PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrNEORAL®

(cyclosporine capsules for microemulsion)

(cyclosporine oral solution for microemulsion)

Soft gelatin capsules, 10, 25, 50 and 100 mg and oral use

Solution, 100 mg/mL and oral use

PrSANDIMMUNE® I.V.

(cyclosporine for injection)

Concentrate for solution for infusion, 50 mg/mL and Intravenous

Immunosuppressant

ATC code L04A D01

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Date of Initial Authorization:
NEORAL: January 13, 1995
SANDIMMUNE: March 23,1984
Date of Revision:
February 23, 2023

Submission Control No: 268008

RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery	01/2023
7 WARNINGS AND PRECAUTIONS, 7.1 Special Population, 7.1.1 Pregnant Women and 7.1.2 Breast Feeding	01/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

1.1 Pediatrics

Pediatrics (< 18 years of age of age):

The safety and efficacy of Neoral in pediatric patients (<18 years) with juvenile rheumatoid arthritis or psoriasis have not been established.

NEORAL is not recommended in children for non-transplant indications other than nephrotic syndrome. Pediatric patients have similar adverse drug reaction profiles as those in the adults (**see 7 WARNINGS AND PRECAUTIONS, and 8 ADVERSE REACTIONS**).

1.2 Geriatrics

Geriatrics (> 65 years of age):

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (See 7.1.4 **Geriatrics**).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to cyclosporine or any of its excipients. For a complete listing, see the 6 **DOSAGE FORMS, STRENGTHS, 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.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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."

4 DOSAGE AND ADMINISTRATION

4.1 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 9 **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 7 **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 7 **WARNINGS AND PRECAUTIONS**).

4.2 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).

Table 1

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 7 **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 7 **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 **7 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 7 **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 7 **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.

4.4 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 1:20 to 1:100, 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 7 **WARNINGS AND PRECAUTIONS**).

Because of the risk of anaphylaxis (see 7 **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.

5 OVERDOSAGE

For management of a suspected drug overdose, 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Nonmedicinal Ingredients
Oral	Soft Gelatin Capsules; 10 mg, 25 mg, 50 mg and 100 mg Cyclosporine capsules for microemulsion	Aluminum Chloride, Carminic Acid (25 and 100 mg), DL-α-Tocopherol, Ethanol (9.4% w/v) v/v 11.8%, Gelatin, Glycerol, hydrogenated castor oil, Hydroxypropyl Methlycellulose, Iron Oxide Black (25 and 100 mg), maize oil, Propylene glycol, Sodium Hydroxide, Titanium Dioxide
Oral	Oral Solution; 100 mg/mL Cyclosporine oral solution for microemulsion	Ethanol (9.5% w/v) v/v 12%, maize oil, hydrogenated castor oil, DL-α-Tocopherol, Propylene glycol
Solution for Injection	Intravenous; 50 mg/mL Cyclosporine Concentrate for Solution for Infusion	Ethanol (94% w/w) 278 mg/mL, Castor oil (Polyoxyethylated) 650 mg/mL

NEORAL soft gelatin capsules: 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: 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):supplied in 1 mL and 5 mL sterile ampoules containing 50 mg of cyclosporine per mL in a polyoxyethylated castor oil/ethanol vehicle.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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 **7 WARNING AND PRECAUTIONS-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 4 **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 9 **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 9 **DRUG INTERACTIONS**).

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 9 **DRUG INTERACTIONS**).

Driving and Operating Machinery

NEORAL or SANDIMMUNE I.V. is neurotoxic and may cause impaired consciousness, convulsions, and visual disturbances (including cortical blindness), loss of motor function, movement disorders and psychiatric disturbances (see **7 WARNINGS AND PRECAUTIONS, Neurologic** and **8 ADVERSE REACTIONS**). Caution should be exercised when driving a motor vehicle or operating machines. No studies on the effects of NEORAL or SANDIMMUNE I.V. on the ability to drive and use machines have been performed.

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 9 **DRUG INTERACTIONS**, 8 **ADVERSE REACTIONS**).

Hyperkalemia/Hyperuricemia/Hypomagnesemia

Cyclosporine enhances the risk of hyperkalemia, especially in patients with renal dysfunction (see 8 **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 9 **DRUG INTERACTIONS**). Control of potassium levels in these situations is advisable.

Caution is required in treating patients with hyperuricemia. (see 9 **DRUG INTERACTIONS** and 8 **ADVERSE REACTIONS**)

Cyclosporine enhances the clearance of magnesium. This can lead to symptomatic hypomagnesemia, especially in the peri-transplant period (see 8 **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 8 **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 8 **ADVERSE REACTIONS**).

Close monitoring of parameters that assess hepatic function is required. Abnormal values may necessitate dose reduction (see 4 **DOSAGE AND ADMINISTRATION** and **10 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 outcomes 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.

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 4 **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 9 **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 4

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 increases 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.

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 7 **WARNINGS & PRECAUTIONS - Monitoring and Laboratory tests, Psoriasis/ Rheumatoid Arthritis/ Nephrotic Syndrome Patient Management**).

Reproductive Health: Female and Male Potential

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

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 16-**NON-CLINICAL TOXICOLOGY**).

Special Excipients: Ethanol

The ethanol content (see **6 DOSAGE FORMS, STRENGTH, COMPOSTION AND PACKAGING**) 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.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate or well-controlled clinical studies in pregnant women using cyclosporine. Data on the use of cyclosporine in pregnant patients from post-marketing experience, including published literature, demonstrated that pregnant women receiving immunosuppressive therapies after transplantation, including cyclosporine and cyclosporine-containing regimens, are at risk of premature delivery (< 37 weeks).

Embryo-foetal developmental (EFD) studies in rats and rabbits with cyclosporine have shown embryo-foetal toxicity at dose levels below the maximum recommended human dose (MRHD) based on body surface area (BSA) (see section **16- NON-CLINICAL TOXICOLOGY**).

NEORAL or SANDIMMUNE I.V. should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. The ethanol content should also be taken into account in pregnant women (see **7 WARNINGS AND PRECAUTIONS**).

Published data from the National Transplantation Pregnancy Registry (NTPR, 2014) described pregnancy outcomes in female kidney (482), liver (97), and heart (43) transplant recipients receiving cyclosporine. The data indicated a live birth rate of 76%, 76.9%, and 64% in kidney, liver, and heart transplant recipients, respectively. Premature delivery (< 37 weeks) was reported in 52%, 35%, and 35% of kidney, liver, and heart transplant recipients, respectively along with low birth weight for gestational age. The rates of miscarriages were 16%, 14%, and 25%, respectively. Newborn complications were reported in 42%, 29%, and 30%, respectively. Major birth defects were reported in 4% and 4.2%, respectively, in kidney, and liver transplant recipients. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The effect of cyclosporine on maternal hypertension, preeclampsia, infections or diabetes could not be excluded given the limitations inherent to registries and post-marketing safety reporting.

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.

Because of the possible disruption of maternal-fetal interaction, the risk/benefit ratio of using Neoral in psoriasis patients during pregnancy should carefully be weighed with serious consideration for discontinuation of Neoral.

7.1.2 Breast-feeding

Cyclosporine is transferred into breast milk. Mothers receiving treatment with NEORAL or SANDIMMUNE I.V. should not breast feed. 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.

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

The ethanol content of NEORAL should also be taken into account (see 7 **WARNINGS AND PRECAUTIONS**).

7.1.3 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 7 **WARNINGS AND PRECAUTIONS**, **1.1 Pediatrics** and 8 **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.

7.1.4 Geriatrics

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 ≥ 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 (See 1.2 **Geriatrics**).

7.1.5 Renal impairment

All indications

Cyclosporine undergoes minimal renal elimination and its pharmacokinetics is not affected by renal impairment (see **10 CLINICAL PHARMACOLOGY**). However, due to its nephrotoxic potential (see 8 **ADVERSE REACTIONS**), a careful monitoring of the renal function is recommended (see 7 **WARNINGS AND PRECAUTIONS, All indications**).

Non-transplant indications

Patients with impaired renal function, except nephrotic syndrome patients, should not receive cyclosporine (see 7 **WARNINGS AND PRECAUTIONS, Non-transplant indications**). In nephrotic syndrome patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg per day.

7.1.6 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 **10 CLINICAL PHARMACOLOGY**). Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see 7 **WARNINGS AND PRECAUTIONS** and **10 CLINICAL PHARMACLOGY**).

8 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.

8.1 Adverse 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 7 **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 7 **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 7 **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 7 **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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to

the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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.

Table 3

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:

Table 4

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

Table 5

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

Body System Adverse Event	**SANDIMMUNE Patients** Initial Dose < 6 mg/kg/d (n=378) (%)	**Placebo-Treated Patients** (n=176) (%)
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.

Table 6

Body System **Adverse Event**	**SANDIMMUNE Patients** **(n=270) (%)**

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).

8.5 Post-Market Adverse 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 7 **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 9.4 **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 7 **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 7 **WARNINGS AND PRECAUTIONS**).

9 DRUG INTERACTIONS

9.2 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. Cyclosporine is a substrate of P-gp, hence inhibitors or inducers of P-gp may alter the concentrations of cyclosporine.

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 is 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.

* 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.

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 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 7 **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 7 **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 7 **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 7 **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 7 **WARNINGS AND PRECAUTIONS**).

9.4 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.

Table 7 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	Barbiturates Bosentan Carbamazepine 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
	and clarithromycin) Lercanidipine Metoclopramide Methylprednisolone Norethisterone or danazol Oral contraceptives Protease inhibitors Voriconazole Nefazodone		
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 7 **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.

Table 8 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.

Interactions resulting in decrease of other drug levels

Concomitant administration of cyclosporin and mycophenolate sodium or mofetil in transplant patients may decrease the mean exposure of mycophenolic acid by 20-50% when compared with other immunosuppressants. This information should be taken into consideration when coadministering these drugs.

The coadministration of a single dose of cyclosporin (200 mg or 600 mg) with a single dose of eltrombopag (50 mg) decreased plasma eltrombopag AUCinf by 18% to 24% and Cmax by 25% to 39%. This decrease in exposure is not considered clinically meaningful.

9.5 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.

9.6 Drug-Herb Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 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 4 **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.

10.2 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.

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 days 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.

10.3 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°C, 93% at 20°C and 98% at 37°C.

With a temperature decrease from 37° to 21°C, 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°C 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.

11 STORAGE, STABILITY AND DISPOSAL

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 1:20 and 1:100 in 5% glucose or normal saline only, immediately prior to use (see 4.4 **ADMINISTRATION**).

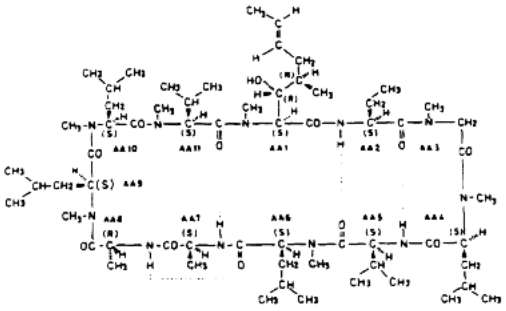
Storage:

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

PART II: SCIENTIFIC INFORMATION

13 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:	$C_{62}H_{111}N_{II}O_{I2}$ and 1202.64
Structural formula:	
Physicochemical properties:	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:	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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

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 4 **DOSAGE AND ADMINISTRATION**).

Clinical studies are displayed in below Tables 9 to 13.

Kidney and pancreas transplantation

Table 9 presents clinical studies that were mainly performed in kidney transplanted patients and Table 10 presents clinical studies performed only in kidney transplanted patients. Table 9 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 9 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 10 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 11) 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 11 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 12), 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 12 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 13 below.

Table 13 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 4 **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).

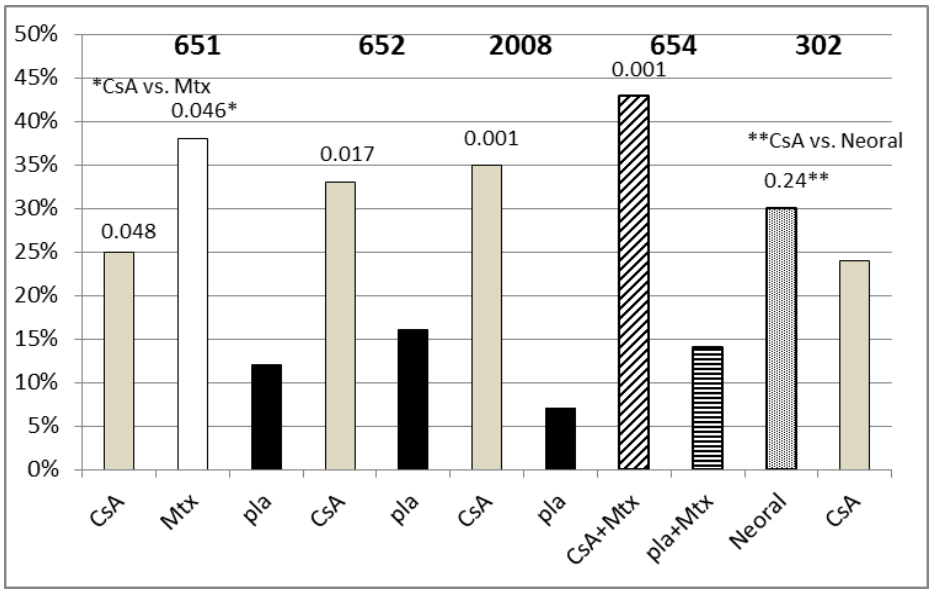
Study 652 enrolled 250 patients with active RA with > 6 active painful or tender joints who had failed at least one major RA drug. Patients were randomized using a 3:3:2 randomization to 1 of 3 treatment arms: (1) 1.5-5 mg/kg/day of cyclosporine, (2) 2.5-5 mg/kg/day of cyclosporine, and (3) placebo. 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 patients 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL 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 14 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 15: 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 16: 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 17: 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 18: 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 19: 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.

Teratological and Reproduction Studies:

Three EFD studies (two oral and one intravenous) are available in rats.

In an EFD study, cyclosporine, 10, 17, 30, 100 and 300 mg/kg/day, was orally administered to pregnant rats from gestation day (GD) 6 to 15. Maternal toxicity characterized by mortality, clinical signs of toxicity and impaired body weight gain were observed at 30 mg/kg/day and above. Cyclosporine has been shown to be embryo- and fetotoxic in rats at maternally toxic doses indicated by an elevated embryonic mortality, reduced fetal weight and a higher incidence of skeletal retardations. There was no embryo- and fetotoxicity observed in rats up to 17 mg/kg/day (below the MRHD based on BSA).

In another EFD study, pregnant rats were administered orally with 4, 10 and 25 mg/kg/day of ciclosporin from GD 7 to 17. An increase in post-implantation resorption, fetal mortality, higher incidence of skeletal retardations and ventricular septal defect were observed at 25 mg/kg/day. The no observed effect level (NOEL) for dams and fetuses were 10 and 4 mg/kg/day (below the MRHD based on BSA), respectively.

In the IV EFD study, rats were administered with 3, 6 and 12 mg/kg/day of cyclosporine from GD 7 to 17. An increase in post implantation loss was observed at 12 mg/kg/day; ventricular septal defect was observed at 6 mg/kg/day and above in foetuses. The NOEL for dams and foetus were 6 and 3 mg/kg/day (below the MRHD based on BSA), respectively, after IV administration.

In rabbits, cyclosporine was orally administered at dose levels of 10, 30, 100 or 300 mg/kg/day from GD 6 to 18. At 100 mg/kg/day and above, reduction in body weight gain of dams and at 300 mg/kg/day abortions were observed. Maternal toxicity, embryo-fetotoxicity as indicated by increased pre- and postnatal mortality, reduced foetal weight together with skeletal

retardations were observed at 100 mg/kg/day and above. The NOEL for dams and foetuses was 30 mg/kg/day (below the MRHD based on BSA).

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

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

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.

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrNEORAL®

cyclosporine capsules for microemulsion, cyclosporine oral solution for microemulsion

PrSANDIMMUNE® I.V.

cyclosporine for injection

Read this carefully before you start taking **NEORAL® or SANDIMMUNE® I.V.** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NEORAL or SANDIMMUNE I.V.**

Serious Warnings and Precautions

- **Transplant Patients:**
  - **You will be prescribed NEORAL or SANDIMMUNE I.V. by a healthcare professional experienced in using immunosuppressive drugs and in the management of organ transplant patients.**
  - **Your healthcare professional will be in direct contact with your transplant centre.**
  - **You must be treated in a medical centre with experienced healthcare professionals where your blood levels of cyclosporine can be monitored.**

- **Patients with Psoriasis, Rheumatoid Arthritis and Nephrotic Syndrome:**
  - **You will be prescribed NEORAL by a healthcare professional experienced with its use. They will closely monitor you while you are being treated.**
  - **If you are taking NEORAL to treat your psoriasis and you have previously been treated with PUVA, methotrexate, other immunosuppressive dugs, UVB, coal tar or radiation therapy you are at an increased risk of developing skin cancer.**

What is NEORAL and SANDIMMUNE I.V. used for?

NEORAL and SANDIUMMUNE I.V. are indicated for the treatment of:

- Organ Transplant: Used to prevent rejection after an organ transplant. It is also used to treat organ rejection in patients who have been treated with other immunosuppressive drugs.

- Bone Marrow Transplant: Used to prevent rejection after a bone marrow transplant. It is also used to prevent or treat graft-versus-host-disease (GVHD).

NEORAL is also indicated for the treatment of:

- Psoriasis: Used to treat severe psoriasis in patients who can't use the usual treatments or in patients who did not respond to the usual treatments.
- Rheumatoid Arthritis: Used to treat severe rheumatoid arthritis in patients who can't use the usual treatments or in patients who did not respond to the usual treatments.
- Nephrotic Syndrome: Used to treat kidney problems that are also being treated with steroids or are resistant to treatment with steroids.

How does NEORAL and SANDIMMUNE I.V. work?

NEORAL and SANDIMMUNE I.V. contain the medicinal ingredient cyclosporine. It belongs to a class of drugs called immunosuppressants. These drugs work to suppress or reduce your body's immune response. Normally your body's immune system 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 they help prolong the life of an organ transplant, or to suppress certain functions of your immune system to treat your psoriasis, rheumatoid arthritis or nephrotic syndrome.

What are the ingredients in NEORAL and SANDIMMUNE I.V.?

Medicinal ingredients: cyclosporine

Non-medicinal ingredients:

- NEORAL capsules: aluminum chloride, carminic acid (25 mg, 100 mg capsules), DL-α-Tocopherol, ethanol (9.4% w/v), gelatin, glycerol, hydrogenated castor oil, hydroxypropyl methlycellulose, iron oxide black (25 mg, 100 mg capsules), maize oil, propylene glycol, sodium hydroxide, titanium dioxide.
- NEORAL oral solution: DL-α-Tocopherol, ethanol (9.5% w/v), hydrogenated castor oil, maize oil, propylene glycol.
- SANDIMMUNE I.V.: castor oil, ethanol (278 mg/mL).

NEORAL and SANDIMMUNE I.V. comes in the following dosage forms:

NEORAL:
soft gelatin capsules; 10 mg, 25, mg, 50 mg, 100 mg
oral solution; 100 mg / mL

SANDIMMUNE I.V.:
solution for injection; 50 mg / mL

Do not use NEORAL and 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 are the ingredients in NEORAL and SANDIMMUNE I.V. ")**
- you are being treated for psoriasis, rheumatoid arthritis or nephrotic syndrome and you have one of the following conditions:
    - kidney problems (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.
- you are taking bosentan, used to treat high blood pressure in the lungs

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NEORAL and SANDIMMUNE I.V. Talk about any health conditions or problems you may have, including:

- if any of the following apply because NEORAL and SANDIMMUNE I.V. contain alcohol:
    - you have or had alcohol related problems
    - you have epilepsy
    - you have any liver problems
    - you are pregnant
    - you are breastfeeding
    - the medicine is to be given to a child

- if you are to receive any vaccinations. NEORAL and SANDIMMUNE I.V. may make vaccinations less effective or increase your risk of getting an illness from a live vaccine.
- if you have high levels of potassium in your blood.
- if you suffer from gout.

Other warnings you should know about:

Tell <u>all</u> healthcare professionals you see (doctors, dentists, nurses, pharmacists) that you are taking NEORAL or SANDIMMUNE I.V. It is also a good idea to wear a Medic-Alert bracelet.

Immune system effects:

- NEORAL and SANDIMMUNE I.V. suppress the function of your immune system. This means you are more likely to get bacterial, fungal or viral infections. To help reduce complications from these infections, talk to your healthcare professional immediately if you get any cold or flu-like symptoms (such as a fever or sore throat), any boils on your skin, or have pain when you urinate.
- The suppressed 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. To help detect any cancers as soon as possible, talk to your healthcare professional immediately if you have any of these symptoms:
    - 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 area 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

Progressive multifocal leukoencephalopathy: Treatment with NEORAL or SANDIMMUNE I.V. can cause a serious infection of the brain called progressive multifocal leukoencephalopathy (PML). Talk to your healthcare professional immediately if you experience vision changes, loss of coordination, clumsiness, memory loss, difficulty speaking or understanding what others say and muscle weakness, as these can be signs of PML.

Pregnancy and Breastfeeding:

- Do not take NEORAL or SANDIMMUNE I.V. if you are pregnant.
- You must use a reliable method of birth control while you are being treated with NEORAL and SANDIMMUNE I.V. and for 2 months after stopping treatment.
- Talk to your healthcare professional immediately if you become pregnant, or think you might be pregnant, while you are taking NEORAL or SANDIMMUNE I.V. You will want to discuss the possible benefits and risks of continuing with this drug.
- Do not breastfeed while you are taking NEORAL or SANDIMMUNE I.V. as it passes into breast milk and may harm your baby. Talk to your healthcare professional about other ways to feed your baby.

Blood tests and monitoring: 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 with

your healthcare professional. Your liver and kidney function and your blood lipids (cholesterol) should be checked regularly. Your healthcare professional will also check your blood pressure before you start treatment and regularly thereafter.

Driving and using machines:

You may feel sleepy, disoriented, or have blurred vision, or experience seizures (fits), coordination or movement problems, or altered thinking or behavior after taking NEORAL. Be careful when driving or operating machinery while you are taking NEORAL until you know how it affects you.

Use in the elderly (65 years of age and older): There is limited experience with the use of NEORAL or SANDIMMUNE I.V. in the elderly. Your healthcare professional will closely monitor your kidney function. If you are over the age of 65 years with psoriasis, you should only be treated in case of disabling disease.

Transplant patients: Your healthcare professional may give you magnesium supplements since NEORAL and SANDIMMUNE I.V. may reduce the amount of magnesium in your body.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NEORAL and SANDIMMUNE I.V.:

- medicines that may affect your blood 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 lowering medicines called calcium antagonists
- methotrexate, a medicine used to treat cancer, severe psoriasis and severe rheumatoid arthritis
- medicines which may increase or decrease the blood levels of NEORAL or SANDIMMUNE I.V.:

    - medicines which may decrease NEORAL or SANDIMMUNE IV blood levels: barbiturates (medicines used to help you sleep), certain anticonvulsives, used to prevent seizures (e.g. carbamazepine, phenytoin, oxcarbazepine), octreotide, an antibiotic medicine used to treat tuberculosis, orlistat (used to help weight loss), herbal medicines containing St. John's Wort (used to treat depression), ticlopidine (used after stroke), certain blood pressure lowering medicines (bosentan), and an antifungal medicine used to treat infections of the toes and nails (terbinafine).
    - medicines which may increase NEORAL or SANDIMMUNE IV blood levels: antibiotics of the macrolides type (e.g. erythromycin, azithromycin), antifungal medicine of the azole type (e.g. voriconazole, itraconazole), medicines used for heart problems or high blood

pressure (e.g. diltiazem, nicardipine, verapamil, amiodarone), metoclopramide (used to stop sickness), oral birth control, danazol (used to treat menstrual disorders), medicines used to treat gout (e.g. allopurinol, colchicines), cholic acid and derivatives (used to treat gallstones), protease inhibitors used to treat HIV, imatinib (used to treat leukemia or tumors), nefazodone (used to treat depression).

- other medicines which may affect the kidneys, such as antibiotic medicines (e.g. gentamycin, tobramycin, ciprofloxacin), antifungal medicines containing amphotericin B, antibiotic medicines containing ciprofloxacin, medicines used to treat urinary tract infection containing trimethoprim, 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), other immunosuppressive drugs called calcineurin inhibitors (e.g. 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).
- medicines whose concentrations may increase when used together with NEORAL including lercanidipine (used to lower high blood pressure), aliskiren (used to treat high blood pressure), digoxin (used to treat heart problems), cholesterol lowering agents (HMG-CoA reductase inhibitors, also called statins), prednisolone (a steroid medicine used to treat inflammation), etoposide (used to treat cancer), dabigatran (oral blood thinner used to prevent stroke), repaglinide (oral medicine to treat diabetes), immunosuppressives (e.g. everolimus, sirolimus), ambrisentan and specific anticancer medicines called anthracyclines (e.g. doxorubicin).
- medicines whose concentration may decrease when used together with NEORAL or SANDIMMUNE I.V. including mycophenolate sodium or mofetil (an immunosuppressant) and eltrombopag (used to treat bleeding disorders).
- caspofungin, used to treat fungal infections.

Do not take NEORAL or SANDIMMUNE I.V. with grapefruit juice.

How to take NEORAL and SANDIMMUNE I.V.?

- Always take NEORAL or SANDIMMUNE I.V. exactly as your healthcare professional has told you. You should check with your healthcare professional if you are unsure.
- NEORAL is an oral medicine that you will take in either capsule or liquid form.
- SANDIMMUNE I.V. is an intravenous medicine that will be given to you by your healthcare professional directly into your vein, usually while you are in the hospital.
- **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.
- Do not change the dose on your own, no matter how you are feeling. Blood tests are one of

the ways your healthcare professional knows how much NEORAL or SANDIMMUNE I.V. you need. Based on these tests, and on your response to this drug, your healthcare professional 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 NEORAL capsules in the blister 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 healthcare professional prescribed. NEORAL capsules have a characteristic smell when the blister foil is opened. This is normal.
- Swallow the NEORAL capsules whole. You may use any kind of drink except grapefruit juice.
- If you suffer from diarrhea or vomiting talk to your healthcare professional as this can stop your body from absorbing the right amount of NEORAL.
- If you were previously taking a different oral formulation of cyclosporine, your healthcare professional will monitor you more closely for a short period after you switch from one oral formulation to another. They will make sure that your cyclosporine blood levels are in the correct range. Never adjust the dose yourself unless your healthcare professional has told you to.

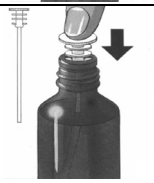
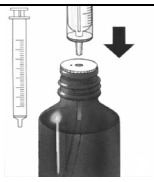
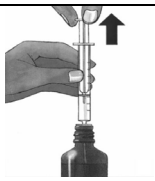
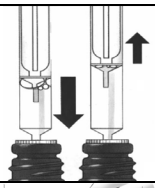
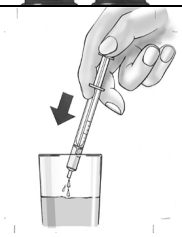
Usual dose:

Your healthcare professional will decide on the dose that is right for you based on your body weight and the condition that is being treated. If you are a transplant patient they will also use your blood levels of cyclosporine.

<u>NEORAL Oral Solution</u>

To open the bottle for the first time:

1.	Raise the plastic cap.	
2.	Tear off the sealing ring completely.	

3.	Remove the grey stopper and throw it away.	
4.	Push the tube unit with the white stopper firmly into the neck of the bottle.	
5.	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 oral solution must be measured accurately. Be sure to ask your healthcare professional if you have any question about how to measure the solution.

Overdose:

If you think you, or a person you are caring for, have taken too much NEORAL or SANDIMMUNE I.V., contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, take it as soon as you remember, unless it is almost time for your next dose. Then skip the missed dose and go on as before. It is a good idea to ask your healthcare professional ahead of time what to do about missed doses.

- 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 healthcare professional prescribes.
- Talk to your healthcare professional 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. Your healthcare professional 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.

What are possible side effects from using NEORAL and SANDIMMUNE I.V.?

These are not all the possible side effects you may have when taking NEORAL or SANDIMMUNE I.V. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- headache (including migraine with vomiting and sensitivity to light)
- loss of appetite, nausea, vomiting, constipation or diarrhea
- weight gain
- acne or oily skin
- slight trembling of the hands
- increased growth of fine hairs on the body
- muscle or joint pains or cramping
- muscle spasm
- pain in legs and feet
- weakness, anxiety
- tingling in the fingers, toes or mouth

- night sweats
- hearing loss
- tender or swollen gums
- hot flushes
- rash
- breast enlargement in men

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
High blood pressure: headache, chest pains, vision problems, ringing in the ears			✓
Kidney problems: decreased urination, nausea, vomiting, swelling of the extremities, fatigue			✓
High blood sugar: frequent urination, thirst, hunger		✓	
COMMON			
Low levels of white blood cells: bacterial, fungal or viral infections, fatigue, fever, sore throat, aches and pains, flu-like symptoms, boils on your skin, pain when urinating			✓
Ulcers: stomach pain during or after eating, burning or dull pain, feeling full, bloating		✓	
Convulsions: seizure or fits, with or without loss of consciousness			✓
UNCOMMON			
Low levels of red blood cells or platelets: pale skin, tiredness, breathlessness, dark urine (sign of breakdown of red blood cells), bruising or bleeding with no obvious reasons, confusion, disorientation, decreased alertness, kidney problems			✓
Liver problems: yellowing of the skin and/or eyes, dark urine, pale stool, abdominal pain, vomiting and nausea, loss of appetite			✓
Allergic reactions: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
RARE			
Abnormal menstrual cycle		✓	
Inflammation of the pancreas: severe abdominal pain that lasts and gets worse when you lie down, nausea, vomiting			✓
VERY RARE			

Cancer: 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 area 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		✓	
UNKNOWN FREQUENCY			
Benign intracranial hypertension (increased pressure in the head): swelling at the back of the eyes which may be associated with blurred vision and possible visual impairment			✓
High levels of potassium in the blood: irregular heartbeat, muscle weakness, generally feeling unwell			✓
Low levels of magnesium in the blood: loss of appetite, nausea and vomiting, fatigue, weakness, shaking, pins and needles, muscle spasms		✓	
Brain disorders: 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			✓
High levels of uric acid in the blood: severe joint pain, joint stiffness, redness and swelling		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep NEORAL and SANDIMMUNE I.V. out of 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.

If you want more information about NEORAL and SANDIMMUNE I.V.:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Last revised: February 23, 2023

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