PRODUCT MONOGRAPH

Pr CYCLOSPORINE
Cyclosporine Capsules

Soft Gelatin Capsule 25, 50 and 100 mg

USP (Modified)

Immunosuppressive agent

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[Pr]Cyclosporine
cyclosporine capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
oral	capsule 25 mg, 50 mg, 100 mg	Ethanol For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Cyclosporine and SANDIMMUNE IV (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 Cyclosporine 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 Cyclosporine treated patients is mandatory. Cyclosporine should only be prescribed for psoriasis, rheumatoid arthritis or nephrotic syndrome by physicians experienced with its use. Cyclosporine is indicated: in patients with severe psoriasis in whom conventional therapy is ineffective or inappropriate and when the psoriasis is of such severity that the risks inherent in treatment with cyclosporine are justified for that patient; for the treatment of severe, active rheumatoid arthritis in patients for whom classical slow-acting antirheumatic agents are inappropriate or ineffective; in patients with steroid dependent and steroid resistant nephrotic syndrome.

INDICATIONS AND CLINICAL USE

Solid Organ Transplantation
Cyclosporine capsules (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
Cyclosporine capsules (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
Cyclosporine capsules (cyclosporine) are indicated for the treatment of severe psoriasis in patients for whom conventional therapy is ineffective or inappropriate.

Rheumatoid Arthritis
Cyclosporine capsules (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
Cyclosporine capsules (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. Cyclosporine can be used to induce remissions and to maintain them. It can also be used for maintenance of steroid induced remissions, allowing withdrawal of, or reduction in the dosage of steroids.

CONTRAINDICATIONS

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

- Cyclosporine 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.

WARNINGS AND PRECAUTIONS

GENERAL

Transplantation

Cyclosporine capsules (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.

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 Cyclosporine.

Psoriasis

Cyclosporine should only be prescribed for psoriatic patients by physicians experienced with its use. All patients to be treated with Cyclosporine 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 Cyclosporine 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

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

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.

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. 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 Cyclosporine should be warned to avoid excess ultraviolet light exposure.

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

ENDOCRINE AND METABOLISM

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

Hyperkalemia/Hyperuricemia/Hypomagnesemia
Cyclosporine enhances the risk of hyperkalemia, especially in patients with renal dysfunction. Caution is also required when cyclosporine is co-administered with potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and potassium containing drugs as well as in patients on a potassium rich diet (see **DRUG INTERACTIONS**). Control of potassium levels in these situations is advisable.

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

Cyclosporine enhances the clearance of magnesium. This can lead to symptomatic hypomagnesemia, especially in the peri-transplant period. Control of serum magnesium levels is therefore recommended in the peri-transplant period, particularly in the presence of neurological 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, occasionally, in liver enzymes.

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

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. As this can lead to a fatal outcome, effective pre-emptive and therapeutic strategies should be employed particularly in patients on multiple long-term immunosuppressive therapy.

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

NEUROLOGIC

Cyclosporine has the potential to induce tremor, convulsions and paresthesia in post-transplant recipients. Rarely, more complex neurological abnormalities including motor spinal cord and cerebellar syndromes have been reported in post-transplant patients.

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. interstitial fibrosis) during long term treatment. Although these renal changes are less common, they may be irreversible. In renal transplant patients, structural changes in the kidney must be differentiated from organ rejection.

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

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

In patients who are treated with cyclosporine for non-transplant indications, the risk of renal structural changes is greater if the serum creatinine level increases more than 30% from the patient's own baseline value. Thus regular measurements of serum creatinine levels must be made (See also **MONITORING AND LABORATORY TESTS**, **Psoriasis/ Rheumatoid Arthritis/ Nephrotic Syndrome Patient Management**).

SPECIAL POPULATIONS

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

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

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

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

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

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

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

Males treated with cyclosporine have fathered normal children.

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

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

However there are no adequate and well-controlled studies in pregnant women and, therefore, Cyclosporine or should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fœtus.

Nursing Women:
As cyclosporine is transferred into breast milk of lactating females, mothers receiving treatment with Cyclosporine or should not breast-feed.

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

Pediatrics:
Experience with cyclosporine in children is still limited. Experience in children is almost entirely based on cyclosporine for injection. In several studies pediatric patients required and tolerated higher doses of cyclosporine for injection per kg body weight than those used in adults.

Geriatrics (> 65 years of age):
Experience with cyclosporine in the elderly is limited, but no particular problems have been reported following the use of the drug at the recommended dose. However, factors sometimes associated with aging, in particular impaired renal function, necessitate careful supervision and may necessitate dosage adjustment.

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

Clinical studies of cyclosporine in transplant and psoriasis patients did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experiences have not

identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

MONITORING AND LABORATORY TESTS

Transplant Patient Management

Clinical
The concentrate for solution for infusion contains polyoxyethylated castor oil which has been reported to cause anaphylactoid reactions. These reactions can consist of flushing of the face and upper thorax, and non-cardiogenic pulmonary edema with acute respiratory distress, dyspnea, wheezing, and blood pressure changes and tachycardia.

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 Cyclosporine dosage is stable. Following discharge from hospital, cyclosporine levels are determined at each clinic visit, which is usually twice weekly for the first two months, weekly until four months and monthly thereafter for the first year.

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

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

Because there is a temperature and time-dependent uptake of cyclosporine by erythrocytes, the concentration of cyclosporine in plasma separated at room temperature and 37°C will differ substantially, the latter being higher. For this reason, it is not recommended to use plasma or serum as the matrix of choice. However, if plasma or serum are 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 Cyclosporine 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 Cyclosporine 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 Cyclosporine Therapy

Clinical
Regular clinical examinations are necessary during treatment with Cyclosporine. 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 cyclosporine pharmacokinetics are recommended (See Drug Interactions). If hypertension is uncontrolled with antihypertensive treatment, Cyclosporine should be discontinued. When Cyclosporine 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 Hodgkins 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 Cyclosporine. Serum creatinine should be measured every 2 weeks for the initial 3 months (see **DOSAGE AND ADMINISTRATION**). Thereafter, if creatinine levels remain stable, measurements should be made every 2 months in patients who are receiving up to 2.5 mg/kg/day and every 4 weeks in patients who are receiving higher doses.

More frequent checks are necessary when the Cyclosporine 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 Cyclosporine 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. This may explain why, in rare cases, cyclosporine- associated structural kidney alterations have been observed without changes in serum creatinine. Renal biopsy should be considered for patients with steroid-dependent minimal change nephropathy in whom cyclosporine therapy has been maintained for more than one year.

Periodic monitoring of cyclosporine trough levels is recommended.

DRUG INTERACTIONS

Caution should be exercised in patients receiving drug treatment with:

- Nephrotoxic Drugs
- Cytotoxic Drugs

- Immunosuppressants or radiation (including PUVA or UVB)
- Drugs affecting metabolism/absorption of cyclosporine
- Lercanidipine
- Methotrexate

ADVERSE REACTIONS

ADVERSE DRUG REACTION OVERVIEW

The following adverse reactions observed with cyclosporine for injection are also likely to occur with Cyclosporine.

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.

Frequency estimate: very common > 10%; common > 1 to <10%; uncommon > 0.1% to <1%; rare > 0.01% to <0.1%; very rare <0.01%.

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

Cardiovascular: Very common: hypertension (particularly in heart transplant patients).

Nervous System: Very common: tremor, headache; **Common**: paresthesia; **Uncommon**: signs of encephalopathy such as convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia; **Rare**: motor polyneuropathy; **Very rare**: optic disc edema including papilloedema, with possible visual impairment secondary to benign intracranial hypertension.

Gastrointestinal Tract and Liver: Common: anorexia, nausea, vomiting, abdominal pain, diarrhea, gingival hyperplasia, hepatic dysfunction; **Rare**: pancreatitis.

Metabolic: **Very common**: hyperlipidemia; **Common**: hyperuricemia, hyperkalemia, hypomagnesemia; **Rare**: hyperglycemia;

Musculoskeletal:
Common: muscle cramps, myalgia; **Rare**: muscle weakness, myopathy.

Hemopoietic: Uncommon: anemia, thrombocytopenia; **Rare**: micro-angiopathic hemolytic anemia, hemolytic uremic syndrome.

Skin and Appendages: **Common**: hypertrichosis; **Uncommon**: allergic rashes.

Body as a Whole: **Common**: fatigue; **Uncommon**: edema, weight increase.

Endocrine: Rare: menstrual disturbances, gynecomastia.

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

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

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

CLINICAL TRIAL ADVERSE DRUG REACTIONS

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

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

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

Paresthesia	16 (4.3%)	5 (11.1%)
Heat Sensations	28 (7.5%)	5 (11.1%)
Others	62 (16.7%)	11 (27.5%)

Psoriasis

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

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

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

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

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

Rheumatoid Arthritis

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

Body System Adverse Event	**IV Conventional Cyclosporine** Intial Dose <6mg/kg/day (n=378) (%)	**Placebo-Treated Patients** (n=176) (%)
Skin Appendages		
Alopecia	3.4	2.3
Hypertrichosis	33.9	5.1
Rash	3.4	6.3
Central and Peripheral		
Cramps	4.0	0.6
Dizziness	4.5	4.5
Headache	15.6	9.7
Paræsthesia	15.9	6.3
Tremor	13.5	3.4
Autonomic Nervous		
Flushing	5.0	1.7
Gastrointestinal		
Abdominal pain	18.8	10.2
Diarrhœa	6.1	6.3
Dyspepsia	9.5	5.7
Gum Disorder	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
Œdema	4.8	2.8
Resistance Change		
Pharyngitis	3.2	2.3

Nephrotic Syndrome

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

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

Body System Adverse Event	**Incidence** **(n=270) (%)**
Skin/Appendages	
Hypertrichosis	31.5
Hypotrichosis	3.0
Musculoskeletal	
Muscle contraction	4.1
Central and Peripheral Nervous System	
Paresthesia	12.2
Headache	5.6
Tremor	5.6
Psychiatric Disorders	
Weakness	4.8
Gastrointestinal	
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	
Hypomagnesæmia	5.2
Cardiovascular	
Hypertension	13.7
Urinary System	
Renal dysfunction	7.0

In nephrotic syndrome of 660 patients treated with cyclosporine for injection, malignancies occurred in 5 patients (3 carcinomas, 2 Hodgkins lymphomas).

POST-MARKETING ADVERSE DRUG REACTIONS

Literature and postmarketing 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.

DRUG INTERACTIONS

OVERVIEW

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 Cyclosporine 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 Cyclosporine to interact with drugs in this class should be considered.

Cyclosporine may reduce the clearance of digoxin[**], colchicine*, prednisolone* and HMG-CoA reductase inhibitors (statins).

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 are 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 postmarketing 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.

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

The concomitant use of these drugs with Cyclosporine capsules (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

[*] 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 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 **WARNINGS AND PRECAUTIONS**).

Lercanidipine
Following concomitant administration of cyclosporine and lercanidipine, the AUC of lercanidipine was increased threefold and the AUC of cyclosporine was increased 21%.

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.

Summary of Drug Interactions

	Drugs Increasing the Serum Concentration of Cyclosporine	Drugs Decreasing the Serum Concentration of Cyclosporine	Drugs Causing Additive Nephrotoxicity
Substantiated Interactions	Ketoconazole Fluconazole Itraconazole Macrolide antibiotics (erythromycin, azithromycin and clarithromycin) Corticosteroids Oral contraceptives Norethisterone or Danazol Calcium-channel blockers -Diltiazem -Verapamil -Nicardipine Metoclopramide Imipenem Methylprednisolone Allopurinol Amiodarone Colchicine Cholic acid and derivatives Protease inhibitors Imatinib Voriconazole lercanidipine	Phenytoin or Phenobarbitone Rifampicin IV Sulfadimine IV and Trimethoprim IV Nafcillin Carbamazepine Octreotide Barbiturates Metamizole Probucol Orlistat *Hypericum perforatum* (St. John's Wort) Ticlodipine Sulfinpyrazone Terbinafine Bosentan Oxcarzepine	Aminoglycosides (incl. Gentamycin, tobramycin) Amphotericin B Ciprofloxacin Colchicine Cotrimoxazole or Trimethoprim (+ sulfamethoxazole) Melphalan Methotrexate Vancomycin
Suspected or Potential Interactions	H_2-antagonists Cephalosporins Thiazide diuretics Furosemide Androgenic steroids Acyclovir Warfarin	Anticonvulsants	Nonsteroidal anti-inflammatory drugs (e.g. diclofenac, naproxen, sulindac) Histamine H2 receptor antagonist (e.g. cimetidine ranitidine) Tacrolimus

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

If combined administration is unavoidable, careful monitoring of blood cyclosporine concentration and appropriate modification of Cyclosporine dosage is essential.

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

and caspofungin should only be used concomitantly in those patients for whom the potential benefit outweighs the potential risk. Patients who develop abnormal liver function tests during concomitant therapy should be monitored and the risk/benefit of continuing therapy should be evaluated.

Miscellaneous Interactions

Alteration of Immunosuppressive Effect	Interactions with Alcohol Content	Others
Propranolol Verapamil Etoposide	Disulfiram Chloropropamide Metronidazole	Caspofungin Digoxin Captopril Toxoids or vaccines Nifedipine* HMG-CoA reductase inhibitors Prednisolone Colchicine Potassiun 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.

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 Cyclosporine.

DOSAGE AND ADMINISTRATION

DOSING CONSIDERATIONS

The dose ranges of Cyclosporine capsules 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. The results obtained will serve as a guide for determining the actual dosage required to achieve the desired target concentration in individual patients.

RECOMMENDED DOSE AND DOSAGE ADJUSTMENT

Solid organ transplantation

Treatment with Cyclosporine may be initiated within 12 hours prior to surgery at a dose of 10 to 15 mg/kg given in two divided doses. This dose should be maintained as the daily dose for one to two weeks post-operatively before being gradually reduced in accordance with blood levels until a maintenance dose of about 2 to 6 mg/kg given in two divided doses is reached. The following table outlines the recommended steady state therapeutic ranges of cyclosporine 12 hour trough levels (the level immediately before

the next dose).

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

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

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

When cyclosporine 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 for the initial treatment) may be used.

Bone marrow transplantation

The initial dose should be given on the day before transplantation. Maintenance treatment with Cyclosporine is at a daily dose of about 12.5 mg/kg given in two divided doses, 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 Cyclosporine 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 Cyclosporine 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 favorably to re-introduction of therapy.

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

Psoriasis

Dose Titration for Induction of Remission, the recommended initial dose is 2.0 mg/kg/day given in two divided oral doses.

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**. 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 Cyclosporine 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 Cyclosporine 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 Cyclosporine.

Monitoring for Psoriasis Patients
Since Cyclosporine 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, Cyclosporine treatment should be discontinued.

Discontinuation of Cyclosporine therapy is also recommended if hypertension developing during Cyclosporine 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. CYCLOSPORINE 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 2.0 mg/kg/day orally given in two divided doses. If necessary, the daily dose may then be increased gradually as **tolerability** permits (see **WARNINGS AND PRECAUTIONS**) but, depending on monitoring of drug tolerance, should not exceed 5 mg/kg/day. Up to 12 weeks of Cyclosporine therapy may be required before full effectiveness is achieved.

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

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

Monitoring for Rheumatoid Arthritis Patients
Since cyclosporine can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored every 2 weeks during the first 3 months of therapy. Thereafter, if creatinine remains stable, measurements can be made every 4 weeks. More frequent checks are necessary when the dose of Cyclosporine 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 Cyclosporine 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, Cyclosporine treatment should be discontinued.

NEPHROTIC SYNDROME

Dose Titration for Induction of Remission
For inducing remission, the recommended initial daily dose, given in two divided oral doses, is

3.5 mg/kg for adults and 4.2 mg/kg for children if, except for proteinuria, renal function is normal. In patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day.

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

Treatment Discontinuation

Treatment should be discontinued if no improvement has been observed after three months' of Cyclosporine 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 Cyclosporine 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 Cyclosporine 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 Cyclosporine therapy has been maintained for more than one year.

Periodic monitoring of cyclosporine trough levels is recommended.

Administration

Cyclosporine should always be given in two divided doses.

Cyclosporine 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.

Capsules should be swallowed whole.

OVERDOSAGE

No experience of acute overdosage of cyclosporine capsules is available. Documented cases include both single and multiple overdoses with the previously marketed conventional formulation of cyclosporine to a maximum overdose of 25,000 mg. High blood levels of cyclosporine result in acute toxic symptoms which may include: nausea, headache, 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. If indicated, general supportive measures should follow. Elimination can be achieved only by nonspecific measures including gastric lavage, as cyclosporine is notdialysable to any great extent nor is it cleared well by charcoal hemoperfusion.

ACTION AND CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

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

Cyclosporine capsules and oral solution include a microemulsion formulation of cyclosporine. Cyclosporine 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 . 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 Cyclosporine administration does not require that meals be considered. In addition, Cyclosporine produces a more even exposure to cyclosporine throughout the day and from day to day on a maintenance regimen, thereby helping to avoid periods of either under-immunosuppression or over-exposure to the drug.

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

Cyclosporine is extensively biotransformed to approximately 15 metabolites. There is no single major metabolic pathway. Elimination is primarily biliary, with only 6% of the oral dose excreted in the urine; only 0.1 % is excreted in the urine as unchanged drug. The distribution of cyclosporine appears to conform to a multicompartmental model in which continued administration leads to eventual saturation of the peripheral compartment.

The half-life of cyclosporine is approximately 18 hours (range 7.7 to 26.9). However there is a high variability in the data reported on the terminal half-life of cyclosporine depending on the assay applied and on the target population. For example, the terminal half-life ranged from 6.3 hours in healthy volunteers to 20.4 hours in patients with severe liver disease.

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

It has however been reported that monitoring with the area under the time concentration

curve for the first 4 hours (AUC_{0-4}) may provide for a more accurate prediction of optimal Cyclosporine 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 Cyclosporine absorption and immunosuppression in organ transplant recipients. When compared to C_0 monitoring, Cyclosporine C_2 monitoring provided lower rates of rejection and toxicity in liver and renal transplant patients who attained C_2 target levels.

Bioequivalence

A comparative, randomized, crossover bioavailability study was conducted comparing Cyclosporine 100 mg soft gelatin capsules manufactured by Sandoz Canada Inc. and Neoral 100 mg soft gelatin capsules (modified formulation of cyclosporine) manufactured by Novartis Canada. A single dose of 200 mg (2 x 100 mg) was administered to healthy males under fasting conditions. The mean comparative pharmacokinetic parameters resulting from the study are tabulated below. The two products were shown to be bioequivalent.

Summary Table of a Comparative Bioavailability Data.
Cyclosporine (test) *versus* Canadian Reference product (Neoral) (2 x 100 mg)
From Measured Data (fasting state)

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Mean (Corrected for Potency)
	Cyclosporine Test	Neoral* Reference	
AUC_T (ng.h/mL)	3161.07 3206.8 (17.8)	3389.61 3439.4 (17.1)	94.6 (93.5)
AUC_{INF} (ng.h/mL)	3275.45 3321.6 (17.5)	3507.11 3556.6 (16.9)	94.9 (93.9)
C_{max} (ng/mL)	871.205 883.89 (17.0)	1001.94 1022.87 (21.0)	87.4 (86.4)
T_{max} (h)	1.250 (22.2)	1.307 (23.2)	--
$T½_{el}$ (h)	5.837 (33.5)	5.530 (20.4)	--

For $T_{max,}$ $T½_{el}$, the arithmetic mean only is presented
*Neoral, (Novartis) purchased in Canada.

A second comparative randomized crossover bioavailability study was performed comparing Cyclosporine 100 mg soft gelatin capsules, manufactured by Sandoz Canada Inc. and Neoral 100 mg soft gelatin capsules (modified formulation of cyclosporine) manufactured by Novartis Canada. A single dose of 200 mg (2 x 100 mg) was administered to healthy adult males under fed conditions. The mean pharmacokinetic parameters resulting from the study are tabulated below. The two products were shown to be bioequivalent.

Summary Table of a Comparative Bioavailability Data
Sandoz Cyclosporine (test) *versus* Canadian Reference product (Neoral) (2 x 100 mg)
From Measured Data (fed state)

Parameter	Geometric Mean Arithmetic (CV%)		Ratio of Geometric Mean (Corrected for Potency)
	Sandoz Cyclosporine Test	Neoral* Reference	
AUC_T (ng.h/mL)	3400.25 3498.0 (23.7)	3258.64 3375.6 (26.6)	104.3 (103.2)
AUC_{INF} (ng.h/mL	3527.97 3627.8 (23.5)	3395.63 3516.7 (26.4)	103.9 (102.7)
C_{max} (ng/mL	871.000 891.15 (20.6)	849.200 *883.72 (28.8)	102.6 (101.4)
T_{max} (h)	1.713 (41.6)	1.563 (40.4)	--
$T½_{el}$ (h)	6.649 (29.5)	6.634 (32.1)	--

For $T_{max,}$ $T½_{el}$, the arithmetic mean only is

PHARMACODYNAMICS

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

PHARMACOKINETICS

Absorption:

When Cyclosporine 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. 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 Cyclosporine administration does not require that meals be considered. In addition, Cyclosporine 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 cyclosporine, Cyclosporine 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 (IV) administration, cyclosporine 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 20X103 ng/mL. However, binding is markedly influenced by temperature; about 70% of the drug is bound at 4^{o}C, 93% at 20^{o}C and 98% at 37^{o}C.

With a temperature decrease from 37^{o} to 21^{o}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^{o}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.

STORAGE AND STABILITY

CYCLOSPORINE Soft Gelatin Capsules
CYCLOSPORINE capsules should be stored at temperatures between 15 and 25°C and should not be removed from the blister packs until required for use. Occasional increases in temperature up to 30°C do not affect the quality of the product.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Cyclosporine USP (modified) 25 mg clear, oblong, soft gelatin capsules imprinted E0932 and filled with a clear, yellowish oil-like liquid, contain 25 mg of cyclosporine. These are supplied in boxes of 30 capsules containing 3 full aluminum blister strips of 10 capsules.

Cyclosporine USP (modified) 50 mg clear, oblong, soft gelatin capsules imprinted E0934 and filled with a clear, yellowish oil-like liquid, contain 50 mg of cyclosporine. These are supplied in boxes of 30 capsules containing 3 full aluminum blister strips of 10 capsules.

Cyclosporine USP (modified) 100 mg clear, oblong, soft gelatin capsules imprinted E0933 and filled with a clear, yellowish oil-like liquid, contain 100 mg of cyclosporine. These are supplied in boxes of 30 capsules containing 3 full aluminum blister strips of 10 capsules.

Composition

Cyclosporine Soft Gelatin Capsules

Active Ingredient:	Cyclosporine A
Nonmedicinal Ingredients:	D-alpha-tocopheryl, polyethylene glycol, ethanol, macrogol-glycerol hydroxystearate, polyethylene glycol 400, NF
Capsule shell:	Gelatin, Glycerol, Sorbitol 70% (noncrystallizing)

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

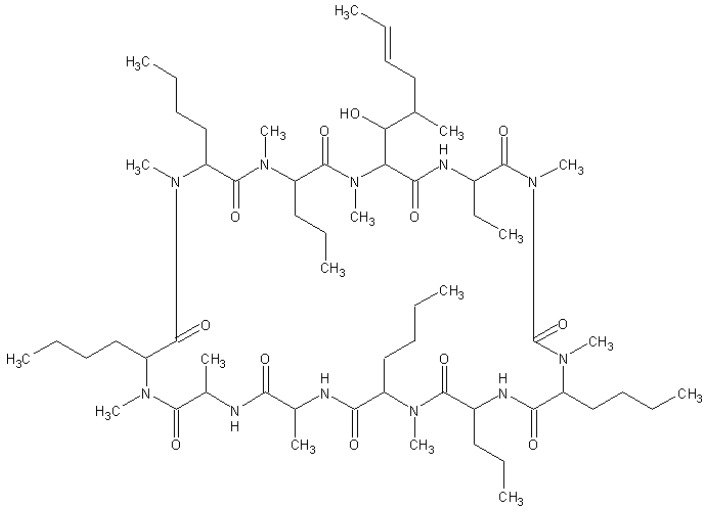
Drug Substance

Proper name: Cyclosporine (USAN)
Cyclosporin (INN)
(cyclosporin A)

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

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

Structural formula:



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

Solubility Profile:

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

Melting Point: 148-151

DETAILED PHARMACOLOGY

Cyclosporine strongly suppresses 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 IL2 mRNA occurs following addition of cyclosporine to human and murine cell lines cultured in the presence of phorbol-12- myristyl-13-acetate. Mitogen restimulation, in the presence of cyclosporine, of a three day old ConA-induced lymphoblast culture, also results in a significant reduction in the synthesis of mRNA for the lymphokines INFγ, B cell stimulating factor, and cytotoxic differentiation factor.

Reproduction and fertility

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

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

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

Fetal loss occurred in 9.1% of the patients, which is within the range found in a normal population. In 4.9% of the patients, the pregnancy was interrupted, either

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

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

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

Males treated with cyclosporine have fathered normal children.

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

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

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

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

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

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

In two published research studies, rabbits exposed to cyclosporine in utero (10 mg/kg/day subcutaneously) demonstrated reduced numbers of nephrons, renal

hypertrophy, systemic hypertension, and progressive renal insufficiency up to 35 weeks of age.
Pregnant rats which received12 mg/kg/day of cyclosporine intravenously (twice the recommended human intravenous dose) had foetuses with an increased incidence of ventricular septal defect.

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

MUTAGENICITY STUDIES

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

TOXICOLOGY

ACUTE TOXICITY

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

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, cramp like movements, stupor, piloerection Death occurred within 3 hours (IV) or (9 days (PO)
Rat	-	IV	14	25.8 104 1480 (1105-1997)	Surviving animals recovered completely
Rabbit		IV IV PO	14 14 14	≥ 10 46 ≥ 1000	No adverse effects
Dog	1.5	IV	1	-	No adverse effects
Monkey	10-13	IV	10	-	

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.

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

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.

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).	No increase in neoplastic or non-neoplastic lesions

	Lymphocytic leukocytosis with atypical Lymphocytes (1/20). Fewer thrombocytes (3/20).	

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

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 Fibroma on left gingivitis upper thigh 1 dog-mononuclear cell infiltration (1 dog)* in hepatic portal fields. Decreased eosinophils, slight leukopenia (1 dog). Some blood chemistry abnormalities (2/8 dogs).	Fibroma on left upper thigh (1 dog)*
45	As above - also temporary sedation, slight alopecia*, slight conjunctivitis*, decreased leukocyte counts and anemia (2/8). General atrophy and diaphragm (2/8)* of lymphoid organs. Slight degeneration of renal tubular epithelium (3/8). Reversible papillomatosis in some dogs.	As above Cystic nodules on pericardium and diaphragm (2/8)*

*Occurs spontaneously in this species (beagle) not necessarily related to cyclosporine.
No toxic effect level = 15 mg/kg/day.

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PART III: CONSUMER INFORMATION

PrCYCLOSPORINE
(cyclosporine capsules)

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

Read this information carefully, even if you have already been taking Cyclosporine.

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

ABOUT THIS MEDICATION

What the medication is used for:

Your doctor has prescribed the drug Cyclosporine. It is used after organ transplantations to help prevent organ rejection, or to treat autoimmune conditions such as severe psoriasis, severe rheumatoid arthritis and nephrotic syndrome.

Cyclosporine is the brand name for a drug called "cyclosporine". It belongs to a family of drugs known as "immunosuppressants". These drugs work to "suppress" or reduce the body's immune response.

What it does:

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

Cyclosporine works to reduce this response, so your body is more likely to accept the new organ.

Cyclosporine do not completely suppresses the immune system, so your body will still have some infection-fighting ability.

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

When it should not be used:

Do not use Cyclosporine if you have ever had a bad, unusual or allergic reaction to cyclosporine or any of the non-medicinal ingredients of Cyclosporine.

For the treatment of psoriasis and rheumatoid arthritis, do not take Cyclosporine if you have one of the following conditions:

- abnormal kidney function;
- 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.

What the medicinal ingredient is:

Cyclosporine contains cyclosporine for microemulsion.

CYCLOSPORINE is the microemulsion formulation of cyclosporine which can be taken orally.

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

What the important non-medicinal ingredients are:

Non-medicinal ingredients for Cyclosporine capsules are the following: Dehydrated Alcohol, D-α tocopheryl, Polyethylene glycol, Macrogol-glycerol hydroxystearate. Capsule shell: gelatin, sorbitol, glycerin.

What dosage forms it comes in:

Cyclosporine comes in one form: a soft gelatin **capsule**

Capsules

Cyclosporine capsules come with 25, 50 or 100 mg of cyclosporine. Each capsule is contained in a foil strip of 10 capsules, 30 capsules per box.

WARNINGS AND PRECAUTIONS

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

Tell **all** health professionals you see (doctor, dentists, nurses, pharmacists) that you are taking Cyclosporine. It is also a good idea to wear a medic-alert bracelet.

Before you use Cyclosporine talk to your doctor or pharmacist if:

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

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

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

• **You receive Cyclosporine for psoriasis, rheumatoid arthritis, or nephrotic syndrome**, your renal function and blood pressure should be checked before initiation of therapy and regularly thereafter. If high blood pressure develops during therapy and cannot be controlled, treatment should be stopped.

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

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

• **You are breast-feeding:** Do not breast feed your baby if you are taking Cyclosporine as it passes into breast milk and may harm your baby.

Do not stop taking Cyclosporine 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 Cyclosporine may lead to rejection of your transplanted organ.

INTERACTIONS WITH THIS MEDICATION

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

• weak analgesic drugs (non-steroid anti-inflammatory drugs),
• digoxin,
• caspofungin
• colchicines,
• HMG-CoA reductase inhibitors (statins),
• prednisolone,
• fibric acid derivatives (e.g . bezafibrate, fenofibrate) .
• methotrexate
• lercanidipine
• potassium sparing drugs (e.g . potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists)
• potassium containing drugs
• bosentan
• oxcarbazepine
• voriconazole

Never take Cyclosporine with grapefruit juice.

Cyclosporine is also used in combination with other immunosuppressive agents. However, do not use it together with other calcineurin inhibitors such as tacrolimus.

PROPER USEOF THIS MEDICATION

Usual dose:

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

• Space your doses of Cyclosporine 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. Cyclosporine 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 Cyclosporine with grapefruit juice.

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

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

Missed Dose:

• For transplant patients, missing even a few doses of Cyclosporine may lead to rejection of your transplanted organ. That is why it is so important to take each of the doses your doctor prescribes.

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

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

• If you ever do miss a dose of Cyclosporine, do not try to catch up on your own. Instead, call your doctor or pharmacist right away for advice. It is also a good idea to ask your doctor ahead of time what to do about missed doses.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Cyclosporine causes side effects in some people. Be sure to talk to your doctor if you have any concerns about this.

The most common side effects noted were:

- high blood pressure;
- kidney or liver problems;
- headache;
- increased levels of lipids (e.g . cholesterol) in the blood;
- loss of appetite, nausea, vomiting or diarrhea;
- acne or oily skin;
- slight trembling of the hands;
- increased growth of fine hairs on the body;
- muscle or joint pains or cramping;
- weakness, anxiety;
- tingling in the fingers, toes or mouth;
- night sweats; hearing loss; swelling of the face;
- increased potassium in the body (your doctor may instruct you to avoid high dietary potassium intake);
- tender or swollen gums

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

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

• Vomiting or diarrhea may stop Cyclosporine from being absorbed (going) into your body.

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Tremor		✓	
	High blood pressure		✓	
	Tingling		✓	
	Bacterial, fungal or viral infection		✓	
	Vomiting or diarrhea		✓	
	Muscle or joint pains or cramping		✓	
	Weakness		✓	
	Anxiety		✓	
	Blurred vision		✓	
	High level of potassium in the blood		✓	
Uncommon	Ulcers		✓	

	Convulsions		✓	
	Allergic reactions		✓	
Very rarely	Tumours/ malignancies		✓	

This is not a complete list of side effects. For any unexpected effects while taking Cyclosporine, contact your doctor or pharmacist.

HOW TO STORE IT

• Keep CYCLOSPORINE out of the reach 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.

• CYCLOSPORINE 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.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 1 866-234-2345
Toll-free fax: 1 866-678-6789
By email: cadrmp@hc-sc.gc.ca
Website: www.healthcanada.gc.ca/medeffect

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document, plus the full Product Monograph prepared for health professionals, can be obtained by contacting the sponsor, Sandoz Canada Inc., at: 1-800-361-3062
or
by written request at:
145, Jules-Léger
Boucherville, (QC), Canada
J4B 7K8

or by e-mail at :
medinfo@sandoz.com

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