INSTRUCTIONS TO AUTHORS

Send manuscripts to the Editor:

Jared J. Grantham, M.D.
JASN
University of Kansas Medical Center .
3901 Rainbow Blvd.
Kansas City, Kansas 66160-7361

The *Journal of the American Society of Nephrology* will publish original manuscripts judged by peers to be of high quality and relevant to the broad field of Nephrology. Nephrology is an alliance of scientists and physicians who seek to understand the functions of the kidneys and the means to improve the medical care of individuals with renal disease. The strength and vitality of the discipline radiate, historically, from the dynamic interaction between the basic and the clinical sciences. The *Journal* strives to nurture this relationship by providing the means for communicating to nephrologists and others in related specialities critical information of broad significance in the field. Subjects appropriate for the *Journal* include, but are not restricted to:

- **clinical nephrology**
- **renal and epithelial physiology**
- **biochemistry**
- **pathology and immunology**
- **cellular and molecular biology**
- **renal pathophysiology**
- **body fluid**
- **electrolyte and acid-base metabolism**
- **hypertension**
- **dialysis**
- **renal transplantation**

General Information

Manuscripts are of four types: **Concise Reports, Comprehensive Studies, Comments** and **Letters to the Editor.**

Concise Reports should contain in not more than 2500 words (including abstract, figures, tables and references) important new observations of sufficient interest to nephrologists to warrant **rapid** publication. **Comprehensive Studies** are traditional full length papers that address research questions with exhaustive experimental design and methodology. **Comments** are brief reports limited to fewer than 1000 words (including introductory paragraph describing the origins and chief conclusions, one figure or table, and fewer than 15 references) that are preliminary, negative or confirmatory. Highly innovative technical advances will be considered. **Letters to the Editor** should be confined to brief scientific commentary about articles published in JASN or to topics of general interest to nephrologists. **Reviews** of basic and clinical topics of interest to the readership will be solicited by the editors.

In the cover letter, designate one author as correspondent. All coauthors should have contributed in substantial ways to the study and manuscript preparation.

Include in the cover letter a statement explaining why the research is especially important. It is at this stage that claims of new or novel findings ("This is the first . . .") should be mentioned, not within the text of the paper. The journal office may solicit editorials to accompany articles that are especially newsworthy or controversial.

Include in the cover letter the names, addresses, telephone and areas of expertise of at least five individuals (peers) who may serve, at the discretion of the editors, as reviewers of the manuscript.

American Renal Training Centers

This series is to serve as a forum for concise yet comprehensive updates on a subject of current interest in clinical nephrology, centered around a patient presentation. The articles are to be authored by fellows in training under the guidance of a senior faculty member. The manuscripts should include:

- **A brief focused patient presentation. If pertinent a radiologic or histologic figure can complement it.**
- **Background—not to exceed one paragraph.**
- **Review of clinical and pathologic presentation of the entity.**
- **An overview of the etiology and the pathogenetic mechanism of the disease.**
- **Review of therapeutic approaches.**
- **A summary—conclusion paragraph that contains a "take home message", and if at all possible, reverts back to the patient.**
- **No more than three tables or figures that confer a critical message or summarize information from various sources.**
- **References should not exceed 20.**
- **The overall length of the communication should not exceed 15 double-spaced typewritten pages.**

Copyright Transfer: Include one of the two following statements on copyright interests signed by **all** authors.

"In consideration of the American Society of Nephrology's taking action in reviewing and editing this submission, the author(s) undersigned hereby transfer(s), assign(s) or otherwise convey(s) all copyright ownership to the ASN in the event this work is published by the ASN.

Federal Government: "I was an employee of the United States Federal Government when this work was investigated and prepared for publication: therefore, it is not protected by the Copyright Act and there is no copyright of which the ownership can be transferred."

These signatures, that **must** accompany the cover letter, indicate that each author approved the final version of the manuscript and is prepared to take public responsibility for the work.

It is the policy of the *Journal* to expedite the review process. Authors will receive within 10 days of receipt at the editorial office, acknowledgment that their manuscript has been forwarded to an associate editor and reviewing editors. Manuscripts that are judged by a panel of screening editors to fall outside the range of interest of the readership or that fail to satisfy technical requirements will be promptly returned to the authors without further review. In order to reduce postage expense, manuscripts sent to outside reviewers as privileged communications will be destroyed and not returned to the authors. Glossy prints and photographs from rejected manuscripts will be returned to authors. Authors who have not received formal notification of manuscript review status 21 days following acknowledged receipt at the editorial office are encouraged to contact the editorial office for a status report.

Manuscript Preparation

• Submit an original manuscript and three photocopies, typed double-spaced in letter-quality print on one side only of standard (8½ × 11 inch) white bond paper.
• Manuscripts submitted as **Concise Reports** and **Comprehensive Studies** should be organized as follows: title page, abstract, introduction, methods, results, discussion, acknowledgments, tables, legends to figures, and references. **Comments** should contain: title page; introductory paragraph; methods, results and discussion; acknowledgements; table or figure legend; and references. A brief

description of methods may be included in the table or figure legends. **Letters to the Editor** will be edited and shortened in consultation with the author.

• On the **title page** type the full names, highest academic degrees and affiliations of all the authors. The title should not exceed 100 characters and spaces. Include an abbreviated title of not more than 40 characters and spaces.

• **Abstract:** State the problem considered, methods, results, and conclusions in less than 250 words. List 5 index terms not included in the title.

• Use of Systeme International d'Unites (SI) for measurements is preferred throughout the manuscript. Factors for converting frequently used components can be found in JAMA (1989:262:200–202).

• Use generic names of drugs.

• Do not use abbreviations in the title or abstract. Define unusual abbreviations on the first use in the body of the manuscript. A list of accepted abbreviations can be found in the July and January issues of JASN.

• Text footnotes should be typed on a separate page.

• Foreign contributors, whose language is not English, should obtain help from colleagues who are proficient in scientific English.

• It is assumed that all clinical investigation described in the manuscript was conducted in accordance with the guidelines proposed in the *Declaration of Helsinki.* Document in the manuscript that informed consent was obtained.

• It is assumed that all animal experimentation described in the manuscript was conducted in accord with the NIH Guide for the Care and Use of Laboratory Animals, and the manuscript should contain a statement to that effect.

• **Tables:** Double-space on separate sheets of standard-sized white bond paper. Title all tables and number in order of appearance in the text. Footnotes may include methods in *Concise Reports* and *Comments.* Use superscript letters to indicate footnotes typed at the bottom of the table.

• **Figures:** Include clear photocopies of the figures with the **original and each copy** of the manuscript as well as three sets of 5 × 7 inch glossy photographs for all line drawings, clearly labeled on the back. Graphs must be of professional quality: computer-generated graphs should be of laser quality. High contrast prints for roentgenographic photographs and electron micrographs are essential; halftones may be custom printed on special paper from engravings approved by the author and at the author's expense. Photomicrographs should be sized to fit one column (8 cm) or two columns (17 cm); the maximum plate size is 17 x 22 cm. Legends should state degree of magnification or scale bars should be used on the photograph and specified in the length.

• **References:** Cite in numerical order, only one reference to a number. Citation of unpublished observations or personal communications (include separately permission to quote from appropriate individual) should be placed in the text in parentheses.

Journal articles, abstracts and books: List all authors when six or fewer; when seven or more, list only the first three and add *et al.* Journal names should be abbreviated according to the BIOSIS list of serials.

• **Examples:**

1. Abramson RG, King VF, Reif MC, Leal-Pinto E, Baruch SB: Urate uptake in membrane vesicles of rat renal cortex: Effect of copper. Am J Physiol 1982;242:F158–F170.
2. Couser WG. Glomerular diseases. In: Stein J. ed. Internal Medicine. 2nd ed. Boston: Little Brown: 1987:834–861.

• **Manuscripts by Electronic Diskettes—Preparation of Disks:**

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• **Manuscript checklist**

1. Include the original typed manuscript and three photocopies.
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3. Include in cover letter: a) copyright transfer statement. b) list of five candidates for peer review.
4. Include all authors' personal signatures.
5. Designate a corresponding author and provide a telephone number and address.

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NEORAL® Soft Gelatin Capsules *(cyclosporine capsules for microemulsion)*
NEORAL® Oral Solution *(cyclosporine oral solution for microemulsion)*

Caution: Federal law prohibits dispensing without prescription.

BRIEF SUMMARY: Please see package insert for full prescribing information.

WARNING: Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Neoral®. 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.

Neoral® may be administered with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the degree of immunosuppression.

Neoral® Soft Gelatin Capsules (cyclosporine capsules for microemulsion) and Neoral® Oral Solution (cyclosporine oral solution for microemulsion) have increased bioavailability in comparison to Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP). Neoral® and Sandimmune® are not bioequivalent and cannot be used interchangeably without physician supervision. It is recommended that cyclosporine blood concentrations be monitored in patients taking Neoral® and that dose adjustments be made in order to avoid toxicity due to high concentrations and possible organ rejection due to low concentrations. For a given trough concentration, cyclosporine exposure will be greater with Neoral® than with Sandimmune®. If a patient who is receiving exceptionally high doses of Sandimmune® is converted to Neoral®, particular caution should be exercised. Comparison of blood concentrations in the published literature with blood concentrations obtained using current assays must be done with detailed knowledge of the assay methods employed.

INDICATIONS AND USAGE: Neoral® is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Neoral® has been used in combination with azathioprine and corticosteroids.

CONTRAINDICATIONS: Neoral® is contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

WARNINGS: *(See boxed WARNINGS)*

Cyclosporine, the active ingredient of Neoral®, can cause nephrotoxicity and hepatotoxicity when used in high doses.

It is not unusual for serum creatinine and BUN levels to be elevated during 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.

Based on the historical Sandimmune® experience with oral solution, nephrotoxicity associated with cyclosporine had 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 renal transplant and consisted of an arrest in the fall of the pre-operative 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 cyclosporine 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 renal rejection episodes, care must be taken to differentiate between them. This form of nephrotoxicity is usually responsive to 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 with one or the other. It should be noted however, that up to 20% of patients may have simultaneous nephrotoxicity and rejection.

A form of a cyclosporine-associated nephropathy is characterized by serial deterioration in renal function and morphologic changes in the kidneys. From 5% to 15% of transplant recipients who have received cyclosporine will fail to show a reduction in rising serum creatinine despite a decrease or discontinuation of cyclosporine therapy. Renal biopsies from these patients will demonstrate one or several of the following alterations: tubular vacuolization, tubular microcalcifications, peritubular capillary congestion, arteriolopathy, and a striped form of interstitial fibrosis with tubular atrophy. Though none of these morphologic changes is entirely specific, a diagnosis of cyclosporine-associated structural nephrotoxicity requires evidence of these findings.

When considering the development of cyclosporine-associated nephropathy, 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 are 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. Reversibility of arteriolopathy has been reported after stopping cyclosporine or lowering the dosage.

Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated.

In the event of severe and unremitting rejection, when rescue therapy with pulse steroids and monoclonal antibodies fail to reverse the rejection episode, it may be preferable to switch to alternative immunosuppresive therapy rather than increase the Neoral® dose to excessive levels.

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 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 associated with cyclosporine use had 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 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 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 resulting in increased risk of infection or malignancy, a treatment regimen containing multiple immunosuppresants should be used with caution.

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

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

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

PRECAUTIONS: General: Cyclosporine is the active ingredient of Neoral®. Hypertension is a common side effect of cyclosporine therapy. *(See ADVERSE REACTIONS)* Mild or moderate hypertension is encountered more frequently 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. Calcium antagonists can be effective agents in treating cyclosporine-associated hypertension. However, care should be taken since interference with cyclosporine metabolism may require a dosage adjustment. *(See Drug Interactions)*

During treatment with 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. Patients should be advised of the potential risks during pregnancy and informed of the increased risk of neoplasia.

Patients should be given careful dosage instructions. Neoral® Oral Solution (cyclosporine oral solution for microemulsion) should be diluted, preferably with orange or apple juice that is at room temperature. Grapefruit and grapefruit juice affect metabolism of cyclosporine and should be avoided. The combination of Neoral® Oral Solution (cyclosporine oral solution for microemulsion) with milk can be unpalatable.

Patients should be advised to take Neoral® on a consistent schedule with regard to time of day and relation to meals.

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.

Drugs That May Potentiate Renal Dysfunction

Antibiotics	*Antifungals*	*Gastrointestinal Agents*
gentamicin	amphotericin B	cimetidine
tobramycin	ketoconazole	ranitidine
vancomycin	*Anti-inflammatory Drugs*	*Immunosuppressives*
trimethoprim with sulfamethoxazole	azapropazon	tacrolimus
Antineoplastics	diclofenac	
melphalan		

Careful monitoring of renal function should be practiced when Neoral® is used with nephrotoxic drugs.

Drugs That Alter Cyclosporine Levels: Cyclosporine is extensively metabolized. Cyclosporine concentrations may be influenced by drugs that affect microsomal enzymes, particularly cytochrome P-450 III-A. 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 Neoral® dosage adjustment are essential when these drugs are used concomitantly.

Drugs That Increase Cyclosporine Concentrations

Calcium Channel Blockers	*Antifungals*	*Antibiotics*	*Glucocorticoids*	*Other Drugs*
diltiazem	fluconazole	clarithromycin	methylprednisolone	allopurinol
nicardipine	itraconazole	erythromycin		bromocriptine
verapamil	ketoconazole			danazol
				metoclopramide

Drugs That Decrease Cyclosporine Concentrations

Antibiotics	*Anticonvulsants*	*Other Drugs*
nafcillin	carbamazepine	octreotide
rifampin	phenobarbital	ticlopidine
	phenytoin	

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.

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 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 gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone. Further information on drugs that have been reported to interact with cyclosporine is available from Sandoz Pharmaceuticals Corporation.

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, 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, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. Doses used in the mouse and rat studies were 0.01 to 0.16 times the clinical maintenance dose. 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 to be 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. Reduction or discontinuance of immunosuppression may cause the lesions to regress.

Pregnancy: ***Pregnancy Category C.*** Cyclosporine has been shown to be embryo- and fetotoxic in rats and rabbits following oral administration at maternally toxic doses. Fetal toxicity was noted in rats at 0.8 and rabbits at 5.4 times the human maintenance dose of 6.0 mg/kg, where dose corrections are based on body surface area. Cyclosporine was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations.

There are no adequate and well-controlled studies in pregnant women. Neoral® 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 cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders, including pre-eclampsia, 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%. Therefore, the risks and benefits of using Neoral® during pregnancy should be carefully weighed.

Nursing Mothers: Since cyclosporine is excreted in human milk, nursing should be avoided.

Pediatric Use: Although no adequate and well controlled studies have been completed in children, patients as young as one year of age have received Neoral® with no unusual adverse effects.

ADVERSE REACTIONS: The principal adverse reactions of 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.

In controlled studies, the nature, severity and incidence of the adverse events that were observed in 493 transplanted patients treated with Neoral® were comparable with those observed in 208 transplanted patients who received Sandimmune® in these same studies when the dosage of the two drugs was adjusted to achieve the same cyclosporine blood trough concentrations.

The following reactions occurred in 2% or less of Sandimmune®-treated 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.

Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the degree of immunosuppression.

Sandoz Pharmaceuticals Corporation, East Hanover, New Jersey 07936 SEPTEMBER 1995 38371902

Introducing

NEORAL®

cyclosporine capsules and oral solution for microemulsion

Please see brief summary of prescribing information on the following page.

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