.

Caspofungin: In two clinical studies, cyclosporine (one 4 mg/kg dose or two 3 mg/kg doses) increased the AUC of caspofungin by approximately 35%. Caspofungin did not increase the blood levels of cyclosporine. There were transient increases in liver ALT and AST when caspofungin and cyclosporine were co-administered. Cyclosporine and caspofungin should only be used concomitantly in those patients for whom the potential benefit outweighs the potential

risk. Patients who develop abnormal liver function tests during concomitant therapy should be monitored and the risk/benefit of continuing therapy should be evaluated.

Miscellaneous Interactions

Alteration of Immunosuppressive Effect	Interactions with Alcohol Content	Others
Etoposide Propranolol Verapamil	Chlorpropamide Disulfiram Metronidazole	Aliskiren (cyclosporine may increase blood levels of concomitant medications that are substrates of P-glycoprotein (Pgp)) Caspofungin Captopril Colchicine Digoxin HMG-CoA reductase inhibitors Nifedipine* Prednisolone Toxoids or vaccines Potassium sparing drugs

*Concurrent administration of nifedipine with cyclosporine may result in an increased rate of gingival hyperplasia compared with that observed when cyclosporine is given alone. The concomitant use of nifedipine should be avoided in patients in whom gingival hyperplasia develops as a side-effect of cyclosporine.

Serious drug interactions may occur between cyclosporine and St. John's Wort, as concomitant administration may decrease cyclosporine level.

Drug-Food Interactions

Grapefruit juice should be avoided owing to its interference with the P450 enzyme system which has been reported to increase the bioavailability of NEORAL®.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dose ranges of NEORAL® capsules and oral solution and SANDIMMUNE® I.V. given below are intended to serve as guideline only. Routine monitoring of cyclosporine blood levels is required; this can be carried out by means of an RIA method based on monoclonal antibodies.

Routine monitoring of cyclosporine blood levels is also required when switching a patient from one oral cyclosporine formulation to another. The results obtained will serve as a guide for determining the actual dosage required to achieve the desired target concentration in individual patients.

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

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

In patients treated for *non-transplant indications*, monitoring of cyclosporine 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 **WARNINGS AND PRECAUTIONS**).

Recommended Dose and Dosage Adjustment

Solid organ transplantation

Treatment with NEORAL® may be initiated within 12 hours prior to surgery at a dose of 10 to 15 mg/kg given in two divided doses, 12 hours apart. This dose should be maintained as the daily dose for one to two 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 two divided doses is reached. The following table outlines the recommended steady state therapeutic ranges of cyclosporine 12 hour trough levels (the level immediately before the next dose).

Target Trough Levels		
RIA METHOD	**Blood ng/mL**	**Plasma/serum ng/mL**
Monoclonal specific[1] Polyclonal non-specific[2]	100-400 150-1500	50-200 50-300

[1]Values are based on HPLC data and the results of a multi-centre comparison of the monoclonal specific RIA with the polyclonal RIA kit. Plasma serum values are based on separation at 37°C. These values will be lower if plasma/serum is separated at room temperature.

[2]Whole blood values are based on a multiplication factor of 3-5x concentration obtained using plasma/serum values. Plasma/serum values are based on separation at 22°C.

When NEORAL® 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 two divided doses 12 hours apart for the initial treatment) may be used.

Recommended Dosage of Concentrate for Solution for Infusion
Patients unable to take NEORAL® soft gelatin capsules or oral solution pre- or postoperatively, may be treated with the SANDIMMUNE® I.V. at one-third the oral dose.

The initial dose of SANDIMMUNE® I.V. is 3 to 5 mg/kg/day. This daily dose is continued post-operatively for up to 2 weeks until the patient can tolerate the NEORAL® soft gelatin capsules or oral solution. Patients should be switched to NEORAL® as soon as possible after surgery. In pediatric usage, the adult dose and dosing regimen have been used initially and adjusted to target blood levels (see **WARNINGS AND PRECAUTIONS**).

Bone marrow transplantation
The initial dose should be given on the day before transplantation. In most cases, intravenous (i.v.) infusion of SANDIMMUNE® is preferred for this purpose (please refer to previous Section). Maintenance treatment with NEORAL® is at a daily dose of about 12.5 mg/kg given in two divided doses, 12 hours apart, and should be continued for at least 3 months (and preferably for 6 months) before the dose is gradually decreased to zero by one year after transplantation. If NEORAL® is used to initiate therapy, the recommended daily dose is 12.5 to 15 mg/kg given in two divided doses, starting on the day before transplantation.

Higher doses of 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 cyclosporine treatment, but usually responds favourably to re-introduction of therapy. In such cases, an initial oral loading dose of 10 to 12.5 mg/kg should be given, followed by daily oral administration of the maintenance dose previously found to be satisfactory.

Low doses of NEORAL® should be used to treat mild, chronic GVHD.

Non-transplantation
When using 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 **WARNINGS AND PRECAUTIONS**).
- The only accepted route of administration is by the mouth (the concentrate for intravenous infusion must not be used), and the daily dose should be given in two divided doses.
- Except in children with nephrotic syndrome, the total daily dose must never exceed 5 mg/kg.
- For maintenance, the lowest effective and well tolerated dosage should be determined individually.
- In patients in whom within a given time no adequate response is achieved or the effective

dose is not compatible with the established safety guidelines, treatment with NEORAL® should be discontinued.

Psoriasis
Dose Titration for Induction of Remission, the recommended initial dose is 2.5 mg/kg/day given in two divided oral doses, 12 hours apart.

If there is no improvement after one month, the daily dose may be gradually increased. Dose adjustments should be made in increments of 0.5 to 1.0 mg/kg/day body weight per month and total daily dose, depending on monitoring of drug tolerance, should not exceed 5 mg/kg/day.

Treatment Discontinuation
Treatment should be discontinued in patients in whom psoriatic lesions do not respond sufficiently within 6 weeks on 5.0 mg/kg/day, **or in whom the effective dose is not compatible with the safety guidelines given below under Monitoring (**see **WARNINGS AND PRECAUTIONS).** As skin lesions improve the dose should be reduced in increments of 0.5-1 mg/kg/day per month.

Long-term Goals of Therapy
Psoriasis generally recurs when NEORAL® treatment is stopped. The goal of maintenance therapy is to optimize therapy and achieve sustained improvement. That is, to keep the patient's disease controlled with the minimal dose of NEORAL® in order to avoid adverse effects. Total clearing of the skin should not always be the ultimate goal.

Maintenance Dose
After reaching a relatively disease-free state, the patient should be given the minimum effective maintenance dose. For maintenance treatment, **doses should be titrated individually to the lowest effective level**, and, depending on monitoring of drug tolerance, should not exceed 5.0mg/kg/day.

If a patient experienced a worsening of the condition during maintenance, therapy can be changed to a dose that is sufficient to control psoriasis **while remaining compatible with the safety guidelines**, i.e. maximum 5.0 mg/kg/day. An attempt should then be made to reduce the dose to the lowest effective level.

Dosage adjustments should follow the guidelines for inducing remission. If no relapse occurs within 6 months, an attempt should be made to wean the patient off NEORAL®.

Monitoring for Psoriasis Patients
Since NEORAL® can impair renal function, serum creatinine should be measured every 2 weeks for the first 3 months of therapy. Thereafter, if creatinine remains stable, measurements should be done every 2 months in patients who are on up to 2.5 mg/kg/day, and at monthly intervals in patients who require higher doses. The dose must be reduced by 25-50% when serum creatinine increases by more than 30% above the patient's own baseline, even if the values are still within the normal range. If dose reduction is not successful within 1 month, NEORAL® treatment

should be discontinued.

Discontinuation of NEORAL® therapy is also recommended if hypertension developing during NEORAL® therapy cannot be controlled with appropriate therapy.

As cyclosporine is an immunosuppressive agent, search should be made for tumours of all kinds, in particular the skin, oral mucosa and major lymph nodes. This physical examination should be made initially at least every 3 months and any skin lesion not typical for psoriasis should be biopsied. NEORAL® treatment should be discontinued if a malignancy occurs, and appropriate treatment of the malignancy instituted.

Rheumatoid Arthritis
For the first 6 weeks of treatment, the recommended initial dose is 2.5 mg/kg/day orally given in two divided doses, 12 hours apart. If necessary, the daily dose may then be increased gradually as **tolerability** permits (see **WARNINGS AND PRECAUTIONS**) but, depending on monitoring of drug tolerance, should not exceed 5 mg/kg/day. Up to 12 weeks of NEORAL® therapy may be required before full effectiveness is achieved.

For maintenance therapy, the dose must be titrated individually to the lowest effective level according to tolerability.

NEORAL® may be given in combination with low-dose corticosteroids and/or non-steroidal anti-inflammatory drugs (see **WARNINGS AND PRECAUTIONS**).

Monitoring for Rheumatoid Arthritis Patients
Since cyclosporine 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 every 2 weeks during the first 3 months of therapy. Thereafter, if creatinine remains stable, measurements can be made every 4 weeks. More frequent checks are necessary when the dose of NEORAL® is increased or concomitant treatment with a non-steroidal anti-inflammatory drug is initiated or its dosage increased. The same precaution applies to the introduction of any drug known to increase cyclosporine blood levels.

Dose adjustment based on creatinine values: If serum creatinine remains increased by more than 30% above baseline at more than one measurement, the dosage of NEORAL® should be reduced. If 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 normal range. If dose reduction is not successful in reducing levels within one month, NEORAL® treatment should be discontinued.

Nephrotic Syndrome

Dose Titration for Induction of Remission

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

renal function is normal (except for proteinuria), the recommended initial dose is given BID in two divided oral doses, 12 hours apart:

- 3.5mg/kg/day for adults
- 4.2mg/kg/day for children

Dose should be titrated for induction of remission and renal function. The combination of NEORAL® with low doses of oral corticosteroids is recommended if the effect of NEORAL® is not satisfactory, especially in steroid-resistant patients.

Treatment Discontinuation
Treatment should be discontinued if no improvement has been observed after three months' of NEORAL® therapy.

Maintenance Dose
The dose must be adjusted individually according to efficacy (proteinuria) and safety (primarily serum creatinine), but, depending on monitoring of drug tolerance, should not exceed 5 mg/kg a day in adults and 6 mg/kg a day in children.

Monitoring for Nephrotic Syndrome Patients
For maintenance treatment, the dose should be slowly reduced to the lowest effective level.

Monitoring for Nephrotic Syndrome Patients
Since NEORAL® can impair renal function, it is necessary to assess renal function frequently and if serum creatine remains increased by more than 30% above baseline at more than one measurement, the dosage of NEORAL® must be reduced by 25% to 50%.

In some patients it may be difficult to detect cyclosporine-induced renal dysfunction because of changes in renal function related to the nephrotic syndrome itself. Renal biopsy should be considered for patients with steroid-dependent minimal change nephropathy in whom NEORAL® therapy has been maintained for more than one year.

Periodic monitoring of cyclosporine trough levels is recommended.

Method of administration

Oral administration

NEORAL® SOFT GELATIN CAPSULES: When the blister package is opened, a characteristic smell is noticeable. This is normal and does not mean that there is anything wrong with the capsule.

NEORAL® capsules should be swallowed whole.

NEORAL® SOLUTION should be diluted with preferably orange juice or apple juice. Grapefruit juice should be avoided for dilution owing to its possible interference with the cytochrome P450 enzyme system. Immediately before taking the solution, it should be stirred well. Other drinks such as soft drinks can be used according to individual taste.

The syringe should not come into contact with the diluent. If the syringe is to be cleaned, do not rinse it but wipe the outside with a dry tissue.

Intravenous administration

SANDIMMUNE® I.V. (50 mg/ml Concentrate for Solution for Infusion) is diluted to l:20 to l:l00, immediately prior to use, with 5% glucose or normal saline and administered by slow intravenous infusion over a period of two to six hours (see **WARNINGS AND PRECAUTIONS**).

Because of the risk of anaphylaxis (see **WARNINGS AND PRECAUTIONS**), the use of the SANDIMMUNE® I.V 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.

IF AVAILABLE, GLASS CONTAINERS SHOULD BE USED. PLASTIC BOTTLES SHOULD ONLY BE USED 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, SINCE POLYOXYETHYLATED CASTOR OIL CONTAINED IN THE CONCENTRATE CAN CAUSE PHATHALATE STRIPPING FROM PVC. CONTAINERS AND STOPPERS SHOULD BE FREE OF SILICONE OIL AND FATTY SUBSTANCES.

OVERDOSAGE

For management of a suspected overdose, please contact your regional Poison Control Centre

Experience with acute overdosage of cyclosporine is limited. Oral doses of cyclosporine of up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia, hyperesthesia in the hands and feet, flushing of face, gum soreness and bleeding, and sensation of increased abdominal girth. Although high levels may cause transient hepato- and nephrotoxicity, no permanent residual or long-term sequelae have been reported. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with cyclosporine in premature neonates.

If overdosage occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary. Cyclosporine is not dialysable to any great extent nor is it cleared well by charcoal hemoperfusion.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Cyclosporine is a potent immunosuppressive agent with a narrow therapeutic range which has been shown in man to prolong the survival of allogenic transplants.

NEORAL® capsules and oral solution include a microemulsion formulation of cyclosporine. NEORAL® provides a more complete and consistent absorption profile and is less influenced by concomitant food intake or by diurnal rhythm than the previously marketed conventional formulation of cyclosporine (SANDIMMUNE® capsules and oral solution). These properties combined yield a lower intra-patient variability, as well as in some cases, a lower inter-patient variability in pharmacokinetics of cyclosporine and a stronger correlation between trough concentration and total exposure (AUC_β) for a more accurate targeting of the level of immunosuppression.

As a consequence of these properties, the time schedule of NEORAL® administration does not require that meals be considered. In addition, NEORAL® produces a more even exposure to cyclosporine throughout the day and from day to day on a maintenance regimen, thereby helping to avoid periods of either under-immunosuppression or over-exposure to the drug.

Cyclosporine is distributed largely outside the blood volume. In the blood, 33 to 47 % is present in plasma, 4 to 9 % in lymphocytes, and 41 to 58 % in erythrocytes. In plasma, approximately 90% is bound to proteins, mostly lipoproteins.

Cyclosporine 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. The distribution of cyclosporine appears to conform to a multicompartmental model in which continued administration leads to eventual saturation of the peripheral compartment.

The half-life of cyclosporine is approximately 18 hours (range 7.7 to 26.9). However there is a

high variability in the data reported on the terminal half-life of cyclosporine depending on the assay applied and on the target population. For example, the terminal half-life ranged from 6.3 hours in healthy volunteers to 20.4 hours in patients with severe liver disease.

The recommended therapeutic range for 12-hour trough (C_0) levels from whole blood which appear to minimize side effects and rejection episodes is between 100-400 ng/mL as measured by the RIA method based on the specific monoclonal antibody (see **DOSAGE AND ADMINISTRATION**).

It has however been reported that monitoring with the area under the time concentration curve for the first 4 hours (AUC_{0-4}) may provide for a more accurate prediction of optimal NEORAL® immunosuppression than trough (C_0) monitoring, thereby minimizing the risk of rejection, nephrotoxicity, neurotoxicity, hepatoxicity, and lowering serum creatinine levels.

Reports in the literature further indicate that using a single sampling point at 2 hours post-dose (C_2) best correlates with AUC_{0-4} and provides for accurate assessment of NEORAL® absorption and immunosuppression in organ transplant recipients. When compared to C_0 monitoring, NEORAL® C_2 monitoring provided lower rates of rejection and toxicity in liver and renal transplant patients who attained C_2 target levels.

Pharmacodynamics

NEORAL® and SANDIMMUNE® I.V. (cyclosporine) strongly suppress cell mediated immunity and are therefore highly effective in preventing allograft rejection. However, interference with the primary activation of T-helper/inducer lymphocytes through the suppression of IL-2 production may be only one of several mechanisms contributing to an immunosuppressed state.

Pharmacokinetics

Bioequivalency of Soft Gelatin Capsules and Oral Solution

In a study of 24 healthy male volunteers it was demonstrated that NEORAL® soft gelatin capsules and NEORAL® solution are bioequivalent.

Absorption:

When NEORAL® is given, it provides improved dose linearity in cyclosporine exposure (AUC_B), a more consistent absorption profile and less influence from concomitant food intake and from diurnal rhythm than does SANDIMMUNE®. These properties combined yield a lower within-patient variability in pharmacokinetics of cyclosporine and a stronger correlation between trough concentration and total exposure (AUC). As a consequence of these additional advantages, the time schedule of NEORAL® administration does not require that meals be considered. In addition, NEORAL® produces a more uniform exposure to cyclosporine throughout the day and from day to day on a maintenance regimen.

Compared to other oral forms of SANDIMMUNE®, NEORAL® capsules and solution 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.

Distribution:
Following intravenous (I.V.) administration, SANDIMMUNE® exhibits multi-compartment behaviour. The initial rapid distribution half-life is 0.10 hours, followed by a second slower distribution half-life of 1.1 hours. Continuous administration of the drug leads to eventual saturation of the peripheral compartment. This is reflected clinically by a decreased dosage requirement with long-term administration to maintain constant cyclosporine levels.

In blood, cyclosporine is highly bound to erythrocytes and plasma lipoprotein. However, all cyclosporine metabolites are less bound to plasma lipoprotein than cyclosporine itself. The relative distribution of cyclosporine in blood is a function of drug concentration, hematocrit, temperature and lipoprotein concentration. At a blood concentration of 500 mg/mL, 58 % of the drug is associated with erythrocytes, 4% with granulocytes, 5% with lymphocytes and the remaining 33% is distributed within the plasma. The plasma concentration of cyclosporine increased linearly with whole blood concentrations up to 1000 ng/mL. Above this concentration, the distribution of cyclosporine between blood and plasma is non-linear. Blood cells appear saturated by cyclosporine at concentrations above 500 ng/mL. Above this concentration there is a sharp decrease in the fraction of cyclosporine absorbed by erythrocytes, with a corresponding increase in the fraction of drug in the plasma.

In transplant recipients, low hematocrit (due to chronic disease or intraoperative blood loss) alters cyclosporine distribution between blood and plasma, resulting in higher levels of the drug in the plasma. This effect is temperature-dependent.

In plasma, more than 80% of cyclosporine is bound to lipoproteins. The major lipoprotein fractions involved are high-(HDL) and low-(LDL) density lipoprotein, which bind more than 80% of cyclosporine in plasma. The binding of cyclosporine to plasma protein is independent of concentration between 20 and $20X10^3$ ng/mL. However, binding is markedly influenced by temperature; about 70% of the drug is bound at 4^oC, 93% at 20^oC and 98% at 37^oC.

With a temperature decrease from 37^o to 21^oC, approximately 50% of cyclosporine diffuses from the plasma to the red blood cells, where it binds to hemoglobin; this process is reversible upon re-equilibration at 37^oC for 2 hours.

Consistent with the lipophilic nature of cyclosporine, body fat contains the highest concentration of the drug. Accumulation also occurs in liver, pancreas, lungs, kidneys, adrenal glands, spleen and lymph nodes. Very low levels are found in brain tissues and cerebrospinal fluid suggesting that cyclosporine does not readily cross the blood brain barrier. The large tissue distribution of cyclosporine is consistent with the large apparent volume of distribution of 3.5-9 litres/kg and results from the high lipid solubility of cyclosporine and its ability to diffuse easily through biological membranes.

Metabolism:
Cyclosporine is primarily metabolized by the hepatic mono-oxygenase multiple forms of

cytochrome P-450. Metabolites and unchanged drug are excreted into bile. Of the 17 suspected metabolites of cyclosporine, 9 have been isolated and identified. All the identified metabolites have the intact cyclic oligopeptide structure of the parent drug. Structural modifications during metabolism include mono- and dihydroxylation as well as N-demethylation, mainly at the N-methyl leucines. Both cyclosporine clearance and half-life are highly variable among patients and seem to be influenced by the type of transplant, age, disease state and concurrent drug therapy.

Since cyclosporine is primarily eliminated by hepatic metabolism, its clearance is impaired in patients with liver disease and in liver transplant recipients in the early post-operative phase. On a bodyweight basis, pediatric patients appear to clear the drug more rapidly as compared to adults. Therefore, children may require more frequent and larger doses of cyclosporine to achieve therapeutic blood levels. The metabolism of cyclosporine is also significantly influenced by changes in the activity of the hepatic drug metabolising system; for example, the induction of the cytochrome P-450 enzyme system by barbiturates, phenytoin and rifampicin markedly accelerated the elimination of cyclosporine, potentially causing inadequate immunosuppression and acute rejection. In contrast, ketoconazole increases cyclosporine levels by inhibiting its metabolism and/or active transport into the bile. A similar interaction is observed with erythromycin.

The administration of high dose methylprednisolone (for acute rejection) and long term steroid therapy may also affect the pharmacokinetics of cyclosporine.

Excretion:
The major route of elimination of cyclosporine is through the bile. Less than 1 % of an administered dose of cyclosporine is excreted in the bile as parent drug. More than 44% of a cyclosporine dose appears in the bile as metabolites when measured by RIA.

Enterohepatic recirculation of parent drug is thus very low. Hepatic functional impairment can reduce total clearance of parent drug and/or metabolite. Renal excretion is a minor pathway with only 6 % of an oral dose excreted in urine; only 0. 1 % is excreted as unchanged drug.

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.

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.

STORAGE AND STABILITY

NEORAL® Soft Gelatin Capsules
NEORAL® capsules should be stored at temperatures between 15 and 25°C and should not be removed from the blister packs until required for use. Increases in temperature up to 30°C for a total of maximum 3 months do not affect the quality of the product.

NEORAL® Solution
Once opened, the contents must be used within 2 months.

NEORAL® solution should be stored and dispensed in the original container. Store between 15 and 30°C, not below 20°C for more than 1 month as it contains oily components of natural origin which tend to solidify at low temperatures. Do not store in the refrigerator and protect from freezing.

A jelly-like formation may occur below 20°C, which is however reversible at temperatures up to 30°C. Minor flakes or a 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 syringe remains accurate.

SANDIMMUNE® I.V. (concentrate for solution for infusion)

Dilution:
The concentrate for solution for infusion should be diluted to between l:20 and l:l00 in 5% glucose or normal saline only, immediately prior to use (see **ADMINISTRATION**).

Storage:
Store the intravenous product, protected from light, between 15 and 30°C. Do not store in the refrigerator and protect from freezing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NEORAL® soft gelatin capsules are supplied in 10 mg, 25 mg, 50 mg and 100 mg strengths of cyclosporine for microemulsion. 10 mg: Packs of 60 capsules contain 6 full aluminum blister strips of 10 capsules each. 25 mg, 50 mg and 100 mg: packs of 30 capsules contain 6 full aluminum blister strips of 5 capsules each.

NEORAL® solution is supplied in 50 mL bottles containing 100 mg of cyclosporine for

microemulsion per mL dissolved. A graduated syringe for dispensing is provided.

SANDIMMUNE® I.V. (concentrate for solution for infusion), is supplied in l mL and 5 mL sterile ampoules containing 50 mg of cyclosporine per mL in a polyoxyethylated castor oil/ethanol vehicle.

Composition

NEORAL® Solution

Active Ingredient:	Cyclosporine for microemulsion
Non-medicinal ingredients:	DL-α-Tocopherol, Ethanol, Hydrogenated Castor Oil, Maize oil, Propylene glycol

NEORAL® Soft Gelatin Capsules

Active Ingredient:	Cyclosporine for microemulsion
Non-medicinal Ingredients:	DL-α-Tocopherol, Ethanol, Hydrogenated Castor Oil, Maize oil, Propylene glycol
Capsule shell:	Gelatin, Glycerol, Propylene glycol
Coloring Agents:	25 and 100 mg: Aluminum Chloride, Carminic Acid, Iron Oxide Black, Hydroxypropyl Methlycellulose, Sodium Hydroxide, Titanium Dioxide 10 and 50 mg: Aluminum Chloride, Hydroxypropyl Methlycellulose, Sodium Hydroxide, Titanium Dioxide

SANDIMMUNE® I.V. Concentrate for Solution for Infusion

		Concentration (mg/ml)
Active Ingredient:	Cyclosporine	50
Non-medicinal Ingredients:	Ethanol[1]	278
	Castor oil[2]	650

[1] 94% w/w
[2]Polyoxyethylated

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

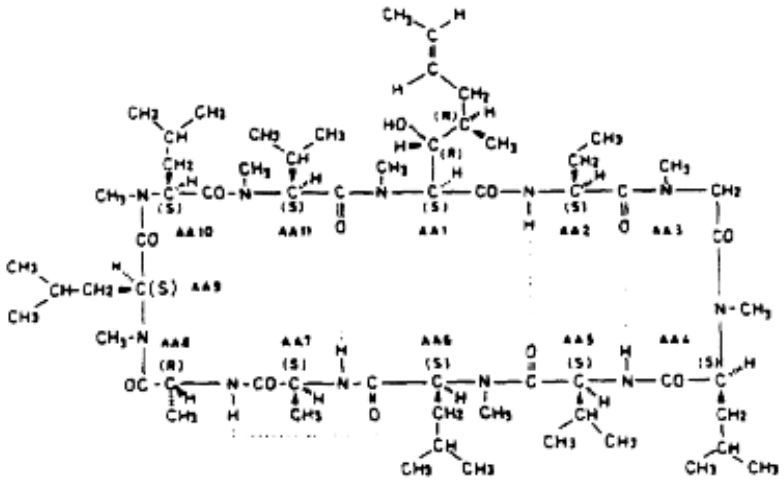
Drug Substance

Proper name: Cyclosporine (USAN)
Cyclosporine (INN)
(cyclosporine A)

Chemical name: (R-[R*,R*-(E)]]-Cyclic(L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N, 4-dimethyl-L-2-amino-6-octenoyl-L-α-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl).

Molecular formula and molecular mass: $C_{62}H_{111}N_{11}O_{12}$ and 1202.64

Structural formula:



Physicochemical properties:

Description: Cyclosporine is a metabolite extracted from the fungal species Tolypocladium inflatum gams. It is a white or off-white finely crystalline powder with a weak characteristic odour.

Solubility Profile:

Water	0.04 mg/g	Diisopropyl ether	> 20 mg/g
Acetone	> 50 mg/g	Ethyl acetate	> 100 mg/g
Chloroform	> 100 mg/g	Cyclohexane	17 mg/g
Acetonitrile	> 100 mg/g	n-Hexane	5.5 mg/g

	Benzene	> 100 mg/g	Isopropyl alcohol > 100 mg/g
	Methanol	> 100 mg/g	Ethanol > 100 mg/g

Melting Point: 148-151

CLINICAL TRIALS

Transplantation indications

Solid organ transplantation

The efficacy of NEORAL® has been demonstrated in 13 global studies which evaluated the success transplantation rate using cyclosporine 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 cyclosporine 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 **DOSAGE AND ADMINISTRATION**).

Clinical studies are displayed in below Tables 1 to 5.

Kidney and pancreas transplantation

Table 1 presents clinical studies that were mainly performed in kidney transplanted patients and Table 2 presents clinical studies performed only in kidney transplanted patients. Table 1 also includes pancreas-transplanted patients. The included studies in these tables confirm that cyclosporine used in combination with steroids is an effective treatment in renal transplantation. The one year graft survival was significantly improved in these cyclosporine-treated patients over control therapy.

Table 1 Solid organ transplant - European Clinical Studies and Australian clinical study

Study Number/ Country	Study Characteristics	Organ (N)	One year Graft survival CsA/control (%)	One year Patient survival CsA/control
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)*	70/ 55%	77/NR
Study #2 Australia	Single center, randomized CsA vs. AZA+CS+ALG	Kidney (29 total; 14 Cyclosporine)	78/73	78/92
Study #3 European Multicenter Trial	Multicenter randomized CsA vs AZA+Pred	Kidney (232 total; 117 Cyclosporine)	73-53	98/94
Study #4 Sweden	Single center; CsA (4 patients) CsA + Pred (16) vs. Historical control	Kidney (20)	55-49	68/72
Study # 5 Finland	Multicenter CsA vs. AZA+MP vs. CsA IV+ MP	Kidney (9) (32) (32)	67 (CsA)- 77(CsA+MP)/73	90(both arms) /87

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

NR: non retrievable data

Table 2 **Solid organ transplant - North American clinical studies**

Study Number Country	**Study characteristics**	**Organ (N)**	**One year graft survival (%) CsA/control**	**One year patient survival (%) CsA/control**
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	76/53	86/83
Study # 5 USA	CsA +low dose pred vs. AZA+ ATG	Kidney (98 total; 47 CsA)	86/82	94/100
Study #7 USA	CsA + CS+ diuretics vs. AZA+ CS+ diuretics	Kidney (27 total; 14 CsA)	71/66*	100/93
Study #15 USA	Open, randomized CsA+pred vs. AZA+pred	Kidney (41 total; 21 CsA)	90/53	100/100
Canadian Multicenter	Randomized, CsA vs. AZA + CS	Kidney (209 ; 103 CsA)	80/64	87/86*

***Statistically significant**

TDD: thoracic duct drainage; CsA: cyclosporine; CS: corticosteroids; Pred: prednisone; ATG: anti-lymphocyte 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 NEORAL® formulation. These 2 studies (Table 3) where SANDIMMUNE® was converted to NEORAL® in 1:1 protocols have shown based on stable steady-state trough concentration, that comparable doses of NEORAL® to SANDIMMUNE®, led to higher C_{max} and AUC values with NEORAL® compared to SANDIMMUNE®.

Table 3 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: SANDIMMUNE®; SIM NEORAL®: SANDIMMUNE® NEORAL®

Liver transplantation

In the liver transplantation (see Table 4), the clinical studies demonstrated that one year patient survival rate was higher in the cyclosporine 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 cyclosporine. The clinical studies demonstrated that cyclosporine and steroid therapy offers considerable advantage over standard therapy using azithromycin and steroids.

Table 4 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. Historical control	Liver 26 (17 adults, 9 children)	64% versus 32% (Historical control)

CsA: cyclosporine; 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 cyclosporine-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 cyclosporine-treated patients.

In both heart and heart-lung transplantation, episodes of suspected hepatotoxicity and nephrotoxicity were controlled by dosage reduction of cyclosporine. 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 5 below.

Table 5 Solid organ transplantation- Heart and Heart/Lung Studies

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

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

Bone marrow transplantation

The efficacy of SANDIMMUNE® 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 cyclosporine in an effort to reverse established acute, severe (Grade III-IV) GVHD. These patients had not been previously treated with cyclosporine 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 cyclosporine 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 cyclosporine used for treatment of GVHD was approximately 15 mg/kg/day. This was tapered over time and discontinued at about 6 months. Cyclosporine was given mostly once or twice daily, but at one center, three times daily. In most studies, if the I.V. formulation of cyclosporine was used, it was given at about 1/3 the oral dose.

Results obtained from the use of CsA in bone marrow transplantation after hematopoietic neoplasia show that CsA appears to be effective for decreasing the severity and possibly also the incidence of GVHD in comparison with the standard of care at the time of the studies. One year survival for all CsA treated patients with matched grafts was close to 70%. Leukemia patients transplanted in first remission showed one year survival (76%) in comparison with patients treated with MTX (52%). In matched grafts the number of deaths associated with GVHD was 8% vs. the number previously reported 25% treated with MTX.

Non-transplantation indications

Nephrotic syndrome

The efficacy of SANDIMMUNE® 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).

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 cyclosporine 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 1-17 years of age) with FSGS, MCN and MG nephrotic syndrome and were steroid dependent or steroid resistant (391 patients from a retrospective study OL 03). 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 cyclosporine) 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 cyclosporine 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 cyclosporine per kilogram of body weight to achieve blood concentrations of the drug similar to those observed in adult patients (see **DOSAGE AND ADMINISTRATION**).

In minimal change nephropathy 54 to 76% of patients developed complete remission and 8 to 21% had a partial remission. In focal segmental glomerulosclerosis 0 up to 29 % had a complete remission and 0- up to 37% had partial remission. Of note, there have been studies that showed 0% rates of remissions, however these included patients with steroid resistant and steroid dependent nephrotic syndrome. In membranous glomerulonephritis, 21 % of patients reached complete remission and 28% partial remission

Rheumatoid arthritis

The efficacy of NEORAL® l in the treatment of severe rheumatoid arthritis was evaluated in 5 clinical studies involving a total of 728 cyclosporine-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 (Figure 1).

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

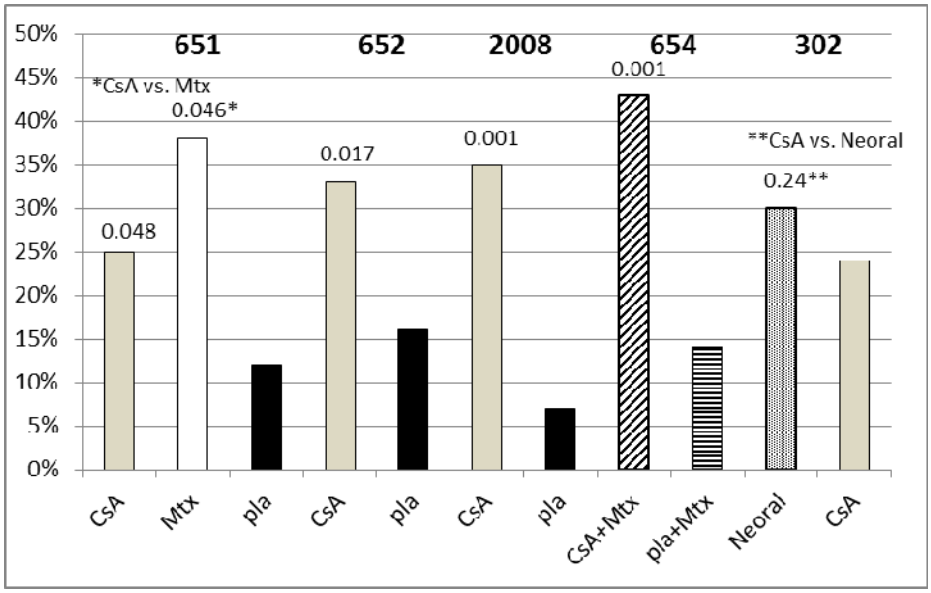
Study 652 enrolled 250 patients with active RA with > 6 active painful or tender joints who had failed at least one major RA drug. Patients were randomized using a 3:3:2 randomization to 1 of 3 treatment arms: (1) 1.5-5 mg/kg/day of cyclosporine, (2) 2.5-5 mg/kg/day of cyclosporine, and (3) placebo. Treatment duration was 16 weeks. The mean cyclosporine dose for group 2 at the last visit was 2.92 mg/kg/day (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) cyclosporine 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 cyclosporine dose at the last visit was 3.63 mg/kg/day (Figure1).

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) cyclosporine 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 cyclosporine dose at the last visit was 2.8 mg /kg/day (range: 1.3-4.1) (Figure 1).

Study 302 enrolled 299 patients with severe active RA, 99% of who 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) cyclosporine, 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 cyclosporine dose at the last visit was 2.91 mg/kg/day (range: 0.72-5.17) for NEORAL® and 3.27 mg/kg/day (range: 0.73-5.68) for cyclosporine (Figure 1).

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



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

Psoriasis

The efficacy of cyclosporine 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 cyclosporine 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 cyclosporine 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 cyclosporine and 38 with etretinate, provided information on long term efficacy, safety and tolerability of different cyclosporine dosing. The two formulation of cyclosporine 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 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

in72% of the 152 patients treated with NEORAL® and in 62% of the 156 patients treated with SANDIMMUNE® (Study OLP302); in both arms the starting dose was 2.5 mg/kg/day.

DETAILED PHARMACOLOGY

NEORAL® and SANDIMMUNE® I.V. (cyclosporine) strongly suppress cell mediated immunity and are therefore highly effective in preventing allograft rejection. However, interference with the primary activation of T-helper/inducer lymphocytes through the suppression of IL-2 production may be only one of several mechanisms contributing to an immunosuppressed state.

Hemopoiesis
All available experimental evidence indicates that unlike cytostatic agents, immunosuppression with cyclosporine neither impairs the number nor the proliferative capacity of hemopoietic stem cells, nor does it affect the function of non-lymphocytic leucocytes.

Hypersensitivity
In experiments with Lewis rats, cyclosporine shows no effect on immediate hypersensitivity reactions, mediated by mast cells, or on Arthus-type skin reactions characterized by immune complex formulation and granulocytic infiltration. Cyclosporine however does inhibit delayed-type hypersensitivity (DTH) reactions (a T-cell mediated response) with a marked decrease in mononuclear cell infiltration. This suppression of DTH is dose dependent and mediated by inhibiting the release of lymphocyte-directed chemotactic factor (LDCT), macrophage migration-inhibition factor (MIF), macrophage activation factor (MAF) and gamma interferon (INF γ).

Humoral Immunity
Generally, cyclosporine appears to suppress the antibody response (IgM, IgG) to thymus dependent antigens and the proliferative response of cultured B lymphocytes to thymus-dependent mitogens such as pokeweed mitogen (PWM). Inhibition of these responses can conceivably occur through an inhibition of T-helper cell function, although cyclosporine inhibition of human tonsillar B lymphocyte response to PWM is resistant to the exogenous addition of growth factors (IL-1 , IL-2, BCGF) alone or in combination.

By contrast, cyclosporine appears to have little or no effect on either humoral immunity or proliferative responses to thymus-independent antigens or mitogens. For example, the proliferative response of cultured murine or human B lymphocytes to the thymus independent activator lipopolysacharide (LPS) or the B95-8 strain of Epstein-Barr virus are unaffected by pre-exposure to cyclosporine. However, in both murine and human models there may be a cyclosporine sensitive component to the cultured B lymphocyte response to some thymus-independent activators. The activation of murine B lymphocytes by the anti-Ig antibody anti-tt, which is believed to mimic the early events of antigen stimulation on B cells, is highly susceptible to inhibition by cyclosporine. Similarly, although the thymus-independent activator anti-μ is not mitogenic for lymphocytes of the CBA/N strain of mice or for human B lymphocytes, the combination of anti-μ and LPS (with CBA/N murine lymphocytes) or anti-μ

and BCGF (with human lymphocytes) results in the generation of a large proliferative response which is totally abrogated by the early addition of cyclosporine. Therefore, cyclosporine may, under certain circumstances, be inhibiting an early T-independent primary stage by which B lymphocytes are activated to enter the GI phase of the cell cycle.

Cell-Mediated Immunity
Abrogation of T lymphocyte activation

Cyclosporine completely suppresses the lymphoproliferative responses of murine, guinea pig and human cultured T lymphocytes to mitogenic stimulation with Concanavalin A (ConA) and Phytohemagglutinin (PHA). Although the 50% inhibitory concentration can vary from 2-200 ng/mL, depending on the mitogen and source of lymphocytes used, cyclosporine must always be present when the cultures are initiated or must be added shortly thereafter, in order to be inhibitory. Cyclosporine also inhibits the proliferative response and the induction of cytotoxic T lymphocytes (CTL) in murine, guinea pig and human allogenic and syngeneic mixed lymphocyte responses (MLR). The doses of cyclosporine required to inhibit are comparable to the levels achieved in vivo with regimens used for clinical immunosuppression (> 100 ng/mL).

Virtually all studies on T cell proliferation following mitogenic stimulation and on CTL induction in a primary MLR show a significant inhibitory effect of cyclosporine on the production of IL-2. The decrease in IL-2 production occurs also in secondary responses with pre-sensitized lymphocytes. The inability of exogenous IL-2 to restore the cyclosporine inhibited CTL activity in a human allogenic MLR or the cyclosporine inhibited primary T cell proliferative response in a guinea pig allogenic MLR, suggests that, in these systems at least, cyclosporine may be inhibiting the precursor CTL (PCTL) from acquiring functional responsiveness to IL-2. Cyclosporine, although not inhibiting the expression of IL-2 receptor (TAC antigen) on ConA or PHA stimulated human lymphocytes, does inhibit the expression of TAC antigen in cultures of human allogenic MLR and ConA stimulated murine lymphocytes.
Cyclosporine also inhibits the production of a number of cytokines other than the lymphokine IL-2. Cyclosporine inhibits the production of the monocyte derived cytokine IL- I by an apparent indirect action on OKT4 (+) T-helper lymphocytes. IL-1 and the lymphokine IL-3 are inhibited following cyclosporine therapy in rats with allogenic heart transplants. The generation, by antigen or mitogen activated guinea pig lymphocytes and murine spleen cells, of lymphocyte-derived chemotactic factor (LDCF) and soluble mediators stimulating macrophage procoagulant activity (MPA) are impaired in the presence of cyclosporine. Cyclosporine also inhibits the production of migration inhibitory factor (MIF) by human lymphocytes stimulated with ConA, and gamma interferon (INFγ) and by human or mouse lymphocytes stimulated with mitogen or alloantigen.

The expression of a number of T lymphocyte surface activation antigens including class II major histocompatibility antigen, antigens detected by OKT9 and OKT10 monoclonal antibodies, and transferring receptors, also appear to be inhibited, to some degree, by cyclosporine.

In contrast to cytotoxic inducer T-helper cells, the suppressor amplifier T-helper cells may be quite resistant to the effect of cyclosporine. This differential effect on activation of T suppressor

versus T cytotoxic cells may facilitate the establishment or re-establishment of a specific state of immune unresponsiveness, as seen with certain experimental models.

Binding Sites and Molecular Effects

Although there is some evidence suggesting that cyclosporine may be blocking initial membrane activation signals, recent studies using fluorescein conjugated, dansylated, or radiolabelled cyclosporine have revealed no competitive binding on membrane receptors for mitogen such as PHA, ConA, the OKT3 monoclonal antibody, HLA-DR receptors or the IL-2 receptor. Cyclosporine does, however, competitively inhibit the binding of the immune regulator prolactin to its cell surface receptor.

The reversible and specific binding of cyclosporine to the cytosolic protein, calmodulin, which mediates the activating effect of Ca++ on intracellular metabolism is consistent with the observation that although cyclosporine does not abrogate mitogen-induced phosphoinositide breakdown in the plasma membrane, or the consequent elevation of intracellular Ca++ or activation of protein kinases, cyclosporine does seem to selectively block the activation of normal lymphocytes by agents which mobilize Ca++, namely ligands which cross-link antigen receptors, or Ca++ ionophores. In contrast, responses to polyclonal activators which do not provoke Ca++ flux (phorbol, esters, lipopolysaccharide, growth factors) are cyclosporine resistant except perhaps in tumour cells.

Cyclosporine also inhibits the induction of ornithine decarboxylase (the rate limiting enzyme step in the production of polyamines required for DNA and MRNA synthesis). Reduction of IL-2 mRNA occurs following addition of cyclosporine to human and murine cell lines cultured in the presence of phorbol-12- myristyl-13-acetate. Mitogen restimulation, in the presence of cyclosporine, of a three day old ConA-induced lymphoblast culture, also results in a significant reduction in the synthesis of mRNA for the lymphokines INFγ, B cell stimulating factor, and cytotoxic differentiation factor.

Reproduction and fertility

Cyclosporine is not teratogenic in animals, but was shown to be both embryo- and feto-toxic in rats and rabbits at 2 to 5 times the human dose.

To date, information has been received on 514 pregnancies with exposure to SANDIMMUNE®. In most patients, the indication for cyclosporine therapy was organ transplantation.

Pregnant women receiving immunosuppressive therapies after transplantation, including cyclosporine and cyclosporine-containing regimens, are at risk of premature delivery (<37 weeks).

Most patients who became pregnant continued cyclosporine therapy throughout pregnancy, usually in combination with other immunosuppressive drugs and further medication.

Fetal loss occurred in 9.1% of the patients, which is within the range found in a normal population. In 4.9% of the patients, the pregnancy was interrupted, either for medical considerations or at the wish of the patient. The course of pregnancy was often complicated by disorders specific to pregnancy, in particular in renal transplant patients, or by disorders relating to the underlying disease. A large proportion of the pregnancies ended in preterm delivery. Accordingly, the main problems seen in the neonates relate to prematurity, best exemplified by the short median gestation duration of 35.7 weeks in the 439 pregnancies completed, and the low median birth weight, 2291 g, of the 446 babies delivered, including 10 twins.

It appears that premature delivery and the delivery of infants small for their age occur more often in patients who have undergone a renal transplantation.

Out of 102 babies born to mothers treated with SANDIMMUNE®, five were born with malformations. It is not clear what role cyclosporine has played in the complications of pregnancy.

Males treated with cyclosporine have fathered normal children.

NEORAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratological and Reproduction Studies:
Rats and rabbits were given cyclosporine 10-300 mg/kg/day in 2 % gelatin, on days 6 to 15 or 6 to 18 post-coitum. Dams and their fetuses were sacrificed at term and examined. In rats, prenatal mortality accompanied maternal toxicity at doses of 30 mg/kg/day and above.

In rabbits, dose levels of 100 and 300 mg/kg/day proved to be increasingly embryo- and fetotoxic. At doses which were well tolerated by the dams, cyclosporine caused neither teratogenic nor embryolethal effects in either species.

In a peri- and post-natal study in rats, 5.0 or 15.0 mg/kg/day (p.o.) given from day 15 post-coitum until day 21 postpartum caused no adverse effects. At 45 mg/kg/day, cyclosporine was toxic to the females and their offspring.

Rats of both sexes were treated orally with cyclosporine 1.5, 5.0 or 15.0 mg/kg/day, from 9 weeks (males) or 2 weeks (females) prior to mating until autopsy. In F0 males, 5.0 and 15.0 mg/kg/day caused toxic effects not seen with prolonged administration of 1.5 mg/kg/day. All but two F0 females tolerated the highest dose level.

The reproductive performance of F0 animals were normal except for an increased perinatal mortality and a questionably impaired postnatal development of F1 pups in single litters at the 15 mg/kg/day dose level. Fertility of randomly selected F1 animals and the development of their offspring was normal.

In two published research studies, rabbits exposed to cyclosporine in utero (10 mg/kg/day

subcutaneously) demonstrated reduced numbers of nephrons, renal hypertrophy, systemic hypertension, and progressive renal insufficiency up to 35 weeks of age.

Pregnant rats which received 12 mg/kg/day of cyclosporine intravenously (twice the recommended human intravenous dose) had foetuses with an increased incidence of ventricular septal defect.

These findings have not been demonstrated in other species and their relevance for humans is unknown.

Mutagenicity Studies

Cyclosporine was not mutagenic in the following tests: Ames Test, using Salmonella typhimurium; mouse Micronucleus Test; Chromosome Analysis Test, using adult Chinese hamsters, and dominant Lethal Test in male mice.

TOXICOLOGY

Acute Toxicity

Acute toxicity of cyclosporine in mice, rats, rabbits, dogs and monkeys was studied after oral or intravenous administration. Animals were observed until death occurred or for a period of 14 days following administration.

Table 6 ACUTE TOXICITY

SPECIES	Dose mg/kg	Route	Number of Days	LDd^{50} mg/kg/day (95% C.L.)	Observations
Mouse	-	IV IV PO	14 14 14	107 148 2329 (1848-3020)	Dyspnea, tachypnea, cramplike movements, stupor, piloerection Death occurred within 3 hours (I.V.) or 9 days (P.O.)
Rat	-	IV	14	25.8 104 1480 (1105-1997)	Surviving animals recovered completely.
Rabbit		IV IV PO	14 14 14	$\geq$ 10 46 $\geq$ 1000	
Dog	1.5	IV	1	-	No adverse effects.
Monkey	10-13	IV	10	-	No adverse effects.

Hemolytic potential was tested in vitro using human erythrocytes and in vivo up to a dose of 1.5 mg/kg given intravenously to dogs. No relevant degree of hemolysis was observed.

Table 7: SUB-ACUTE TOXICITY Rats:Cyclosporine was given in the feed for 13 weeks

Dosage (mg/kg/day)	Observations
14	No clinical adverse findings. Slight reduction in circulating lymphocytes after 3 weeks. Occasional erythrocytes in urinary sediment. Loose, divergent or overgrown incisors in several rats. Some lymphoid atrophy and slight adaptive changes in kidneys and livers of males.
45-90	Lethal to 6/20 rats at mid and 18/20 rats at high dose levels due to hepatic and renal toxicity. After 6 weeks without drug, survivors' BUN and SGPT returned to normal. Loosening of incisor teeth and hair loss.

No toxic effect level = 14 mg/kg/day

Table 8: SUB-ACUTE TOXICITY Monkeys:
Daily oral administration (gelatin capsules) for 13 weeks:

Dosage (mg/kg/day)	Observations
20	No adverse effects.
60	Transient decrease in leukocyte count - normal by week 13.
200-300[1]	Slightly impaired weight gain. Normal bone marrow. Atrophy of lymphatic tissues. Some G.I. irritation. Renal and hepatic changes. Reduced mitogenic responses.

[1]300 mg/kg/day for the last 4 weeks.

No toxic effect level = 60 mg/kg/day.

Table 9: CHRONIC TOXICITY Mice:
Cyclosporine given in feed for 78 weeks:

Dosage (mg/kg/day)	Toxic Effects	Carcinogenicity
1.0	none	none
4.0	Slight to distinct anemia in 2 mice, none with reticulocytosis.	none
16.0	Increased mortality rate especially in males. Distinct anemia (4/20). Lymphocytic leukocytosis with atypical lymphocytes (1/20). Fewer thrombocytes (3/20).	No increase in neoplastic or non-neoplastic lesions

Table 10: CHRONIC TOXICITY Rats:

Cyclosporine given in feed for 2 years.

Dosage (mg/kg/day)	Toxic Effects	Carcinogenicity
0.52	Divergent incisors (2/50)	
2.1	Slightly reduced weight gain and increased mortality in females. Slight anemia, leukopenia (transient), slight renal toxicity in males.	
8.0	Distinct inhibition of weight gain. Reduced food intake and increased mortality. Divergent incisors (7/100). Slight to moderate anemia. Slight hepato- and nephrotoxicity seen in males. Transient decrease in leukocyte count.	Not different from controls

No toxic effect level = 0.52 - 2.1 mg/kg/day

Table 11: CHRONIC TOXICITY Beagle Dogs:
Oral administration in olive oil for 52 weeks:

Dosage (mg/kg/day)	Toxic Effects	Carcinogenicity
5	Emesis (1/8); slight decrease in sedimentation rate and serum albumin concentration	-
15	As above - also periodontitis and gingivitis (1 dog) -mononuclear cell infiltration (1 dog)* in hepatic portal fields. Decreased eosinophils, slight leukopenia (1 dog). Some blood chemistry abnormalities (2/8 dogs).	Fibroma on left upper thigh (1 dog)*
45	As above - also temporary sedation, slight alopecia*, slight conjunctivitis*, decreased leukocyte counts and anemia (2/8). General atrophy and diaphragm (2/8)* of lymphoid organs. Slight degeneration of renal tubular epithelium (3/8). Reversible papillomatosis in some dogs.	As above Cystic nodules on pericardium and diaphragm (2/8)*

*Occurs spontaneously in this species (beagle) not necessarily related to cyclosporine.

No toxic effect level = 15 mg/kg/day.

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PART III: CONSUMER INFORMATION

PrNEORAL®
(cyclosporine capsules)
(cyclosporine oral solution)
for microemulsion

AND

PrSANDIMMUNE® I.V.
(cyclosporine for injection)

This leaflet is part III of a three-part "Product Monograph" published when NEORAL® or SANDIMMUNE® I.V was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NEORAL® and SANDIMMUNE® I.V. Contact your doctor or pharmacist if you have any questions about the drug.

Read this information carefully, even if you have already been taking NEORAL® or SANDIMMUNE® I.V.

This information should not replace your doctor's or pharmacist's advice. If any information in this text concerns you, talk to your doctor or pharmacist right away.

ABOUT THIS MEDICATION

What the medication is used for:

Your doctor has prescribed the drug NEORAL® or SANDIMMUNE® I.V.. It is used after organ or bone marrow transplantations to help prevent organ rejection, or to treat autoimmune conditions such as severe psoriasis, severe rheumatoid arthritis and nephrotic syndrome.

NEORAL® or SANDIMMUNE® I.V. are the brand name for a drug called "cyclosporine". It belongs to a family of drugs known as "immunosuppressants". These drugs work to "suppress" or reduce the body's immune response.

What it does:

Your body's immune system normally works to protect you from infections and other foreign material. When you receive a transplant, this system does not recognize the new organ, and will try to reject it.

NEORAL® and SANDIMMUNE® I.V. work to reduce this response, so your body is more likely to accept the new organ.

NEORAL® and SANDIMMUNE® I.V. do not completely suppress the immune system, so your body will still have some infection-fighting ability.

NEORAL® and SANDIMMUNE® I.V. may be given alone, but are often given with other drugs which also suppress your immune system. Together these help prolong the life of an organ transplant, or to suppress certain function of your immune system to treat your psoriasis, rheumatoid arthritis or nephrotic syndrome.

When it should not be used:

Do not use NEORAL® or SANDIMMUNE® I.V if you have ever had a bad, unusual or allergic reaction to cyclosporine or any of the non-medicinal ingredients of NEORAL® or SANDIMMUNE® I.V. **(See "What the important non-medicinal ingredients are")**

For the treatment of psoriasis, rheumatoid arthritis and nephrotic syndrome, do not take NEORAL® or SANDIMMUNE® I.V. if you have one of the following conditions:

- abnormal kidney function (except for nephrotic syndrome);
- uncontrolled blood pressure;
- any type of cancer (except a skin cancer which is not a melanoma);
- uncontrolled infection (not treated or cured);
- inherited or acquired immune deficiency.

Do not use NEORAL® or SANDIMMUNE® I.V with bosentan**.**

What the medicinal ingredient is:

NEORAL® contains cyclosporine for microemulsion.

NEORAL® is the microemulsion formulation of cyclosporine which can be taken orally, while SANDIMMUNE® is the intravenous form of cyclosporine which you may need to receive during your stay in hospital.

The "microemulsion" formulation allows more reliable absorption of cyclosporine from your stomach compared to conventional types of oral dosage forms. This means almost the same amount will go into your body each time you take the drug, and that food will have less of an effect on the amount of cyclosporine that gets absorbed.

SANDIMMUNE® I.V. contains cyclosporine for injection.

What the important non-medicinal ingredients are:

Non-medicinal ingredients for NEORAL® capsules are the following: DL-α-Tocopherol, ethanol, propylene glycol, maize oil, hydrogenated castor oil. Capsule shell: glycerol, propylene glycol, gelatin, iron oxide black, titanium dioxide. Imprint: caminic acid, aluminum chloride, sodium hydroxide, hydroxypropyl methylcellulose.

Non-medicinal ingredients for NEORAL® oral solution are the following: DL-α-Tocopherol propylene glycol, ethanol, maize oil, hydrogenated castor oil.

Non-medicinal ingredients for SANDIMMUNE® I.V. are the following: ethanol and castor oil.

What dosage forms it comes in:

NEORAL® comes in two forms: a soft gelatin **capsule** and an **oral solution**. The following points tell you how to take the form you have been given.

Capsules
NEORAL® capsules come with 10 mg, 25 mg, 50 mg or 100 mg of cyclosporine. Each capsule is contained in a foil strip.

Solution
NEORAL® solution comes in 50 millilitre bottles.

SANDIMMUNE® I.V. (concentrate for solution for infusion), is supplied in l mL and 5 mL sterile ampoules containing 50 mg of cyclosporine per mL in a polyoxyethylated castor oil and ethanol.

WARNINGS AND PRECAUTIONS

Medicines which suppress the immune system, such as NEORAL® or SANDIMMUNE® I.V. may influence your body's ability to fight against infection and may increase the risk of developing cancers, particularly of the skin and lymphoid system. Therefore you should limit your exposure to sunlight and UV light by wearing appropriate protective clothing and frequently applying a sunscreen with a high protection factor.

Tell all health professionals you see (doctor, dentists, nurses, pharmacists) that you are taking NEORAL® or SANDIMMUNE® I.V. It is also a good idea to wear a Medic-Alert bracelet.

Before you use and because of the alcohol contained in NEORAL® or SANDIMMUNE® I.V, talk to your doctor or pharmacist if:
- You have or had alcohol related problems
- You have epilepsy or have any liver problems
- You are pregnant
- You breast-feed your child
- The medicine is given to a child

Before you use NEORAL® or SANDIMMUNE® I.V. talk to your doctor or pharmacist if:

- You have any current or have had past health conditions.

- **You are taking other drugs**: Do not take any other drugs without asking your doctor or pharmacist first including over-the-counter medicines and herbal or home remedies. NEORAL® or SANDIMMUNE® I.V. is often given with other medicines. Make sure you know if you are to stop, or to continue, other immunosuppressant drugs you had been taking.

- **You are to receive vaccinations**: NEORAL® or SANDIMMUNE® I.V. may make vaccinations less effective or increase your risk of getting an illness from a live vaccine. Always discuss this possibility with your doctor before you get any vaccinations or immunizations.

- **You receive NEORAL® or SANDIMMUNE® I.V.** the level of cyclosporine in your blood (especially for transplant patients), your liver and kidney function and your blood lipids should be checked regularly. Your blood pressure should be checked before initiation of therapy and regularly thereafter. If high blood pressure develops during therapy and cannot be controlled, treatment should be stopped.

- **You have high levels of potassium in your blood.**

- **You suffer from gout.**

- **You have had a transplant or just after your operation,** your doctor may give you magnesium supplements due to the fact that NEORAL® or SANDIMMUNE® I.V. may reduce the amount of magnesium in your body.

- **You are or become pregnant**: There is an increased risk of difficult pregnancies (up to 25% of pregnancies) in patients who have taken cyclosporine during pregnancy. These difficult pregnancies have resulted in an increased risk to the babies during and immediately after birth. As well, some babies have been born with abnormalities.

For these reasons it is recommended that you do not take NEORAL® or SANDIMMUNE® I.V. if you are, or become, pregnant. During your treatment with NEORAL® and for 2 months after stopping your NEORAL® or SANDIMMUNE® I.V. treatment, you must use a reliable method of birth control. Should you become pregnant during the time you are taking your NEORAL® or SANDIMMUNE® I.V. you should inform your doctor at once. You will want to discuss the possible benefits and risks of continuing with this drug.

- **You are breast-feeding:** Do not breast feed your baby if you are taking NEORAL® or SANDIMMUNE® I.V. as it passes into breast milk and may harm your baby.

There is a limited experience with NEORAL® or SANDIMMUNE® I.V. in elderly. Your renal function should be monitored with particular care. If you are over the age of 65 years with psoriasis, you should only be treated in case of disabling disease.

Do not stop taking NEORAL® or SANDIMMUNE® I.V. on your own even if you have been taking it for several years. Transplant patients: Although you may not notice any symptoms of rejection for several weeks, missing even a few doses of NEORAL® or SANDIMMUNE® I.V. may lead to rejection of your transplanted organ.

INTERACTIONS WITH THIS MEDICATION

Make sure your doctor knows if you are taking, or begin to take, any other medicines, including drugs, or herbal (natural) products that you can buy without a prescription while you take NEORAL® or SANDIMMUNE® I.V.. Some medicines may interact with NEORAL® or SANDIMMUNE® I.V. such as:

- medicines that may impact your potassium levels such as potassium containing medicines or potassium sparing medicines (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists)
- certain blood pressure reducing agents of the calcium antagonist type
- methotrexate, a medicine to treat tumors, severe psoriasis and severe rheumatoid arthritis
- medicines which may increase or reduce the blood levels of NEORAL® or SANDIMMUNE® I.V. The doctor might check the cyclosporine concentration in your blood when initiating or discontinuing other medical treatment.
  - medicines which may decrease the NEORAL® concentrations: barbiturates (medicines used to help to sleep), certain anticonvulsives (e.g carbamazepine, phenytoin), octreotide, antibacterial medicines used to treat tuberculosis, orlistat (used to help weight loss), herbal medicines containing St. John's Wort, ticlopidine (used after stroke), certain blood pressure reducing agents (bosentan), and an antifungal medicine used to treat infections of the toes and nails (terbinafine).
  - medicines which may increase NEORAL® concentrations: antibiotics of the macrolides type (e.g erythromycin, azithromycin), antifungal medicine of the azole type (voriconazole, itraconazole), medicines used for heart problems or high blood pressure (diltiazem, nicardipine, verapamil, amiodarone), metoclopramide (used to stop sickness), oral contraceptives, danazol (used to treat menstrual disorders), medicines used to treat gout (allopurinol), cholic acid and derivatives (used to treat gallstones), protease inhibitors used to treat HIV, imatinib (used to treat leukaemia or tumors), colchicines
  - other medicines which may affect the kidneys, such as antibacterial agents (gentamycine, tobramycine, ciprofloxacine), antifungal agents containing amphotericine B, antibacterial agents containing ciprofloxacin, agents against urinary tract infection containing trimetoprim, anti-cancer agents containing melphalan, medicines used to reduce the amount of acid in your stomach (acid secretion inhibitors of the H2-receptor antagonist type), tacrolimus, pain killers (non-steroid anti-inflammatory medicines such as diclofenac), fibric acid derivatives (e.g. bezafibrate, fenofibrate) used to lower fat in the blood.
  - nifedipine (used to treat high blood pressure and heart pain), you might get swollen gums that spread over your teeth.
  - medicines whose concentrations may increase when used together with NEORAL® including aliskiren (to treat high blood pressure), digoxin (used to treat heart problems), cholesterol lowering agents (HMG-CoA reductase inhibitors (also called statins), prednisolone, etoposide (used to treat cancer), dabigatran (oral anticoagulant used to prevent stroke), repaglinide (oral antidiabetic agent), immunosuppressives (everolimus, sirolimus), ambrisentan and specific anticancer medicines called anthracyclines (e.g. doxorubicine).
- caspofungin
- lercanidipine
- oxcarbazepine
- nefazodone

Never take NEORAL® or SANDIMMUNE® I.V. with grapefruit juice.

NEORAL® or SANDIMMUNE® I.V. is also used in combination with other immunosuppressive agents. However, do not use it together with other calcineurin inhibitors such as tacrolimus.

Use of NEORAL® or SANDIMMUNE® I.V. with aliskiren is not recommended and use of NEORAL® or SANDIMMUNE® I.V. with dabigatran should be avoided.

PROPER USE OF THIS MEDICATION

Usual dose:

- Always take NEORAL® or SANDIMMUNE® I.V. exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. Do not change the dose on your own, no matter how you are feeling. Blood tests are one of the ways your doctor tells how much NEORAL® or SANDIMMUNE® I.V. you need. Based on these tests, and on your response to this drug, your doctor may change your dose from time to time.

- Space your doses of NEORAL® as evenly as you can throughout the day. For example, if you take the drug 2 times a day, leave about 12 hours between each dose.

- Try to take your dose(s) at the same time(s) each day. This will help keep a constant amount of drug in your body and will also help you remember each dose. NEORAL® may be taken with or without food. But it is best to be consistent: once you decide when you are going to take it in relation to food, do it the same way each time.

- Never take NEORAL® or SANDIMMUNE® I.V with grapefruit juice.

- Leave the capsules in the foil until you need a dose. When you are ready to take a dose, remove the number of capsules you need to make up the dose your doctor prescribed.

- Swallow the capsules whole. You may use any kind of drink except grapefruit juice.

- If you were previously taking a different oral formulation of cyclosporine, your doctor will monitor you more closely for a short period following transfer from one oral formulation to another to ensure that cyclosporine blood levels are in the correct range. Never adjust the dose yourself unless the doctor has told you to.

SANDIMMUNE® I.V: The usual dose is 3 to 5 mg/kg body weight per day starting on the day before your transplant and continuing for up to two weeks after the operation. You will be started on NEORAL® (capsules or oral solution) as soon as possible after the operation.

NEORAL®:If you have had an organ or bone marrow transplant, the total dose is usually within the range of 2 mg/kg body weight per day and 15 mg/kg body weight per day divided in two doses.

- For the treatment of **nephrotic syndrome**, the total daily dose is usually within the range of 2.5 mg/kg body weight per day and 5 mg/kg body weight per day.

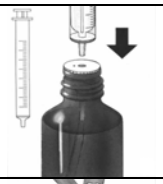
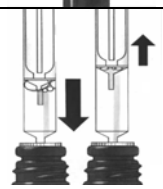
- For the treatment of **severe rheumatoid arthritis**, the total daily dose is usually within the range of 3 mg/kg body weight per day and 5 mg/kg body weight per day divided in two doses.

- For the treatment of **psoriasis and eczema**, the total dose is usually within the range of 2.5 mg/kg body weight per day and 5.0 mg/kg body weight per day divided in two doses.

- SANDIMMUNE® I.V. will be diluted with normal saline or 5% glucose and given to you by slow infusion.

NEORAL® Oral Solution

To open the bottle for the first time:

1.	Raise the plastic cap.	
2.	Tear off the sealing ring completely.	
3.	Remove the black stopper and throw it away	
4.	Push the tube unit with the white stopper firmly into the neck of the bottle.	
5.	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. Do not let the syringe touch the liquid in the cup. Most drinks other than grapefruit juice can be used at room temperature, for example, apple juice, orange juice, or a soft drink. Once you have chosen a drink, use the same one each time. The medicine can be mixed just before you take it. Stir and drink the entire mixture right away. Please take the medicine immediately after preparation.	
9.	After use, wipe syringe on outside only with a dry tissue and replace in its case. Do not rinse the syringe with water, alcohol, or any other liquid. White stopper and tube should remain in bottle. Close bottle with cap provided.	

Once the bottle is opened the first time, you can start at point number 5 above for your next dose.

- Each dose of NEORAL® solution must be measured accurately. Be sure to ask your doctor, nurse or pharmacist if you have any question about how to measure the solution.

Overdose:

In case of drug overdose, contact a health care practitioner (e.g. doctor) hospital emergency department or regional poison control centre, even if there are no symptoms.

Missed Dose:

- For transplant patients, missing even a few doses of NEORAL® or SANDIMMUNE® I.V. may lead to rejection of your transplanted organ. That is why it is so important to take each of the doses your doctor prescribes.

- Talk to your doctor, nurse or pharmacist if you have trouble remembering doses, or if you are uncertain about how to take them. Also be sure to discuss any concerns you have about taking this drug as prescribed. These people can often suggest ways to overcome problems you have taking your medication.

- Never allow your medication to run out between refills. Plan to order your refills about one week ahead of time — that way you will always have a supply in case the pharmacy is closed or out of the drug. Also be sure to take enough medication with you when you go on a holiday.

If you forget to take a dose, take another one as soon as you remember, unless it is almost time for your next dose. Then go on as before. It is also a good idea to ask your doctor ahead of time what to do about missed doses.

Be sure to keep all appointments at your clinic. Some of these visits will be used to check the level of cyclosporine in your blood. For transplant patients, levels that are too low can cause transplant rejection, while levels that are too high may cause damage to other organs. It is therefore very important not to miss any tests or check-ups your doctor orders.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, NEORAL® or SANDIMMUNE® I.V. can cause side effects, although not everybody gets them. Be sure to talk to your doctor if you have any concerns about this.

The most common side effects noted were:

- high blood pressure;
- kidney or liver problems;
- headache (including migraine);
- increased levels of lipids (e.g. cholesterol) in the blood;
- loss of appetite, nausea, vomiting, constipation or diarrhea;
- acne or oily skin;
- slight trembling of the hands;
- increased growth of fine hairs on the body;
- muscle or joint pains or cramping;
- weakness, anxiety;
- tingling in the fingers, toes or mouth;
- night sweats; hearing loss; swelling of the face;
- increased potassium in the body (your doctor may instruct you to avoid high dietary potassium intake);
- tender or swollen gums
- decreased ability to fight infection
- low level of white blood cells
- high level of sugar in the blood
- hot flushes
- stomach ulcer
- rash

- If you develop liver problems while taking this drug, which could occur with or without the following symptoms: jaundice (yellowing of the skin and/or eyes and/or dark urine), abdominal pain, vomiting and nausea, contact your doctor immediately.

- Because NEORAL® or SANDIMMUNE® I.V. reduces the function of your immune system, you are more likely to get bacterial, fungal or viral infections. To help reduce complications from these infections, tell your doctor right away about any cold or flu-like symptoms (such as a fever or sore throat), any boils on your skin, or pain when you urinate (pass your water).

- The decreased function of your immune system may also increase your chances of developing cancer. Although very rare, cancers of the white blood cells (lymphomas) and other types of cancer have occurred in people taking cyclosporine. The following are some possible warning signs of cancer. To help detect any cancers as soon as possible, report any of these symptoms to your doctor right away: a change in your bowel or bladder habits; any sore that doesn't heal; unusual bleeding or discharge; the appearance of a lump or thickened areas in your breast or anywhere else on your body; unexplained stomach upset or any trouble with swallowing; an obvious change in a wart or a mole; a nagging cough or hoarseness; night sweats

- If you experience vision changes, loss of coordination, clumsiness, memory loss, difficulty speaking or understanding what others say, and muscle weakness, these can be the signs and symptoms of an infection of the brain called progressive multifocal leukoencephalopathy. Contact your doctor right away if these symptoms occur.

- Vomiting or diarrhea may stop NEORAL® from being absorbed (going) into your body.

Some side effects occurred with unknown frequency and were:

- Low levels of magnesium in the blood
- Vomiting and sensitivity to light
- Inflammation of the pancreas with severe upper
- stomach pain
- Muscle spasm
- Pain in legs and feet
- Breast enlargement in men
- Tiredness and weight gain
- High level of acid uric in the blood

Be sure to tell your doctor right away if you notice any of these symptoms listed above, and especially if they continue, bother you in any way, or seem to increase in intensity. Remember, only a doctor can tell if these symptoms might be from NEORAL® or SANDIMMUNE® I.V.. If you think you are having side effects, talk to your doctor right away. Do not stop taking this drug on your own.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common	Tremor		√	†
	High blood pressure		√	
	Tingling		√	
	Bacterial, fungal or viral infection		√	
	Vomiting or diarrhea		√	
	Muscle or joint pains or cramping		√	
	Weakness		√	
	Anxiety		√	
	Swelling at the back of the eyes which may be associated with blurred vision and possible visual impairment due to an increase in pressure inside the head (benign intracranial hypertension)		√	
	High level of potassium in the blood		√	
	Low level of red blood cells or platelets;which may be associated with pale skin, tiredness, breathlessness, dark urine (sign of breakdown of red blood cells), bruising or bleed with no obvious reasons, confusion, disorientation, decreased alertness, and kidney problems		√	
Uncommon	Ulcers		√	†
	Convulsions		√	
	Brain disorder with signs such as seizures, confusion, disorientation, decreased responsiveness, personality changes, agitation, sleeplessness, sight disturbances, blindness, coma, paralysis of part or all of the body, stiff neck, loss of coordination with or without abnormal speech and eye movements		√	
	Allergic reactions		√	
Rare	Abnormal menstrual cycle		√	
Very rare	Tumours/ malignancies		√	†

† Do not stop your medicines unless you have discussed this with your doctor first.

This is not a complete list of side effects. For any unexpected effects while taking NEORAL® or SANDIMMUNE® I.V.,

contact your doctor or pharmacist.

HOW TO STORE IT

- Keep NEORAL® out of the reach and sight of children. A child who accidentally takes this drug may be seriously harmed. A locked drawer or cupboard is best if you have small children in the house.

- NEORAL® capsules should be kept in a dry place, at a temperature between 15 and 25°C. Remember to leave each capsule in its foil pack until you need to take it.

- NEORAL® oral solution should be kept at room temperature (15-30°C), preferably not below 20°C for prolonged periods. Do not put it in the fridge, and do not let it freeze. Once the bottle has been opened, the contents must be used within 2 months. Be sure to keep the solution in the original bottle.

- A jelly-like formation may occur if the oral solution goes below 20°C. This should go away when the solution is warmed to 30°C. Little flakes (or a slight sediment) may still be seen. Having this happen does not change the effectiveness or safety of the product, and dosing by means of the syringe remains accurate.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Post Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.novartis.ca, or by contacting Novartis at 1-800-363-8883.

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