NOVARTIS

T2002-89
89016102

Sandimmune® Soft Gelatin Capsules

(cyclosporine capsules, USP)

Sandimmune® Oral Solution

(cyclosporine oral solution, USP)

Sandimmune® Injection

(cyclosporine injection, USP)

FOR INFUSION ONLY

Rx only

WARNING

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Sandimmune® (cyclosporine). Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Sandimmune® (cyclosporine) should be administered with adrenal corticosteroids but not with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP) have decreased bioavailability in comparison to Neoral® Soft Gelatin Capsules (cyclosporine capsules, USP) MODIFIED and Neoral® Oral Solution (cyclosporine oral solution, USP) MODIFIED.

Sandimmune® and Neoral® are not bioequivalent and cannot be used interchangeably without physician supervision.

The absorption of cyclosporine during chronic administration of Sandimmune® Soft Gelatin Capsules and Oral Solution was found to be erratic. It is recommended that patients taking the soft gelatin capsules or oral solution over a period of time be monitored at repeated intervals for cyclosporine blood levels and subsequent dose adjustments be made in order to avoid toxicity due to high levels and possible organ rejection due to low absorption of cyclosporine. This is of special importance in liver transplants. Numerous assays are being developed to measure blood levels of cyclosporine. Comparison of levels in published literature to patient levels using current assays must be done with detailed knowledge of the assay methods employed. *(See Blood Level Monitoring under DOSAGE AND ADMINISTRATION)*

DESCRIPTION

Cyclosporine, the active principle in Sandimmune® (cyclosporine) is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Beauveria nive*a.

Chemically, cyclosporine is designated as [*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-amino-butyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl).

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) are available in 25 mg and 100 mg strengths.

Each 25 mg capsule contains:
cyclosporine, USP..... 25 mg
alcohol, USP dehydrated ..... max 12.7% by volume

Each 100 mg capsule contains:
cyclosporine, USP..... 100 mg
alcohol, USP dehydrated ..... max 12.7% by volume

Inactive Ingredients: corn oil, gelatin, glycerol, Labrafil M 2125 CS (polyoxyethylated glycolysed glycerides), red iron oxide (25 mg and 100 mg capsule only), sorbitol, titanium dioxide, and other ingredients.

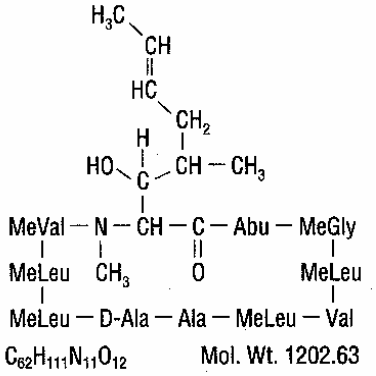
Sandimmune® Oral Solution (cyclosporine oral solution, USP) is available in 50 mL bottles.

Each mL contains:
cyclosporine, USP..... 100 mg
alcohol, Ph. Helv..... 12.5% by volume
dissolved in an olive oil, Ph. Helv./Labrafil M 1944 CS (polyoxyethylated oleic glycerides) vehicle which must be further diluted with milk, chocolate milk, or orange juice before oral administration.

Sandimmune® Injection (cyclosporine injection, USP) is available in a 5 mL sterile ampul for I.V. administration.

Each mL contains:
cyclosporine, USP ....50 mg
*Cremophor® EL (polyoxyethylated castor oil)..... 650 mg
alcohol, Ph. Helv..... 32.9% by volume
nitrogen .....qs
which must be diluted further with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use.

The chemical structure of cyclosporine (also known as cyclosporin A) is



CLINICAL PHARMACOLOGY

Sandimmune® (cyclosporine) is a potent immunosuppressive agent which in animals prolongs survival of allogeneic transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine, and lung. Sandimmune® (cyclosporine) has been demonstrated to suppress some humoral immunity and to a greater extent, cell-mediated reactions such as allograft rejection, delayed hypersensitivity,

experimental allergic encephalomyelitis, Freund's adjuvant arthritis, and graft vs. host disease in many animal species for a variety of organs.

Successful kidney, liver, and heart allogeneic transplants have been performed in man using Sandimmune® (cyclosporine).

The exact mechanism of action of Sandimmune® (cyclosporine) is not known. Experimental evidence suggests that the effectiveness of cyclosporine is due to specific and reversible inhibition of immunocompetent lymphocytes in the G_0- or G_1-phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Sandimmune® (cyclosporine) also inhibits lymphokine production and release including interleukin-2 or T-cell growth factor (TCGF).

No functional effects on phagocytic (changes in enzyme secretions not altered, chemotactic migration of granulocytes, macrophage migration, carbon clearance *in vivo*) or tumor cells (growth rate, metastasis) can be detected in animals. Sandimmune® (cyclosporine) does not cause bone marrow suppression in animal models or man.

The absorption of cyclosporine from the gastrointestinal tract is incomplete and variable. Peak concentrations (C_{max}) in blood and plasma are achieved at about 3.5 hours. C_{max} and area under the plasma or blood concentration/time curve (AUC) increase with the administered dose; for blood the relationship is curvilinear (parabolic) between 0 and 1400 mg. As determined by a specific assay, C_{max} is approximately 1.0 ng/mL/mg of dose for plasma and 2.7-1.4 ng/mL/mg of dose for blood (for low to high doses). Compared to an intravenous infusion, the absolute bioavailability of the oral solution is approximately 30% based upon the results in 2 patients. The bioavailability of Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) is equivalent to Sandimmune® Oral Solution, (cyclosporine oral solution, USP).

Cyclosporine is distributed largely outside the blood volume. In blood the distribution is concentration dependent. Approximately 33%-47% is in plasma, 4%-9% in lymphocytes, 5%-12% in granulocytes, and 41%-58% in erythrocytes. At high concentrations, the uptake by leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins.

The disposition of cyclosporine from blood is biphasic with a terminal half-life of approximately 19 hours (range: 10-27 hours). Elimination is primarily biliary with only 6% of the dose excreted in the urine.

Cyclosporine is extensively metabolized but there is no major metabolic pathway. Only 0.1% of the dose is excreted in the urine as unchanged drug. Of 15 metabolites characterized in human urine, 9 have been assigned structures. The major pathways consist of hydroxylation of the Cγ-carbon of 2 of the leucine residues, Cη-carbon hydroxylation, and cyclic ether formation (with oxidation of the double bond) in the side chain of the amino acid 3-hydroxyl-*N*,4-dimethyl-L-2-amino-6-octenoic acid and *N*-demethylation of *N*-methyl leucine residues. Hydrolysis of the cyclic peptide chain or conjugation of the aforementioned metabolites do not appear to be important biotransformation pathways.

INDICATIONS AND USAGE

Sandimmune® (cyclosporine) is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. It is always to be used with adrenal corticosteroids. The drug may also be used in the treatment of chronic rejection in patients previously treated with other immunosuppressive agents.

Because of the risk of anaphylaxis, Sandimmune® Injection (cyclosporine injection, USP) should be reserved for patients who are unable to take the soft gelatin capsules or oral solution.

CONTRAINDICATIONS

Sandimmune® Injection (cyclosporine injection, USP) is contraindicated in patients with a hypersensitivity to Sandimmune® (cyclosporine) and/or Cremophor® EL (polyoxyethylated castor oil).

WARNINGS

(See boxed WARNINGs): Sandimmune® (cyclosporine), when used in high doses, can cause hepatotoxicity and nephrotoxicity.

It is not unusual for serum creatinine and BUN levels to be elevated during Sandimmune® (cyclosporine) therapy. These elevations in renal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated before dosage adjustment is initiated.

Nephrotoxicity has been noted in 25% of cases of renal transplantation, 38% of cases of cardiac transplantation, and 37% of cases of liver transplantation. Mild nephrotoxicity was generally noted 2-3 months after transplant and consisted of an arrest in the fall of the preoperative elevations of BUN and creatinine at a range of 35-45 mg/dl and 2.0-2.5 mg/dl respectively. These elevations were often responsive to dosage reduction.

More overt nephrotoxicity was seen early after transplantation and was characterized by a rapidly rising BUN and creatinine. Since these events are similar to rejection episodes care must be taken to differentiate between them. This form of nephrotoxicity is usually responsive to Sandimmune® (cyclosporine) dosage reduction.

Although specific diagnostic criteria which reliably differentiate renal graft rejection from drug toxicity have not been found, a number of parameters have been significantly associated to one or the other. It should be noted however, that up to 20% of patients may have simultaneous nephrotoxicity and rejection.

Nephrotoxicity vs Rejection

Parameter	Nephrotoxicity	Rejection
History	Donor > 50 years old or hypotensive	Antidonor immune response
	Prolonged kidney preservation	Retransplant patient
	Prolonged anastomosis time	
	Concomitant nephrotoxic drugs	
Clinical	Often > 6 weeks postop[b]	Often < 4 weeks postop[b]
	Prolonged initial nonfunction	Fever > 37.5°C
	(acute tubular necrosis)	Weight gain > 0.5 kg
		Graft swelling and tenderness
		Decrease in daily urine volume > 500 mL (or 50%)
Laboratory	CyA serum trough level > 200 ng/mL	CyA serum trough level < 150 ng/mL
	Gradual rise in Cr (< 0.15 mg/dl/day)[a]	Rapid rise in Cr (> 0.3 mg/dl/day)[a]
	Cr plateau < 25% above baseline	Cr > 25% above baseline
	BUN/Cr ≥ 20	BUN/Cr < 20
Biopsy	Arteriolopathy (medial hypertrophy[a], hyalinosis, nodular deposits, intimal thickening, endothelial vacuolization, progressive scarring)	Endovasculitis[c] (proliferation[a], intimal arteritis[b], necrosis, sclerosis)
	Tubular atrophy, isometric vacuolization, isolated calcifications	Tubulitis with RBC[b] and WBC[b] casts, Some irregular vacuolization
	Minimal edema	Interstitial edema[c] and hemorrhage[b]
	Mild focal infiltrates[c]	Diffuse moderate to severe mononuclear infiltrates[d]
	Diffuse interstitial fibrosis, often striped form	Glomerulitis (mononuclear cells)[c]

Aspiration Cytology	CyA deposits in tubular and endothelial cells Fine isometric vacuolization of tubular cells	Inflammatory infiltrate with mononuclear phagocytes, macrophages, lymphoblastoid cells, and activated T-cells These strongly express HLA-DR antigens
Urine Cytology	Tubular cells with vacuolization and granularization	Degenerative tubular cells, plasma cells, and hocyturia > 20% of sediment
Manometry	Intracapsular pressure < 40 mm Hg[b]	Intracapsular pressure > 40 mm Hg[b]
Ultra-sonography	Unchanged graft cross-sectional area	Increase in graft cross-sectional area AP diameter ≥Transverse diameter
Magnetic Resonance Imagery	Normal appearance	Loss of distinct corticomedullary junction, swelling, image intensity of parachyma approaching that of psoas, loss of hilar fat
Radionuclide Scan	Normal or generally decreased perfusion Decrease in tubular function (^{131}I-hippuran) > decrease in perfusion (^{99m}Tc DTPA)	Patchy arterial flow Decrease in perfusion > decrease in tubular function Increased uptake of Indium 111 labeled platelets or Tc-99m in colloid
Therapy	Responds to decreased Sandimmune® (cyclosporine)	Responds to increased steroids or antilymphocyte globulin

[a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$, [d]$p < 0.0001$

A form of chronic progressive cyclosporine-associated nephrotoxicity is characterized by serial deterioration in renal function and morphologic changes in the kidneys. From 5%-15% of transplant recipients will fail to show a reduction in a rising serum creatinine despite a decrease or discontinuation of cyclosporine therapy. Renal biopsies from these patients will demonstrate an interstitial fibrosis with tubular atrophy. In addition, toxic tubulopathy, peritubular capillary congestion, arteriolopathy, and a striped form of interstitial fibrosis with tubular atrophy may be present. Though none of these morphologic changes is entirely specific, a histologic diagnosis of chronic progressive cyclosporine-associated nephrotoxicity requires evidence of these.

When considering the development of chronic nephrotoxicity it is noteworthy that several authors have reported an association between the appearance of interstitial fibrosis and higher cumulative doses or persistently high circulating trough levels of cyclosporine. This is particularly true during the first 6 posttransplant months when the dosage tends to be highest and when, in kidney recipients, the organ appears to be most vulnerable to the toxic effects of cyclosporine. Among other contributing factors to the development of interstitial fibrosis in these patients must be included, prolonged perfusion time, warm ischemia time, as well as episodes of acute toxicity, and acute and chronic rejection. The reversibility of interstitial fibrosis and its correlation to renal function have not yet been determined.

Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated. In patients with persistent high elevations of BUN and creatinine who are unresponsive to dosage adjustments, consideration should be given to switching to other immunosuppressive therapy. In the event of severe and unremitting rejection, it is preferable to allow the kidney transplant to be rejected and removed rather than increase the Sandimmune® (cyclosporine) dosage to a very high level in an attempt to reverse the rejection.

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of

rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of Sandimmune® (cyclosporine) and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans. *(See ADVERSE REACTIONS)*

Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients.

Hepatotoxicity has been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of Sandimmune® (cyclosporine) were used and consisted of elevations of hepatic enzymes and bilirubin. The chemistry elevations usually decreased with a reduction in dosage.

As in patients receiving other immunosuppressants, those patients receiving Sandimmune® (cyclosporine) are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents. Because of the danger of oversuppression of the immune system, which can also increase susceptibility to infection, Sandimmune® (cyclosporine) should not be administered with other immunosuppressive agents except adrenal corticosteroids. The efficacy and safety of cyclosporine in combination with other immunosuppressive agents have not been determined.

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone.

Encephalopathy has been described both in post-marketing reports and in the literature. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances. In many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. Predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high cyclosporine blood concentrations, and graft-versus-host disease have been noted in many but not all of the reported cases. The changes in most cases have been reversible upon discontinuation of cyclosporine, and in some cases improvement was noted after reduction of dose. It appears that patients receiving liver transplant are more susceptible to encephalopathy than those receiving kidney transplant.

Rarely (approximately 1 in 1000), patients receiving Sandimmune® Injection (cyclosporine injection, USP) have experienced anaphylactic reactions. Although the exact cause of these reactions is unknown, it is believed to be due to the Cremophor® EL (polyoxyethylated castor oil) used as the vehicle for the I.V. formulation. These reactions have consisted of flushing of the face and upper thorax, acute respiratory distress with dyspnea and wheezing, blood pressure changes, and tachycardia. One patient died after respiratory arrest and aspiration pneumonia. In some cases, the reaction subsided after the infusion was stopped.

Patients receiving Sandimmune® Injection (cyclosporine injection, USP) should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If anaphylaxis occurs, the infusion should be stopped. An aqueous solution of epinephrine 1:1000 should be available at the bedside as well as a source of oxygen.

Anaphylactic reactions have not been reported with the soft gelatin capsules or oral solution which lack Cremophor® EL (polyoxyethylated castor oil). In fact, patients experiencing anaphylactic reactions have been treated subsequently with the soft gelatin capsules or oral solution without incident.

Care should be taken in using Sandimmune® (cyclosporine) with nephrotoxic drugs. *(See PRECAUTIONS)*

Because Sandimmune® is not bioequivalent to Neoral®, conversion from Neoral® to Sandimmune® using a 1:1 ratio (mg/kg/day) may result in a lower cyclosporine blood concentration. Conversion from Neoral® to Sandimmune® should be made with increased blood concentration monitoring to avoid the potential of underdosing.

PRECAUTIONS

General

Patients with malabsorption may have difficulty in achieving therapeutic levels with Sandimmune® Soft Gelatin Capsules or Oral Solution.

Hypertension is a common side effect of Sandimmune® (cyclosporine) therapy. *(See ADVERSE REACTIONS)* Mild or moderate hypertension is more frequently encountered than severe hypertension and the incidence decreases over time. Antihypertensive therapy may be required. Control of blood pressure can be accomplished with any of the common antihypertensive agents. However, since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used. While calcium antagonists can be effective agents in treating cyclosporine-associated hypertension, care should be taken since interference with cyclosporine metabolism may require a dosage adjustment. *(See Drug Interactions)*

During treatment with Sandimmune® (cyclosporine), vaccination may be less effective; and the use of live attenuated vaccines should be avoided.

Information for Patients

Patients should be advised that any change of cyclosporine formulation should be made cautiously and only under physician supervision because it may result in the need for a change in dosage.

Patients should be informed of the necessity of repeated laboratory tests while they are receiving the drug. They should be given careful dosage instructions, advised of the potential risks during pregnancy, and informed of the increased risk of neoplasia.

Patients using cyclosporine oral solution with its accompanying syringe for dosage measurement should be cautioned not to rinse the syringe either before or after use. Introduction of water into the product by any means will cause variation in dose.

Laboratory Tests

Renal and liver functions should be assessed repeatedly by measurement of BUN, serum creatinine, serum bilirubin, and liver enzymes.

Drug Interactions

All of the individual drugs cited below are well substantiated to interact with cyclosporine. In addition, concomitant non-steroidal anti-inflammatory drugs, particularly in the setting of dehydration, may potentiate renal dysfunction.

Drugs That May Potentiate Renal Dysfunction

Antibiotics	*Antineoplastic*	*Anti-Inflammatory Drugs*	*Gastrointestinal Agents*
gentamicin	melphalan	azapropazon	cimetidine
tobramycin		diclofenac	ranitidine
vancomycin		naproxen	
trimethoprim	*Antifungals*	sulindac	*Immunosuppressives*

with sulfamethoxazole	amphotericin B ketoconazole	colchicine	tacrolimus

Drugs That Alter Cyclosporine Concentrations:

Compounds that decrease cyclosporine absorption such as orlistat should be avoided. Cyclosporine is extensively metabolized by cytochrome P-450 3A. Substances that inhibit this enzyme could decrease metabolism and increase cyclosporine concentrations. Substances that are inducers of cytochrome P-450 activity could increase metabolism and decrease cyclosporine concentrations. Monitoring of circulating cyclosporine concentrations and appropriate Sandimmune® dosage adjustment are essential when these drugs are used concomitantly. (See Blood Concentration Monitoring)

Drugs That Increase Cyclosporine Concentrations

Calcium Channel Blockers	*Antifungals*	*Antibiotics*	*Glucocorticoids*	*Other Drugs*
diltiazem	fluconazole	clarithromycin	methylprednisolone	allopurinol
nicardipine	itraconazole	erythromycin		bromocriptine
verapamil	ketoconazole	quinupristin/ dalfopristin		danazol
				metoclopromide
				colchicine
				amiodarone

The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 3A and thus could potentially increase the concentrations of cyclosporine, however no formal studies of the interaction are available. Care should be exercised when these drugs are administered concomitantly.

Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine, thus should be avoided.

Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations

Antibiotics	*Anticonvulsants*	*Other Drugs/Dietary Supplements*
nafcillin	carbamazepine	octreotide
rifampin	phenobarbital	ticlopidine
	phenytoin	orlistat
		St. John's Wort

There have been reports of a serious drug interaction between cyclosporine and the herbal dietary supplement, St. John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss.

Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these two drugs are administered concomitantly.

Nonsteroidal Anti-inflammatory Drug (NSAID) Interactions: Clinical status and serum creatinine should be closely monitored when cyclosporine is used with nonsteroidal anti-inflammatory agents in rheumatoid arthritis patients. *(See WARNINGS)*

Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function, as determined by ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) and (*p*-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood levels of cyclosporine, it has been associated with approximate doubling of diclofenac blood levels and occasional reports of reversible decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

Methotrexate Interaction: Preliminary data indicate that when methotrexate and cyclosporine were co-administered to rheumatoid arthritis patients (N=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine concentrations do not appear to have been altered (N=6).

Other Drug Interactions: ~~Reduced clearance of prednisolone, digoxin, and lovastatin has been observed when these drugs are administered with cyclosporine. In addition, a decrease in the apparent volume of distribution of digoxin has been reported after cyclosporine administration. Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin.~~
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 need 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.

Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur.

During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided. ~~Myositis has occurred with concomitant lovastatin,~~ ~~frequent~~ Frequent gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone have been reported.

Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive concurrent cyclosporine because of the possibility of excessive immunosuppression.

For additional information on Cyclosporine Drug Interactions please contact Novartis Medical Affairs Department at 888-NOW-NOVA (888-669-6682).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Cyclosporine gave no evidence of mutagenic or teratogenic effects in appropriate test systems. Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. *(See Pregnancy)*

Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.

No impairment in fertility was demonstrated in studies in male and female rats.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A recent study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE), at high concentrations in this system.

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

Pregnancy

Pregnancy Category C. Sandimmune® Oral Solution (cyclosporine oral solution, USP) has been shown to be embryo- and fetotoxic in rats and rabbits when given in doses 2-5 times the human dose. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), Sandimmune® Oral Solution (cyclosporine oral solution, USP) was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. In the well-tolerated dose range (rats at up to 17 mg/kg/day and rabbits at up to 30 mg/kg/day), Sandimmune® Oral Solution (cyclosporine oral solution, USP) proved to be without any embryolethal or teratogenic effects.

There are no adequate and well-controlled studies in pregnant women. Sandimmune® (cyclosporine) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The following data represent the reported outcomes of 116 pregnancies in women receiving Sandimmune® (cyclosporine) during pregnancy, 90% of whom were transplant patients, and most of whom received Sandimmune® (cyclosporine) throughout the entire gestational period. Since most of the patients were not prospectively identified, the results are likely to be biased toward negative outcomes. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. It is not possible to separate the effects of Sandimmune® (cyclosporine) on these pregnancies from the effects of the other immunosuppressants, the underlying maternal disorders, or other aspects of the transplantation milieu. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, preeclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility and fetoplacental dysfunction. Preterm delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%. In a report of 23 children followed up to 4 years, postnatal development was said to be normal. More information on cyclosporine use in pregnancy is available from Novartis Pharmaceuticals Corporation.

Nursing Mothers

Since Sandimmune® (cyclosporine) is excreted in human milk, nursing should be avoided.

Pediatric Use

Although no adequate and well-controlled studies have been conducted in children, patients as young as 6 months of age have received the drug with no unusual adverse effects.

Geriatric Use

Clinical studies of Sandimmune did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses 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.

ADVERSE REACTIONS

The principal adverse reactions of Sandimmune® (cyclosporine) therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.

Hypertension, which is usually mild to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

Glomerular capillary thrombosis has been found in patients treated with cyclosporine and may progress to graft failure. The pathologic changes resemble those seen in the hemolytic-uremic syndrome and include thrombosis of the renal microvasculature, with platelet-fibrin thrombi occluding glomerular capillaries and afferent arterioles, microangiopathic hemolytic anemia, thrombocytopenia, and decreased renal function. Similar findings have been observed when other immunosuppressives have been employed posttransplantation.

Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine therapy. Although magnesium-depletion studies in normal subjects suggest that hypomagnesemia is associated with neurologic disorders, multiple factors, including hypertension, high dose methylprednisolone, hypocholesterolemia, and nephrotoxicity associated with high plasma concentrations of cyclosporine appear to be related to the neurological manifestations of cyclosporine toxicity.

The following reactions occurred in 3% or greater of 892 patients involved in clinical trials of kidney, heart, and liver transplants:

Body System/ Adverse Reactions	Randomized Kidney Patients		All Sandimmune® (cyclosporine) Patients		
	Sandimmune® (N=227) %	Azathioprine (N=228) %	Kidney (N=705) %	Heart (N=112) %	Liver (N=75) %
Genitourinary					
Renal Dysfunction	32	6	25	38	37
Cardiovascular					
Hypertension	26	18	13	53	27
Cramps	4	< 1	2	< 1	0
Skin					
Hirsutism	21	< 1	21	28	45
Acne	6	8	2	2	1
Central Nervous System					
Tremor	12	0	21	31	55
Convulsions	3	1	1	4	5
Headache	2	< 1	2	15	4
Gastrointestinal					
Gum Hyperplasia	4	0	9	5	16
Diarrhea	3	< 1	3	4	8
Nausea/Vomiting	2	< 1	4	10	4
Hepatotoxicity	< 1	< 1	4	7	4
Abdominal Discomfort	< 1	0	< 1	7	0
Autonomic Nervous System					
Paresthesia	3	0	1	2	1
Flushing	< 1	0	4	0	4
Hematopoietic					
Leukopenia	2	19	< 1	6	0
Lymphoma	< 1	0	1	6	1
Respiratory					
Sinusitis	< 1	0	4	3	7
Miscellaneous					
Gynecomastia	< 1	0	< 1	4	3

The following reactions occurred in 2% or less of patients: allergic reactions, anemia, anorexia, confusion, conjunctivitis, edema, fever, brittle fingernails, gastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic ulcer, thrombocytopenia, tinnitus.

The following reactions occurred rarely: anxiety, chest pain, constipation, depression, hair breaking, hematuria, joint pain, lethargy, mouth sores, myocardial infarction, night sweats, pancreatitis, pruritus, swallowing difficulty, tingling, upper GI bleeding, visual disturbance, weakness, weight loss.

Renal Transplant Patients in Whom Therapy Was Discontinued			
	Randomized		All Sandimmune® Patients
	Sandimmune® (N=227)	Azathioprine (N=228)	(N=705)
Reason for Discontinuation	**%**	**%**	**%**
Renal Toxicity	5.7	0	5.4
Infection	0	0.4	0.9
Lack of Efficacy	2.6	0.9	1.4
Acute Tubular Necrosis	2.6	0	1.0
Lymphoma/Lymphoproliferative Disease	0.4	0	0.3
Hypertension	0	0	0.3
Hematological Abnormalities	0	0.4	0
Other	0	0	0.7

Sandimmune® (cyclosporine) was discontinued on a temporary basis and then restarted in 18 additional patients.

Infectious Complications in the Randomized Renal Transplant Patients		
	Sandimmune® Treatment (N=227)	Standard Treatment* (N=228)
Complication	**% of Complications**	**% of Complications**
Septicemia	5.3	4.8
Abscesses	4.4	5.3
Systemic Fungal Infection	2.2	3.9
Local Fungal Infection	7.5	9.6
Cytomegalovirus	4.8	12.3
Other Viral Infections	15.9	18.4
Urinary Tract Infections	21.1	20.2
Wound and Skin Infections	7.0	10.1
Pneumonia	6.2	9.2

*Some patients also received ALG.

Cremophor® EL (polyoxyethylated castor oil) is known to cause hyperlipemia and electrophoretic abnormalities of lipoproteins. These effects are reversible upon discontinuation of treatment but are usually not a reason to stop treatment.

OVERDOSAGE

There is a minimal experience with overdosage. Because of the slow absorption of Sandimmune® Soft Gelatin Capsules or Oral Solution, forced emesis would be of value up to 2 hours after administration. Transient hepatotoxicity and nephrotoxicity may occur which should resolve following drug withdrawal. General supportive measures and symptomatic treatment should be followed in all cases of overdosage. Sandimmune® (cyclosporine) is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion. The oral LD_{50} is 2329 mg/kg in mice, 1480 mg/kg in rats, and > 1000 mg/kg in rabbits. The I.V. LD_{50} is 148 mg/kg in mice, 104 mg/kg in rats, and 46 mg/kg in rabbits.

DOSAGE AND ADMINISTRATION

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP): Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP) have decreased bioavailability in comparison to Neoral® Soft Gelatin Capsules (cyclosporine capsules, USP) MODIFIED and Neoral® Oral Solution (cyclosporine oral solution, USP) MODIFIED. Sandimmune® and Neoral® are not bioequivalent and cannot be used interchangeably without physician supervision.

The initial oral dose of Sandimmune® (cyclosporine) should be given 4-12 hours prior to transplantation as a single dose of 15 mg/kg. Although a daily single dose of 14-18 mg/kg was used in most clinical trials, few centers continue to use the highest dose, most favoring the lower end of the scale. There is a trend towards use of even lower initial doses for renal transplantation in the ranges of 10-14 mg/kg/day. The initial single daily dose is continued postoperatively for 1-2 weeks and then tapered by 5% per week to a maintenance dose of 5-10 mg/kg/day. Some centers have successfully tapered the maintenance dose to as low as 3 mg/kg/day in selected *renal* transplant patients without an apparent rise in rejection rate.

(See Blood Level Monitoring below)

In pediatric usage, the same dose and dosing regimen may be used as in adults although in several studies children have required and tolerated higher doses than those used in adults.

Adjunct therapy with adrenal corticosteroids is recommended. Different tapering dosage schedules of prednisone appear to achieve similar results. A dosage schedule based on the patient's weight started with 2.0 mg/kg/day for the first 4 days tapered to 1.0 mg/kg/day by 1 week, 0.6 mg/kg/day by 2 weeks, 0.3 mg/kg/day by 1 month, and 0.15 mg/kg/day by 2 months and thereafter as a maintenance dose. Another center started with an initial dose of 200 mg tapered by 40 mg/day until reaching 20 mg/day. After 2 months at this dose, a further reduction to 10 mg/day was made. Adjustments in dosage of prednisone must be made according to the clinical situation.

To make Sandimmune® Oral Solution (cyclosporine oral solution, USP) more palatable, the oral solution may be diluted with milk, chocolate milk, or orange juice preferably at room temperature. Patients should avoid switching diluents frequently. Sandimmune® Soft Gelatin Capsules and Oral Solution should be administered on a consistent schedule with regard to time of day and relation to meals.

Take the prescribed amount of Sandimmune® (cyclosporine) from the container using the dosage syringe supplied after removal of the protective cover, and transfer the solution to a glass of milk, chocolate milk, or orange juice. Stir well and drink at once. Do not allow to stand before drinking. It is best to use a glass container and rinse it with more diluent to ensure that the total dose is taken. After use, replace the dosage syringe in the protective cover. Do not rinse the dosage syringe with water or other cleaning agents either before or after use. If the dosage syringe requires cleaning, it must be completely dry before resuming use. Introduction of water into the product by any means will cause variation in dose.

Sandimmune® Injection (cyclosporine injection, USP)

FOR INFUSION ONLY

Note: Anaphylactic reactions have occurred with Sandimmune® Injection (cyclosporine injection, USP). *(See WARNINGS)*

Patients unable to take Sandimmune® Soft Gelatin Capsules or Oral Solution pre- or postoperatively may be treated with the I.V. concentrate**. Sandimmune® Injection (cyclosporine injection, USP) is administered at 1/3 the oral dose.** The initial dose of Sandimmune® Injection (cyclosporine injection, USP) should be given 4-12 hours prior to transplantation as a single I.V. dose of 5-6 mg/kg/day. This daily single dose is continued postoperatively until the patient can tolerate the soft gelatin capsules or oral solution. Patients should be switched to Sandimmune® Soft Gelatin Capsules or Oral Solution as soon as possible after surgery. In pediatric usage, the same dose and dosing regimen may be used, although higher doses may be required.

Adjunct steroid therapy is to be used. *(See aforementioned)*

Immediately before use, the I.V. concentrate should be diluted 1 mL Sandimmune® injection (cyclosporine injection, USP) in 20 mL-100 mL 0.9% Sodium Chloride Injection or 5% Dextrose Injection and given in a slow intravenous infusion over approximately 2-6 hours.

Diluted infusion solutions should be discarded after 24 hours.

The Cremophor® EL (polyoxyethylated castor oil) contained in the concentrate for intravenous infusion can cause phthalate stripping from PVC.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Blood Level Monitoring: Several study centers have found blood level monitoring of cyclosporine useful in patient management. While no fixed relationships have yet been established, in one series of 375 consecutive cadaveric renal transplant recipients, dosage was adjusted to achieve specific whole blood 24-hour trough levels of 100-200 ng/mL as determined by high-pressure liquid chromatography (HPLC).

Of major importance to blood level analysis is the type of assay used. The above levels are specific to the parent cyclosporine molecule and correlate directly to the new monoclonal specific radioimmunoassays (mRIA-sp). Nonspecific assays are also available which detect the parent compound molecule and various of its metabolites. Older studies often cited levels using a nonspecific assay which were roughly twice those of specific assays. Assay results are not interchangeable and their use should be guided by their approved labeling. If plasma specimens are employed, levels will vary with the temperature at the time of separation from whole blood. Plasma levels may range from 1/2-1/5 of whole blood levels. Refer to individual assay labeling for complete instructions. In addition, *Transplantation Proceedings* (June 1990) contains position papers and a broad consensus generated at the Cyclosporine-Therapeutic Drug Monitoring conference that year. Blood level monitoring is not a replacement for renal function monitoring or tissue biopsies.

HOW SUPPLIED

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP)

25 mg: Oblong, pink, branded " S 78/240". Unit dose packages of 30 capsules, 3 blister cards of 10 capsules NDC 0078-0240-15

100 mg: Oblong, dusty rose, branded " S 78/241". Unit dose packages of 30 capsules, 3 blister cards of 10 capsules NDC 0078-0241-15

***Store and Dispense*:** Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature]

An odor may be detected upon opening the unit dose container, which will dissipate shortly thereafter. This odor does not affect the quality of the product.

Sandimmune® Oral Solution (cyclosporine oral solution, USP): Supplied in 50 mL bottles containing 100 mg of cyclosporine per mL (NDC 0078-0110-22). A dosage syringe is provided for dispensing.

Store and Dispense: In the original container at temperatures below 30°C (86°F). Do not store in the refrigerator. Protect from freezing. Once opened, the contents must be used within 2 months.

Sandimmune® Injection (cyclosporine injection, USP*)*

FOR INTRAVENOUS INFUSION

Supplied as a 5 mL sterile ampul containing 50 mg of cyclosporine per mL, in boxes of 10 ampuls (NDC 0078-0109-01).

Store and Dispense: At temperatures below 30°C (86°F) and protected from light.

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP)

Manufactured by:
R.P. Scherer GmbH, Eberbach/Baden, Germany

Distributed by:
Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936

Sandimmune® Oral Solution (cyclosporine oral solution, USP)

Manufactured by:
Novartis Pharma S.A., Huningue, France

Distributed by:
Novartis Pharmacueticals Corporation, East Hanover, New Jersey 07936

Sandimmune® Injection (cyclosporine injection, USP)

FOR INFUSION ONLY

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

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