CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-025

Approval Letter

ANDA 65-025

MAR 3 2000

Abbott Laboratories
Pharmaceutical Products Division
Attention: Rebecca Welch
D-491/AP6B-1
100 Abbott Park Road
Abbott Park, IL 60064-3500

Dear Madam:

This is in reference to your abbreviated new drug application dated August 14, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cyclosporine Oral Solution USP (MODIFIED), 100 mg/mL. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

Reference is also made to your amendments dated July 15, December 7, 1999, January 5, and January 21, 2000

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cyclosporine Oral Solution USP (MODIFIED), 100 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Neoral® Oral Solution, 100 mg/mL, of Novartis Pharmaceuticals Corp.).

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the

proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

3/3/00

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-025

FINAL PRINTED LABELING

Each mL contains:
cyclosporine, USP .....100 mg

Usual Dosage: See enclosure for prescribing information.

Store and dispense in tightly closed container at controlled room temperature 59°F to 86°F (15°C to 30°C). (See USP). Do not refrigerate or freeze. Once opened, the contents must be used within two months.

TM – Trademark
*Sandimmune® is a registered trademark of Novartis Pharmaceuticals Corp.
©Abbott
Abbott Laboratories
North Chicago, IL 60064, U.S.A.

Exp.
Lot
02-8187-2/R1

NDC 0074-7269-50

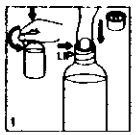
GENGRAF™
(cyclosporine oral solution, USP [MODIFIED])

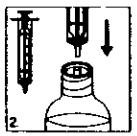
APPROVED
FEB 24 2000

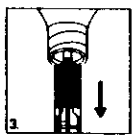
100 mg/mL 50 mL

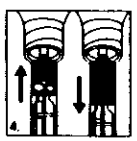
WARNING: Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) is NOT BIOEQUIVALENT to Sandimmune®* (cyclosporine oral solution, USP [NON-MODIFIED]). Do NOT use interchangeably without a physician's supervision.

℞ only









Precision syringe allows accurate dosing, less waste, less mess. **DO NOT RINSE SYRINGE BEFORE USE.**

1. To open, push down on child-resistant cap and turn. Push in bottle insert. The lip of insert should be flush to bottle.
2. Insert tip of syringe firmly into opening of bottle insert. Note, do not rinse syringe before use. If water gets into the product through the syringe or any other means, it will cause variation in dose.
3. Invert bottle. Draw-up the prescribed amount of Gengraf™ (cyclosporine oral solution, USP **[MODIFIED]**).
4. **If large bubbles form in syringe during withdrawal, empty the Gengraf™ solution back into the bottle and repeat withdrawal procedure.**
5. After use, wipe syringe with dry tissue, **do not rinse**. Store syringe in a clean, dry location. Note, the bottle insert should remain in the bottle. Reseal bottle with child-resistant cap.

EXP

LOT

GENGRAF™
(cyclosporine oral solution, USP **[MODIFIED]**)

Do not use if tamper-evident tape over carton top or bottom is broken or missing.

GENGRAF™
(cyclosporine oral solution, USP **[MODIFIED]**)
100 mg/mL

Each mL contains:
cyclosporine, USP .....100 mg

Usual Dosage: See enclosure for prescribing information.

WARNING: Gengraf™ (cyclosporine oral solution, USP **[MODIFIED]**) is **NOT BIOEQUIVALENT** to Sandimmune®* (cyclosporine oral solution, USP **[NON-MODIFIED]**). Do NOT use interchangeably without a physician's supervision.

Store and Dispense:
In the original container at controlled room temperature 59° to 86°F (15° to 30°C). (See USP). Use contents after opening within 2 months. Do not refrigerate. At temperatures less than 68°F (20°C), a gel may form; slight sediment or flakes may also form. Allow contents to reach room temperature to reverse these effects. There is no impact on product performance or dose.

TM – Trademark
*Sandimmune® is a registered trademark of Novartis Pharmaceuticals Corp.
©Abbott
Abbott Laboratories
North Chicago, IL 60064, U.S.A.

13-1896-2/R1

50 mL
NDC 0074-7269-50

GENGRAF™
(cyclosporine oral solution, USP **[MODIFIED]**)
100 mg/mL

APPROVED
FEB 24 2000

WARNING: Gengraf™ (cyclosporine oral solution, USP **[MODIFIED]**) is **NOT BIOEQUIVALENT** to Sandimmune®* (cyclosporine oral solution, USP **[NON-MODIFIED]**). Do NOT use interchangeably without a physician's supervision.

Each mL contains:
cyclosporine, USP .....100 mg

℞ only

Area for dispensing & pharmacy label.

GENGRAF™
(cyclosporine oral solution, USP **[MODIFIED]**)
100 mg/mL

0074726950

gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the coadministration of a variety of agents (*see PRECAUTIONS, Drug Interactions*). At least 25 metabolites have been identified from human bile, feces, blood, and urine. The biological activity of the metabolites and their contributions to toxicity are considerably less than those of the parent compound. The major metabolites (M1, M9, and M4N) result from oxidation at the 1-beta, 9-gamma, and 4-N-demethylated positions, respectively. At steady state following the oral administration of cyclosporine (NON-MODIFIED), the mean AUCs for blood concentrations of M1, M9 and M4N are about 70%, 21%, and 7.5% of the AUC for blood cyclosporine concentrations, respectively. Based on blood concentration data from stable renal transplant patients (13 patients administered cyclosporine (MODIFIED) and cyclosporine (NON-MODIFIED) in a crossover study), and bile concentration data from *de novo* liver transplant patients (4 administered cyclosporine (MODIFIED), 3 administered cyclosporine (NON-MODIFIED), the percentage of dose present as M1, M9, and M4N metabolites is similar when either cyclosporine (MODIFIED) or cyclosporine (NON-MODIFIED) is administered.

Excretion: Only 0.1% of a cyclosporine dose is excreted unchanged in the urine. Elimination is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in the urine. Neither dialysis nor renal failure alter cyclosporine clearance significantly.

Drug Interactions: (*see PRECAUTIONS, Drug Interactions*). When diclofenac or methotrexate was co-administered with cyclosporine in rheumatoid arthritis patients, the AUC of diclofenac and methotrexate, each was significantly increased (*see PRECAUTIONS, Drug Interactions*). No clinically significant pharmacokinetic interactions occurred between cyclosporine and aspirin, ibuprofen, piroxicam, or indomethacin.

Special Population: *Pediatric Population:* Pharmacokinetic data from pediatric patients administered cyclosporine (MODIFIED) or cyclosporine (NON-MODIFIED) are very limited. In 15 renal transplant patients aged 3-16 years, cyclosporine whole blood clearance after IV administration of cyclosporine (NON-MODIFIED) was 10.6±3.7 mL/min/kg (assay: Cyclo-trac specific RIA). In a study of 7 renal transplant patients aged 2-16, the cyclosporine clearance ranged from 9.8 to 15.5 mL/min/kg. In 9 liver transplant patients aged 0.6 to 5.6 years, clearance was 9.3±5.4 mL/min/kg (assay: HPLC).

In the pediatric population, cyclosporine (MODIFIED) also demonstrates an increased bioavailability as compared to cyclosporine (NON-MODIFIED). In 7 liver *de novo* transplant patients aged 1.4 to 10 years, the absolute bioavailability of cyclosporine (MODIFIED) was 43% (range 30% to 68%) and for cyclosporine (NON-MODIFIED) in the same individuals absolute bioavailability was 28% (range 17% to 42%).

Pediatric Pharmacokinetic Parameters (mean±SD)

Patient Population	Dose/day (mg/d)	Dose/weight (mg/kg/d)	AUC[1] (ng•hr/mL)	C_{max} (ng/mL)	CL/F (mL/min)	CL/F (mL/min/kg)
Stable liver transplant[2]						
Age 2-8, Dosed TID (N=9)	101±25	5.95±1.32	2163±801	629±219	285±94	16.6±4.3
Age 8-15, Dosed BID (N=8)	188±55	4.96±2.09	4272±1462	975±281	378±80	10.2±4.0
Stable liver transplant[3]						
Age 3, Dosed BID (N=1)	120	8.33	5832	1050	171	11.9
Age 8-15, Dosed BID (N=5)	158±55	5.51±1.91	4452±2475	1013±635	328±121	11.0±1.9
Stable liver transplant[3]						
Age 7-15, Dosed BID (N=5)	328±83	7.37±4.11	6922±1988	1827±487	418±143	8.7±2.9

[1]AUC was measured over one dosing interval.
[2]Assay: Cyclo-trac specific monoclonal radioimmunoassay.
[3]Assay: TDx specific monoclonal fluorescence polarization immunoassay.

Geriatric Population: Comparison of single dose data from both normal elderly volunteers (N=18, mean age 69 years) and elderly rheumatoid arthritis patients (N=16, mean age 68 years) to single dose data in young adult volunteers (N=16, mean age 26 years) showed no significant difference in the pharmacokinetic parameters.

CLINICAL TRIALS: Rheumatoid Arthritis: The effectiveness of cyclosporine (NON-MODIFIED) and cyclosporine (MODIFIED) in the treatment of severe rheumatoid arthritis was evaluated in five clinical studies involving a total of 728 cyclosporine treated patients and 273 placebo treated patients.

A summary of the results is presented for the "responder" rates per treatment group, with a responder being defined as a patient having *completed* the trial with a 20% improvement in the tender and the swollen joint count and a 20% improvement in 2 of 4 of investigator global, patient global, disability, and erythrocyte sedimentation rates (ESR) for the Studies 651 and 652 and 3 of 5 of investigator global, patient global, disability, visual analog pain, and ESR for Studies 2008, 654, and 302.

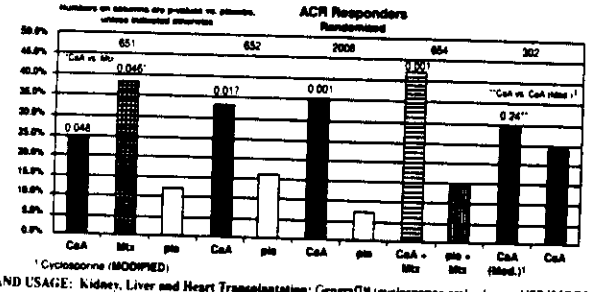
Study 651 enrolled 264 patients with active rheumatoid arthritis with at least 20 involved joints, who had *failed* at least one major RA drug, using a 3:3:2 randomization to one of the following three groups: (1) cyclosporine dosed at 2.5-5 mg/kg/day, (2) methotrexate at 7.5-15 mg/week, or (3) placebo. Treatment duration was 24 weeks. The mean cyclosporine dose at the last visit was 3.1 mg/kg/day. See Graph below.

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

Study 2008 enrolled 144 patients with active RA and >6 active joints who had unsuccessful treatment courses of aspirin and gold or Penicillamine. Patients were randomized to one of two treatment groups: (1) cyclosporine 2.5-5 mg/kg/day with adjustments after the first month to achieve a target trough level and (2) placebo. Treatment-duration was 24 weeks. The mean cyclosporine dose at the last visit was 3.63 mg/kg/day. See Graph below.

Study 654 enrolled 148 patients who remained with active joint counts of 6 or more despite treatment with maximally tolerated methotrexate doses for at least three months. Patients continued to take their current dose of methotrexate and were randomized to receive, in addition, one of the following medications: (1) cyclosporine 2.5 mg/kg/day with dose increases of 0.5 mg/kg/day at weeks 2 and 4 if there was no evidence of toxicity and further increases of 0.5 mg/kg/day at weeks 8 and 16 if a <30% decrease in active joint count occurred without any significant toxicity; dose decreases could be made at any time for toxicity or (2) placebo. Treatment duration was 24 weeks. The mean cyclosporine dose at the last visit was 2.8 mg/kg/day (range 1.3-4.1). See Graph below.

Study 302 enrolled 299 patients with severe active RA, 99% of whom were unresponsive or intolerant to at least one prior major RA drug. Patients were randomized to 1 of 2 treatment groups (1) cyclosporine (MODIFIED) and (2) cyclosporine (NON-MODIFIED), both of which were started at 2.5 mg/kg/day and increased after 4 weeks for inefficacy in increments of 0.5 mg/kg/day to a maximum of 5 mg/kg/day and decreased at any time for toxicity. Treatment duration was 24 weeks. The mean cyclosporine dose at the last visit was 2.91 mg/kg/day (range: 0.72-5.17) for cyclosporine (MODIFIED) and 3.27 mg/kg/day (range: 0.73-5.68) for cyclosporine (NON-MODIFIED). See Graph below.



[1] Cyclosporine (MODIFIED)

INDICATIONS AND USAGE: Kidney, Liver and Heart Transplantation: Gengraf™ (cyclosporine oral solution, USP (MODIFIED)) is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Cyclosporine (MODIFIED) has been used in combination with azathioprine and corticosteroids.

Rheumatoid Arthritis: Gengraf™ (cyclosporine oral solution, USP (MODIFIED)) is indicated for the treatment of patients with severe active, rheumatoid arthritis where the disease has not adequately responded to methotrexate. Gengraf™ can be used in combination with methotrexate in rheumatoid arthritis patients who do not respond adequately to methotrexate alone.

Psoriasis: Gengraf™ (cyclosporine oral solution, USP (MODIFIED)) is indicated for the treatment of *adult nonimmunocompromised* patients with severe (i.e., extensive and/or disabling), recalcitrant, plaque psoriasis who have failed to respond to at least one systemic therapy (e.g., PUVA, retinoids, or methotrexate) or in patients for whom other systemic therapies are contraindicated, or cannot be tolerated.

While rebound rarely occurs, most patients will experience relapse with Gengraf™ as with other therapies upon cessation of treatment.

CONTRAINDICATIONS: General: Gengraf™ (cyclosporine oral solution, USP (MODIFIED)) is contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

Rheumatoid Arthritis: Rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension or malignancies should not receive Gengraf™ (cyclosporine oral solution, USP (MODIFIED)).

Psoriasis: Psoriasis patients who are treated with Gengraf™ (cyclosporine oral solution, USP (MODIFIED)) should not receive concomitant PUVA or UVB therapy, methotrexate or other immunosuppressive agents, coal tar or radiation therapy. Psoriasis patients with abnormal renal function,

(No. 7269) 03-4918-R1-Rev Nov. 1999

GENGRAF™ Oral Solution

(cyclosporine oral solution, USP [MODIFIED])

Rx only

034918

WARNING

Only physicians experienced in the management of systemic immunosuppressive therapy for the indicated disease should prescribe Gengraf™ (cyclosporine oral solution, USP [MODIFIED]). At doses used in solid organ transplantation, only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should prescribe Gengraf™. 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.

Gengraf™, a systemic immunosuppressant, may increase the susceptibility to infection and the development of neoplasia. In kidney, liver, and heart transplant patients Gengraf™ may be administered with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the increase in the degree of immunosuppression in transplant patients.

Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) has increased bioavailability in comparison to Sandimmune®* (cyclosporine oral solution, USP [NON-MODIFIED]). Gengraf™ and Sandimmune®* are not bioequivalent and cannot be used interchangeably without physician supervision. For a given trough concentration, cyclosporine exposure will be greater with Gengraf™ than with Sandimmune®*. If a patient who is receiving exceptionally high doses of Sandimmune®* is converted to Gengraf™, particular caution should be exercised. Cyclosporine blood concentrations should be monitored in transplant and rheumatoid arthritis patients taking Gengraf™ to avoid toxicity due to high concentrations. Dose adjustments should be made in transplant patients to minimize possible organ rejection due to low concentrations. 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.

For Psoriasis Patients ***(see also Boxed WARNINGS above)***

Psoriasis patients previously treated with PUVA and to a lesser extent, methotrexate or other immunosuppressive agents, UVB, coal tar, or radiation therapy, are at an increased risk of developing skin malignancies when taking Gengraf™ (cyclosporine oral solution, USP [MODIFIED]).

Cyclosporine, the active ingredient in Gengraf™, in recommended dosages, can cause systemic hypertension and nephrotoxicity. The risk increases with increasing dose and duration of cyclosporine therapy. Renal dysfunction, including structural kidney damage, is a potential consequence of cyclosporine, and therefore, renal function must be monitored during therapy.

DESCRIPTION: Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) is a modified oral formulation of cyclosporine that forms a lipid-free aqueous dispersion in an aqueous environment.

NOTE: The nomenclature "Cyclosporine Oral Suspension for Microemulsion" has been changed throughout the insert to read "Cyclosporine, Oral Solution USP (MODIFIED)".

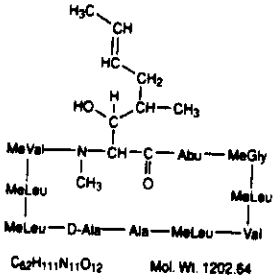
Cyclosporine, the active principle in Gengraf™ Oral Solution, is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Aphanocladium album*.

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).

Gengraf™ Oral Solution (cyclosporine oral solution, USP [MODIFIED]) is available in 50 mL bottles. Each mL contains: cyclosporine 100 mg/mL.

Inactive Ingredients: Polyoxyl 40 hydrogenated castor oil NF, propylene glycol USP, sorbitan monooleate NF.

The chemical structure for cyclosporine USP is:



$C_{62}H_{111}N_{11}O_{12}$ Mol. Wt. 1202.64

CLINICAL PHARMACOLOGY: Cyclosporine is a potent immunosuppressive agent that in animals prolongs survival of allogeneic transplants involving skin, kidney, liver, heart, pancreas, bone marrow, small intestine, and lung. Cyclosporine has been demonstrated to suppress some humoral immunity and to a greater extent, cell-mediated immune 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.

The effectiveness of cyclosporine results from specific and reversible inhibition of immunocompetent lymphocytes in the G_0- and 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. Cyclosporine also inhibits lymphokine production and release including interleukin-2.

No effects on phagocytic function (changes in enzyme secretions, chemotactic migration of granulocytes, macrophage migration, carbon clearance *in vivo*) have been detected in animals. Cyclosporine does not cause bone marrow suppression in animal models or man.

Pharmacokinetics: The immunosuppressive activity of cyclosporine is primarily due to parent drug. Following oral administration, absorption of cyclosporine is incomplete. The extent of absorption of cyclosporine is dependent on the individual patient, the patient population, and the formulation. Elimination of cyclosporine is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in urine. The disposition of cyclosporine from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range 5 to 18 hours). Following intravenous administration, the blood clearance of cyclosporine (assay: HPLC) is approximately 5 to 7 mL/min/kg in adult recipients of renal or liver allografts. Blood cyclosporine clearance appears to be slightly slower in cardiac transplant patients.

The relationship between administered dose and exposure (area under the concentration versus time curve, AUC) is linear within the therapeutic dose range. The intersubject variability (total, % CV) of cyclosporine exposure (AUC) when cyclosporine (MODIFIED) or cyclosporine (NON-MODIFIED) is administered ranges from approximately 20% to 50% in renal transplant patients. This intersubject variability contributes to the need for individualization of the dosing regimen for optimal therapy (*see DOSAGE and ADMINISTRATION*). Intrasubject variability of AUC in renal transplant recipients (% CV) was 9-21% for cyclosporine (MODIFIED) and 19-26% for cyclosporine (NON-MODIFIED). In the same studies, intrasubject variability of trough concentrations (% CV) was 17-30% for cyclosporine (MODIFIED) and 16-38% for cyclosporine (NON-MODIFIED).

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Absorption: Cyclosporine (MODIFIED) has increased bioavailability compared to cyclosporine (NON-MODIFIED). The absolute bioavailability of cyclosporine administered as Sandimmune® (cyclosporine [NON-MODIFIED]) is dependent on the patient population, estimated to be less than 10% in liver transplant patients and as great as 89% in renal patients. The absolute bioavailability of cyclosporine administered as cyclosporine (MODIFIED) has not been determined in adults. In studies of renal transplant, rheumatoid arthritis and psoriasis patients the mean cyclosporine AUC was approximately 20% to 50% greater and the peak blood cyclosporine concentration (C_{max}) was approximately 40% to 106% greater following administration of cyclosporine (MODIFIED) compared to following administration of cyclosporine (NON-MODIFIED). The dose normalized AUC in *de novo* liver transplant patients administered cyclosporine (MODIFIED) 28 days after transplantation was 50% greater and C_{max} was 90% greater than in those patients administered cyclosporine (NON-MODIFIED). AUC and C_{max} are also increased cyclosporine (MODIFIED) relative to cyclosporine (NON-MODIFIED) in heart transplant patients, but data are very limited. Although the AUC and C_{max} values are higher on cyclosporine (MODIFIED) relative to cyclosporine (NON-MODIFIED), the pre-dose trough concentrations (dose-normalized) are similar for the two formulations.

Following oral administration of cyclosporine (MODIFIED), the time to peak blood cyclosporine concentration (T_{max}) ranged from 1.5 to 2.0 hours. The administration of food with cyclosporine (MODIFIED) decreases the AUC and C_{max} of cyclosporine. A high fat meal (669 kcal, 45 grams fat) consumed within one-half hour before cyclosporine (MODIFIED) administration decreased the AUC by 13% and C_{max} by 33%. The effects of a low fat meal (667 kcal, 15 grams fat) were similar.

The effect of T-tube diversion of bile on the absorption of cyclosporine from cyclosporine (MODIFIED) was investigated in eleven *de novo* liver transplant patients. When the patients were administered cyclosporine (MODIFIED) with and without T-tube diversion of bile, very little difference in absorption was observed, as measured by the change in maximal cyclosporine blood concentrations from pre-dose values with the T-tube closed relative to when it was open: 6.9±41% (range -55% to 68%).

Pharmacokinetic Parameters (mean±SD)

Patient Population	Dose/day[1] (mg/d)	Dose/weight (mg/kg/d)	AUC[2] (ng•hr/mL)	C_{max} (ng/mL)	Trough[3] (ng/mL)	CL/F (mL/min)	CL/F (mL/min/kg)
De novo renal transplant[4] Week 4 (N=37)	597±174	7.95±2.81	8772±2089	1802±428	361±129	593±204	7.8±2.9
Stable renal transplant[4] (N=55)	344±122	4.10±1.58	6035±2194	1333±469	251±116	492±140	5.9±2.1
De novo liver transplant[5] Week 4 (N=18)	458±190	6.89±3.68	7187±2816	1555±740	268±101	577±309	8.6±5.7
De novo rheumatoid arthritis[6] (N=23)	182±55.6	2.37±0.36	2641±877	728±263	96.4±37.7	613±196	8.3±2.8
De novo psoriasis[6] Week 4 (N=18)	189±69.8	2.48±0.65	2324±1048	655±186	74.9±46.7	723±186	10.2±3.9

[1]Total daily dose was divided into two doses administered every 12 hours.
[2]AUC was measured over one dosing interval.
[3]Trough concentration was measured just prior to the morning cyclosporine (MODIFIED) dose, approximately 12 hours after the previous dose.
[4]Assay: TDx specific monoclonal fluorescence polarization immunoassay).
[5]Assay: Cyclo-trac specific monoclonal radioimmunoassay.
[6]Assay: INCSTAR specific monoclonal radioimmunoassay.

Distribution: Cyclosporine is distributed largely outside the blood volume. The steady state volume of distribution during intravenous dosing has been reported as 3-5 L/kg in solid organ transplant recipients. 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 binding capacity of leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins. Cyclosporine is excreted in human milk (*see PRECAUTIONS, Nursing Mothers*).

Metabolism: Cyclosporine is extensively metabolized by the cytochrome P-450 III-A enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the coadministration of a variety of agents (*see PRECAUTIONS, Drug Interactions*). At least 25 metabolites have been identified from human bile, feces, blood, and urine. The biological activity of the metabolites and their contributions to toxicity are considerably less than those of the parent compound. The major metabolites (M1, M9, and M4N) result from oxidation at the 1-beta, 9-gamma, and 4-N-desmethylated positions, respectively. At steady state following the oral administration of cyclosporine (NON-MODIFIED), the mean AUCs for blood concentrations of M1, M9 and M4N are about 70%, 21%, and 7.5% of the AUC for blood cyclosporine concentrations, respectively. Based on blood concentration data from stable renal transplant patients (13 patients administered cyclosporine (MODIFIED) and cyclosporine (NON-MODIFIED) in a crossover study), and bile concentration data from *de novo* liver transplant patients (4 administered cyclosporine (MODIFIED), 3 administered cyclosporine (NON-MODIFIED), the percentage of dose present as M1, M9, and M4N metabolites is similar when either cyclosporine (MODIFIED) or cyclosporine (NON-MODIFIED) is administered.

Excretion: Only 0.1% of a cyclosporine dose is excreted unchanged in the urine. Elimination is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in the urine. Neither dialysis nor renal failure alter cyclosporine clearance significantly.

Drug Interactions: (*see PRECAUTIONS, Drug Interactions*). When diclofenac or methotrexate was co-administered with cyclosporine in rheumatoid arthritis patients, the AUC of diclofenac and methotrexate, each was significantly increased (*see PRECAUTIONS, Drug Interactions*). No clinically significant pharmacokinetic interactions occurred between cyclosporine and aspirin, ketoprofen, piroxicam, or indomethacin.

Special Population: *Pediatric Population*: Pharmacokinetic data from pediatric patients administered cyclosporine (MODIFIED) or cyclosporine (NON-MODIFIED) are very limited. In 15 renal transplant patients aged 3-16 years, cyclosporine whole blood clearance after IV administration of cyclosporine (NON-MODIFIED) was 10.6±3.7 mL/min/kg (assay: Cyclo-trac specific RIA). In a study of 7 renal transplant patients aged 2-16, the cyclosporine clearance ranged from 9.8 to 15.5 mL/min/kg. In 9 liver transplant patients aged 0.6 to 5.6 years, clearance was 9.3±5.4 mL/min/kg (assay: HPLC).

In the pediatric population, cyclosporine (MODIFIED) also demonstrates an increased bioavailability as compared to cyclosporine (NON-MODIFIED). In 7 liver *de novo* transplant patients aged 1.4 to 10 years, the absolute bioavailability of cyclosporine (MODIFIED) was 43% (range 30% to 68%) and for cyclosporine (NON-MODIFIED) in the same individuals absolute bioavailability was 28% (range 17% to 42%).

Pediatric Pharmacokinetic Parameters (mean±SD)

Patient Population	Dose/day (mg/d)	Dose/weight (mg/kg/d)	AUC[1] (ng•hr/mL)	C_{max} (ng/mL)	CL/F (mL/min)	CL/F (mL/min/kg)
Stable liver transplant[2]						
Age 2-8, Dosed TID (N=9)	101±25	5.95±1.32	2163±801	629±219	285±94	16.6±4.3
Age 8-15, Dosed BID (N=8)	188±55	4.96±2.09	4272±1462	975±281	378±80	10.2±4.0
Stable liver transplant[3]						
Age 3, Dosed BID (N=1)	120	8.33	5832	1050	171	11.9
Age 8-15, Dosed BID (N=5)	158±55	5.51±1.91	4452±2475	1013±635	328±121	11.0±1.9
Stable liver transplant[3]						
Age 7-15, Dosed BID (N=5)	328±83	7.37±4.11	6922±1988	1827±487	418±143	8.7±2.9

[1]AUC was measured over one dosing interval.
[2]Assay: Cyclo-trac specific monoclonal radioimmunoassay.
[3]Assay: TDx specific monoclonal fluorescence polarization immunoassay.

Geriatric Population: Comparison of single dose data from both normal elderly volunteers (N=18, mean age 69 years) and elderly rheumatoid arthritis patients (N=16, mean age 68 years) to single dose data in young adult volunteers (N=16, mean age 26 years) showed no significant difference in the pharmacokinetic parameters.

CLINICAL TRIALS: Rheumatoid Arthritis: The effectiveness of cyclosporine (NON-MODIFIED) and cyclosporine (MODIFIED) in the treatment of severe rheumatoid arthritis was evaluated in five clinical studies involving a total of 728 cyclosporine treated patients and 273 placebo treated patients.

A summary of the results is presented for the "responder" rates per treatment group, with a responder being defined as a patient having *completed* the trial with a 20% improvement in the tender and the swollen joint count and a 20% improvement in 2 of 4 of investigator global, patient global, disability, and erythrocyte sedimentation rates (ESR) for the Studies 651 and 652 and 3 of 5 of investigator global, patient global, disability, visual analog pain, and ESR for Studies 2008, 654, and 302.

Study 651 enrolled 264 patients with active rheumatoid arthritis with at least 20 involved joints, who had failed at least one major RA drug, using a 3:3:2 randomization to one of the following three groups: (1) cyclosporine dosed at 2.5-5 mg/kg/day, (2) methotrexate at 7.5-15 mg/week, or (3) placebo. Treatment duration was 24 weeks. The mean cyclosporine dose at the last visit was 3.1 mg/kg/day. See Graph below.

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

Study 2008 enrolled 144 patients with active RA and ≥6 active joints who had unsuccessful treatment courses of aspirin and gold or Penicillamine. Patients were randomized to one of two treatment groups: (1) cyclosporine 2.5-5 mg/kg/day with adjustments after the first month to achieve a target trough level and (2) placebo. Treatment duration was 24 weeks. The mean cyclosporine dose at the last visit was 3.63 mg/kg/day. See Graph below.

Study 654 enrolled 148 patients who remained with active joint counts of 6 or more despite treatment with maximally tolerated methotrexate doses for at least three months. Patients continued to take their current dose of methotrexate and were randomized to receive, in addition, one of the following medications: (1) cyclosporine 2.5 mg/kg/day with dose increases of 0.5 mg/kg/day at weeks 2 and 4 if there was no evidence of toxicity and further increases of 0.5 mg/kg/day at weeks 8 and 16 if a <30% decrease in active joint count occurred without any significant toxicity; dose decreases could be made at any time for toxicity or (2) placebo. Treatment duration was 24 weeks. The mean cyclosporine dose at the last visit was 2.8 mg/kg/day (range 1.3-4.1). See Graph below.

Study 302 enrolled 299 patients with severe active RA, 99% of whom were unresponsive or intolerant to at least one prior major RA drug. Patients were randomized in a 2:2:1 ratio to (1) cyclosporine (MODIFIED) and (2) cyclosporine (NON-MODIFIED), both of which were started at

uncontrolled hypertension or malignancies should not receive Gengraf™.

WARNINGS: (*see also BOXED WARNINGS*) **All Patients:** Cyclosporine, the active ingredient of Gengraf™ (cyclosporine oral solution, USP [MODIFIED]), can cause nephrotoxicity and hepatotoxicity. The risk increases with increasing doses of cyclosporine. Renal dysfunction including structural kidney damage is a potential consequence of Gengraf™ and therefore renal function must be monitored during therapy. Care should be taken in using cyclosporine with nephrotoxic drugs (*see PRECAUTIONS*).

Patients receiving Gengraf™ require frequent monitoring of serum creatinine (*see Special Monitoring under DOSAGE and ADMINISTRATION*). Elderly patients should be monitored with particular care, since decreases in renal function also occur with age. If patients are not properly monitored and doses are not properly adjusted, cyclosporine therapy can be associated with the occurrence of structural kidney damage and persistent renal dysfunction.

An increase in serum creatinine and BUN may occur during Gengraf™ therapy and reflect a reduction in the glomerular filtration rate. Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated. The frequency and severity of serum creatinine elevations increase with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced without dose reduction or discontinuation.

Because Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) is not bioequivalent to Sandimmune®* (cyclosporine [NON-MODIFIED]), conversion from Gengraf™ to Sandimmune®* (cyclosporine [NON-MODIFIED]) using a 1:1 ratio (mg/kg/day) may result in lower cyclosporine blood concentrations. Conversion from Gengraf™ to Sandimmune®* (cyclosporine [NON-MODIFIED]) should be made with increased monitoring to avoid the potential of underdosing.

Kidney, Liver, and Heart Transplant: Cyclosporine, the active ingredient of Gengraf™ (cyclosporine oral solution, USP [MODIFIED]), 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 instituted.

Based on the historical cyclosporine (NON-MODIFIED) 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.

Nephrotoxicity vs. Rejection

Parameter	Nephrotoxicity	Rejection
History	Donor > 50 years old or hypotensive Prolonged kidney preservation Prolonged anastomosis time Concomitant nephrotoxic drugs	Antidonor immune response Retransplant patient
Clinical	Often > 6 weeks post-op[b] Prolonged initial nonfunction (acute tubular necrosis)	Often < 4 weeks post-op[b] Fever > 37.5°C 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 Gradual rise in Cr (< 0.15 mg/dL/day)[a] Cr plateau < 25% above baseline BUN/Cr ≥ 20	CyA serum trough level < 150 ng/mL Rapid rise in Cr (> 0.3 mg/dL/day)[a] Cr > 25% above baseline BUN/Cr < 20
Biopsy	Arteriolopathy (medial hypertrophy, hyalinosis, nodular deposits, intimal thickening, endothelial vacuolization, progressive scarring) Tubular atrophy, isometric vacuolization, isolated calcifications Minimal edema Mild focal infiltrates Diffuse interstitial fibrosis, often striped form	Endovasculitis (proliferative intimal arteritis[b], necrosis, sclerosis) Tubulitis with RBC[c] and WBC[c] casts, some irregular vacuolization Interstitial edema and hemorrhage[b] Diffuse moderate to severe mononuclear infiltrates[d] Glomerulitis (mononuclear cells)[c]
Aspiration Cytology	CyA deposits in tubular and endothelial cells Fine isometric vacuolization of tubular cells	Inflammatory infiltrates 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 lymphocytosis > 20% of sediment
Manometry Ultrasonography	Intracapsular pressure < 40 mm Hg[b] Unchanged renal cross sectional area	Intracapsular pressure > 40 mm Hg[b] Increase in graft cross sectional area AP diameter ≥ Transverse diameter
Magnetic Resonance Imagery	Normal appearance	Loss of distinct corticomedullary junction, swelling image intensity of parenchyma 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 cyclosporine	Responds to increased steroids or antilymphocyte globulin

[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$, [d] $p < 0.000$

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 post-transplant 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 ischemic 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 immunosuppressive therapy rather than increase the Gengraf™ 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 immunosuppressants 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*).

Rheumatoid Arthritis: Cyclosporine nephropathy was detected in renal biopsies of six out of 60 (10%) rheumatoid arthritis patients after the average treatment duration of 19 months. Only one patient, out of these 6 patients, was treated with a dose ≤4 mg/kg/day. Serum creatinine improved in all but one patient after discontinuation of cyclosporine. The "maximal creatinine increase" appears to be a factor in predicting cyclosporine nephropathy.

There is a potential, as with other immunosuppressive agents, for an increase in the occurrence of malignant lymphomas with cyclosporine. It is not clear whether the risk with cyclosporine is greater than that in Rheumatoid Arthritis patients or in Rheumatoid Arthritis patients on cytotoxic treatment for this indication. Five cases of lymphoma were detected: four in a survey of approximately 2,300 patients treated with cyclosporine for rheumatoid arthritis, and another case of lymphoma was reported in a clinical trial. Although other tumors (12 skin cancers, 24 solid tumors of divers types, and 1 multiple myeloma) were also detected in this survey, epidemiologic analyses did not support a relationship to cyclosporine other than for malignant

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Patients should be thoroughly evaluated before and during Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) treatment for the development of malignancies. Moreover, use of Gengraf™ therapy with other immunosuppressive agents may induce an excessive immunosuppression which is known to increase the risk of malignancy.

Psoriasis: (*see also BOXED WARNINGS for Psoriasis*). Since cyclosporine is a potent immunosuppressive agent with a number of potentially serious side effects, the risks and benefits of using Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) should be considered before treatment of patients with psoriasis. Cyclosporine, the active ingredient in Gengraf™, can cause nephrotoxicity and hypertension (*see PRECAUTIONS*) and the risk increases with increasing dose and duration of therapy. Patients who may be at increased risk such as those with abnormal renal function, uncontrolled hypertension or malignancies, should not receive Gengraf™.

Renal dysfunction is a potential consequence of Gengraf™, therefore renal function must be monitored during therapy.

Patients receiving Gengraf™ require frequent monitoring of serum creatinine (*see Special Monitoring under DOSAGE and ADMINISTRATION*). Elderly patients should be monitored with particular care, since decreases in renal function also occur with age. If patients are not properly monitored and doses are not properly adjusted, cyclosporine therapy can cause structural kidney damage and persistent renal dysfunction.

An increase in serum creatinine and BUN may occur during Gengraf™ therapy and reflect a reduction in the glomerular filtration rate.

Kidney biopsies from 86 psoriasis patients treated for a mean duration of 23 months with 1.2-7.6 mg/kg/day of cyclosporine showed evidence of cyclosporine nephropathy in 18/86 (21%) of the patients. The pathology consisted of renal tubular atrophy and interstitial fibrosis. On repeat biopsy of 13 of these patients maintained on various dosages of cyclosporine for a mean of 2 additional years, the number with cyclosporine induced nephropathy rose to 26/86 (30%). The majority of patients (19/26) were on a dose of ≥5.0 mg/kg/day (the highest recommended dose is 4 mg/kg/day). The patients were also on cyclosporine for greater than 15 months (18/26) and/or had a clinically significant increase in serum creatinine for greater than 1 month (21/26). Creatinine levels returned to normal range in 7 of 11 patients in whom cyclosporine therapy was discontinued.

There is an increased risk for the development of skin and lymphoproliferative malignancies in cyclosporine-treated psoriasis patients. The relative risk of malignancies is comparable to that observed in psoriasis patients treated with other immunosuppressive agents.

Tumors were reported in 32 (2.2%) of 1439 psoriasis patients treated with cyclosporine worldwide from clinical trials. Additional tumors have been reported in 7 patients in cyclosporine postmarketing experience. Skin malignancies were reported in 16 (1.1%) of these patients: all but 2 of them had previously received PUVA therapy. Methotrexate was received by 7 patients. UVB and coal tar have been used by 2 and 3 patients, respectively. Seven patients had either a history of previous skin cancer or a potentially predisposing lesion was present prior to cyclosporine exposure. Of the 16 patients with skin cancer, 11 patients had 18 squamous cell carcinomas and 7 patients had 10 basal cell carcinomas.

There were two lymphoproliferative malignancies, one case of non-Hodgkin's lymphoma which required chemotherapy, and one case of mycosis fungoides which regressed spontaneously upon discontinuation of cyclosporine. There were four cases of benign lymphocytic infiltration: 3 regressed spontaneously upon discontinuation of cyclosporine, while the fourth regressed despite continuation of the drug. The remainder of the malignancies, 13 cases (0.9%), involved various organs.

Patients should not be treated concurrently with cyclosporine and PUVA or UVB, other radiation therapy, or other immunosuppressive agents, because of the possibility of excessive immunosuppression and the subsequent risk of malignancies (*see CONTRAINDICATIONS*). Patients should also be warned to protect themselves appropriately when in the sun, and to avoid excessive sun exposure. Patients should be thoroughly evaluated before and during treatment for the presence of malignancies remembering that malignant lesions may be hidden by psoriatic plaques. Skin lesions not typical of psoriasis should be biopsied before starting treatment. Patients should be treated with Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) only after complete resolution of suspicious lesions, and only if there are no other treatment options (*see Special Monitoring for Psoriasis Patients*).

PRECAUTIONS: General: *Hypertension:* Cyclosporine is the active ingredient of Gengraf™ (cyclosporine oral solution, USP [MODIFIED]). Hypertension is a common side effect of cyclosporine therapy which may persist (*see ADVERSE REACTIONS and DOSAGE and ADMINISTRATION for monitoring recommendations*). Mild or moderate hypertension is encountered more frequently than severe hypertension and the incidence decreases over time. In recipients of kidney, liver, and heart allografts treated with cyclosporine, antihypertensive therapy may be required (*see Special Monitoring of Rheumatoid Arthritis and Psoriasis Patients*). 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, they can interfere with cyclosporine metabolism (*see Precautions, Drug Interactions*).

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

Special Monitoring of Rheumatoid Arthritis Patients: Before initiating treatment, a careful physical examination, including blood pressure measurements (on at least two occasions) and two creatinine levels to estimate baseline should be performed. Blood pressure and serum creatinine should be evaluated every 2 weeks during the initial 3 months and then monthly if the patient is stable. It is advisable to monitor serum creatinine and blood pressure always after an increase of the dose of nonsteroidal antiinflammatory drugs and after initiation of new non-steroidal antiinflammatory drug therapy during Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) treatment. If coadministered with methotrexate, CBC and liver function tests are recommended to be monitored monthly (*see also PRECAUTIONS, General, Hypertension*).

In patients who are receiving cyclosporine, the dose of Gengraf™ should be decreased by 25-50% if hypertension occurs. If hypertension persists, the dose of Gengraf™ should be further reduced or blood pressure should be controlled with antihypertensive agents. In most cases, blood pressure has returned to baseline when cyclosporine was discontinued.

In placebo-controlled trials of rheumatoid arthritis patients, systolic hypertension (defined as an occurrence of two systolic blood pressure readings >140 mmHg) and diastolic hypertension (defined as two diastolic blood pressure readings >90 mmHg) occurred in 33% and 19% of patients treated with cyclosporine, respectively. The corresponding placebo rates were 22% and 7%.

Special Monitoring for Psoriasis Patients: Before initiating treatment, a careful dermatological and physical examination, including blood pressure measurements (on at least two occasions) should be performed. Since Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) is an immunosuppressive agent, patients should be evaluated for the presence of occult infection on their first physical examination and for the presence of tumors initially, and throughout treatment with Gengraf™. Skin lesions not typical for psoriasis should be biopsied before starting Gengraf™. Patients with malignant or premalignant changes of the skin should be treated with Gengraf™ only after appropriate treatment of such lesions and if no other treatment option exists.

Baseline laboratories should include serum creatinine (on two occasions), BUN, CBC, serum magnesium, potassium, uric acid, and lipids.

The risk of cyclosporine nephropathy is reduced when the starting dose is low (2.5 mg/kg/day), the maximum dose does not exceed 4.0 mg/kg/day, serum creatinine is monitored regularly while cyclosporine is administered, and the dose of Gengraf™ is decreased when the rise in creatinine is greater than or equal to 25% above the patients pretreatment level. The increase in creatinine is generally reversible upon timely decrease of the dose of Gengraf™ or its discontinuation.

Serum creatinine and BUN should be evaluated every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable. If the serum creatinine is greater than or equal to 25% above the patient's pretreatment level, serum creatinine should be repeated within two weeks. If the change in serum creatinine remains greater than or equal to 25% above baseline, Gengraf™ should be reduced by 25-50%. If at any time the serum creatinine increases by greater than or equal to 50% above pretreatment level, Gengraf™ should be reduced by 25-50%. Gengraf™ should be discontinued if reversibility (within 25% of baseline) of serum creatinine is not achievable after two dosage modifications. It is advisable to monitor serum creatinine after an increase of the dose of nonsteroidal antiinflammatory drug and after initiation of new nonsteroidal antiinflammatory therapy during Gengraf™ treatment.

Blood pressure should be evaluated every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable, or more frequently when dosage adjustments are made. Patients without a history of previous hypertension before initiation of treatment with Gengraf™, should have the drug reduced by 25%-50% if found to have sustained hypertension. If the patient continues to be hypertensive despite multiple reductions of Gengraf™, then Gengraf™ should be discontinued. For patients with treated hypertension, before the initiation of Gengraf™ therapy, their medication should be adjusted to control hypertension while on Gengraf™. Gengraf™ should be discontinued if a change in hypertension management is not effective or tolerable.

CBC, uric acid, potassium, lipids, and magnesium should also be monitored every 2 weeks for the first 3 months of therapy, and then monthly if the patient is stable or more frequently when dosage adjustments are made. Gengraf™ dosage should be reduced by 25%-50% for any abnormality of clinical concern.

In controlled trials of cyclosporine in psoriasis patients, cyclosporine blood concentrations did not correlate well with either improvement or with side effects such as renal dysfunction.

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 cyclosporine. Patients should be advised of the potential risks during pregnancy and informed of the increased risk of neoplasia. Patients should also be informed of the risk of hypertension and renal dysfunction.

Patients should be advised that during treatment with cyclosporine, vaccinations may be less effective, and the use of live [illegible]

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Serum creatinine and BUN should be evaluated every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable. If the serum creatinine is greater than or equal to 25% above the patient's pretreatment level, serum creatinine should be repeated within two weeks. If the change in serum creatinine remains greater than or equal to 25% above baseline, Gengraf™ should be reduced by 25-50%. If at any time the serum creatinine increases by greater than or equal to 50% above pretreatment level, Gengraf™ should be reduced by 25-50%. Gengraf™ should be discontinued if reversibility (within 25% of baseline) of serum creatinine is not achievable after two dosage modifications. It is advisable to monitor serum creatinine after an increase of the dose of nonsteroidal antiinflammatory drug and after initiation of new nonsteroidal antiinflammatory therapy during Gengraf™ treatment.

Blood pressure should be evaluated every 2 weeks during the initial 3 months of therapy and then monthly if the patient is stable, or more frequently when dosage adjustments are made. Patients without a history of previous hypertension before initiation of treatment with Gengraf™, should have the drug reduced by 25%-50% if found to have sustained hypertension. If the patient continues to be hypertensive despite multiple reductions of Gengraf™, then Gengraf™ should be discontinued. For patients with treated hypertension, before the initiation of Gengraf™ therapy, their medication should be adjusted to control hypertension while on Gengraf™. Gengraf™ should be discontinued if a change in hypertension management is not effective or tolerable.

CBC, uric acid, potassium, lipids, and magnesium should also be monitored every 2 weeks for the first 3 months of therapy, and then monthly if the patient is stable or more frequently when dosage adjustments are made. Gengraf™ dosage should be reduced by 25%-50% for any abnormality of clinical concern.

In controlled trials of cyclosporine in psoriasis patients, cyclosporine blood concentrations did not correlate well with either improvement or with side effects such as renal dysfunction.

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 cyclosporine. Patients should be advised of the potential risks during pregnancy and informed of the increased risk of neoplasia. Patients should also be informed of the risk of hypertension and renal dysfunction.

Patients should be advised that during treatment with cyclosporine, vaccination may be less effective and the use of live attenuated vaccines should be avoided.

Patients should be given careful dosage instructions. Gengraf™ (cyclosporine oral solution, USP (MODIFIED)) should be diluted, preferably with orange or apple juice that is at room temperature. The combination of Gengraf™ with milk can be unpalatable.

Patients should be advised to take Gengraf™ on a consistent schedule with regard to time of day and relation to meals. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.

Laboratory Tests: In all patients treated with cyclosporine, renal and liver functions should be assessed repeatedly by measurement of serum creatinine, BUN, serum bilirubin, and liver enzymes. Serum lipids, magnesium, and potassium should also be monitored. Cyclosporine blood concentrations should be routinely monitored in transplant patients (*see DOSAGE and ADMINISTRATION, Blood Concentration Monitoring in Transplant Patients*), and periodically monitored in rheumatoid arthritis patients.

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

Drugs That May Potentiate Renal Dysfunction

Antibiotics
gentamicin
tobramycin
vancomycin
trimethoprim with sulfamethoxazole

Antineoplastics
melphalan

Antifungals
amphotericin B
ketoconazole

Antiinflammatory Drugs
azapropazon
diclofenac
naproxen
sulindac

Gastrointestinal Agents
cimetidine
ranitidine

Immunosuppressives
tacrolimus

Drugs That Alter Cyclosporine Concentrations: 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 Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) dosage adjustment are essential when these drugs are used concomitantly (*see DOSAGE and ADMINISTRATION, Blood Concentration Monitoring*).

Drugs That Increase Cyclosporine Concentrations

Calcium Channel Blockers
diltiazem
nicardipine
verapamil

Antifungals
fluconazole
itraconazole
ketoconazole

Antibiotics
clarithromycin
erythromycin

Glucocorticoids
methylprednisolone

Other Drugs
allopurinol
bromocriptine
danazol
metoclopramide

The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 III-A and increase the concentration of drugs metabolized by the cytochrome P-450 system. The interaction between HIV protease inhibitors and cyclosporine has not been studied. 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 That Decrease Cyclosporine Concentrations

Antibiotics
nafcillin
rifampin

Anticonvulsants
carbamazepine
phenobarbital
phenytoin

Other Drugs
octreotide
ticlopidine

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 Antiinflammatory Drug (NSAID) Interactions: Clinical status and serum creatinine should be closely monitored when cyclosporine is used with nonsteroidal antiinflammatory 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 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.

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.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: 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 (6 mg/kg). The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. Published reports indicate the conversion of hairless mice with UV irradiation and cyclosporine or other immunosuppressive agents shortens the time to skin tumor formation compared to UV irradiation alone.

Cyclosporine was not mutagenic in appropriate test systems. 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.

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

Widely distributed papillomatosis of the skin was observed after chronic treatment of dogs with cyclosporine at 9 times the human initial psoriasis treatment dose of 2.5 mg/kg, where doses are expressed on a body surface area basis. This papillomatosis showed a spontaneous regression upon discontinuation of cyclosporine.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants and patients with rheumatoid arthritis and psoriasis. 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.

In psoriasis patients on cyclosporine, development of malignancies, especially those of the skin has been reported (*see WARNINGS*). Skin lesions not typical for psoriasis should be biopsied before starting cyclosporine treatment. Patients with malignant or premalignant changes of the skin should be treated with cyclosporine only after appropriate treatment of such lesions and if no other treatment option exists.

Pregnancy: ***Pregnancy Category C.*** Cyclosporine was not teratogenic in appropriate test systems. Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. 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 transplant doses in humans 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 retardation.

There are no adequate and well-controlled studies in pregnant women. Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) 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 Gengraf™ during pregnancy should be carefully weighed.

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

Nursing Mothers: Since cyclosporine is excreted in human milk, breast-feeding should be avoided.

Pediatric Use: Although no adequate and well-controlled studies have been completed in children, transplant recipients as young as one year of age have received cyclosporine (MODIFIED) with no unusual adverse effects. The safety and efficacy of cyclosporine (MODIFIED) treatment in pediatric patients with juvenile rheumatoid arthritis or psoriasis below the age of 18 have not been established.

Geriatric Use: 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.

ADVERSE REACTIONS: Kidney, Liver, and Heart Transplantation: 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 post-transplantation.

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 cyclosporine (MODIFIED) were comparable with those observed in 208 transplanted patients who received cyclosporine (NON-MODIFIED) in these same studies when the dosage of the two drugs was adjusted to achieve the same cyclosporine blood trough concentrations.

Based on the historical experience with cyclosporine (NON-MODIFIED), the following reactions occurred in 3% or greater of 892 patients involved in clinical trials of kidney, heart, and liver transplants:

		Randomized Kidney Patients		Cyclosporine Patients Cyclosporine, (NON-MODIFIED)		
Body System	Adverse Reactions	Cyclosporine (NON-MODIFIED) (N=227)%	Azathioprine (N=228)%	Kidney (N=708)%	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

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Body System	Adverse Reactions	Cyclosporine (NON-MODIFIED) (N=227)%	Azathioprine (N=220)%	Kidney (N=705)%	Heart (N=136)%	Liver (N=79)%
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

Among 705 kidney transplant patients treated with cyclosporine oral solution (NON-MODIFIED) in clinical trials, the reason for treatment discontinuation was renal toxicity in 5.4%, infection in 0.9%, lack of efficacy in 1.4%, acute tubular necrosis in 1.0%, lymphoproliferative disorders in 0.3%, hypertension in 0.3%, and other reasons in 0.7% of the patients.

The following reactions occurred in 2% or less of cyclosporine (NON-MODIFIED)-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.

Infectious Complications in Historical Randomized Studies in Renal Transplant Patients Using Cyclosporine (NON-MODIFIED)

Complication	Cyclosporine Treatment (N=227) % of Complications	Azathioprine with Steroids* (N=220) % 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.

Rheumatoid Arthritis: The principal adverse reactions associated with the use of cyclosporine in rheumatoid arthritis are renal dysfunction (*see WARNINGS*), hypertension (*see PRECAUTIONS*), headache, gastrointestinal disturbances and hirsutism/hypertrichosis.

In rheumatoid arthritis patients treated in clinical trials within the recommended dose range, cyclosporine therapy was discontinued in 5.3% of the patients because of hypertension and in 7% of the patients because of increased creatinine. These changes are usually reversible with timely dose decrease or drug discontinuation. The frequency and severity of serum creatinine elevations increase with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced without dose reduction or discontinuation.

The following adverse events occurred in controlled clinical trials:

Cyclosporine (MODIFIED)/Cyclosporine (NON-MODIFIED) Rheumatoid Arthritis
Percentage of Patients with Adverse Events ≥3% in any Cyclosporine Treated Group

		Studies 001 + 002 +2000	Study 302	Study 004	Study 004	Study 302	Studies 001 + 002 + 2000
Body System	Preferred Term	Cyclosporine (NON-MODIFIED) (N=208)	Cyclosporine (NON-MODIFIED) (N=150)	Methotrexate & Cyclosporine (NON-MODIFIED) (N=76)	Methotrexate & Placebo (N=73)	Cyclosporine (MODIFIED) (N=140)	Placebo (N=391)
Autonomic Nervous System Disorders	Flushing	2%	2%	3%	0%	5%	2%
Body as a Whole - General Disorders	Accidental Trauma	0%	1%	10%	4%	4%	0%
	Edema NOS*	5%	14%	12%	4%	10%	<1%
	Fatigue	6%	3%	8%	12%	3%	2%
	Fever	2%	3%	0%	0%	2%	4%
	Influenza-like Symptoms	<1%	6%	1%	0%	3%	2%
	Pain	6%	9%	10%	15%	13%	4%
	Rigors	1%	1%	4%	0%	3%	1%
Cardiovascular Disorders	Arrhythmia	2%	5%	5%	6%	2%	1%
	Chest Pain	4%	5%	1%	1%	6%	1%
	Hypertension	8%	26%	16%	12%	25%	2%
Central and Peripheral Nervous System Disorders	Dizziness	8%	6%	7%	3%	8%	3%
	Headache	17%	23%	22%	11%	25%	9%
	Migraine	2%	3%	0%	0%	3%	1%
	Paresthesia	8%	7%	8%	4%	11%	1%
	Tremor	8%	7%	7%	3%	13%	4%
Gastrointestinal System Disorders	Abdominal Pain	15%	15%	15%	7%	15%	10%
	Anorexia	3%	3%	1%	0%	3%	3%
	Diarrhea	12%	12%	18%	15%	13%	8%
	Dyspepsia	12%	12%	10%	8%	8%	4%
	Flatulence	5%	5%	5%	4%	4%	1%
	Gastrointestinal Disorder NOS*	0%	2%	1%	4%	4%	0%
	Gingivitis	4%	3%	0%	0%	0%	1%
	Gum Hyperplasia	2%	4%	1%	3%	4%	1%
	Nausea	23%	14%	24%	15%	18%	14%
	Rectal Hemorrhage	0%	3%	0%	0%	1%	1%
	Stomatitis	7%	5%	16%	12%	6%	8%
	Vomiting	9%	8%	14%	7%	6%	5%
Hearing and Vestibular Disorders	Ear Disorders NOS*	0%	5%	0%	0%	1%	0%
Metabolic and Nutritional Disorders	Hypomagnesemia	0%	4%	0%	0%	6%	0%
Musculo-Skeletal System Disorders	Arthropathy	0%	5%	0%	1%	4%	0%
	Leg Cramps/Involuntary Muscle Contractions	2%	11%	11%	3%	12%	1%
Psychiatric Disorders	Depression	3%	6%	3%	1%	1%	2%
	Insomnia	4%	1%	1%	0%	3%	2%
Renal Disorders	Creatinine Elevations ≥30%	43%	39%	55%	19%	48%	13%
	Creatinine Elevations ≥50%	24%	18%	26%	8%	18%	3%
Reproductive Disorders, Female	Leukorrhea	1%	0%	4%	0%	1%	0%
	Menstrual Disorder	3%	2%	1%	0%	1%	1%
Respiratory System Disorders	Bronchitis	1%	3%	1%	0%	1%	3%
	Coughing	5%	3%	5%	7%	4%	4%
	Dyspnea	5%	1%	3%	3%	1%	2%
	Increased [illegible]*	0%	5%	0%	2%	3%	10%

*Some patients also received ALG.

Rheumatoid Arthritis: The principal adverse reactions associated with the use of cyclosporine in rheumatoid arthritis are renal dysfunction (*see WARNINGS*), hypertension (*see PRECAUTIONS*), headache, gastrointestinal disturbances and hirsutism/hypertrichosis.

In rheumatoid arthritis patients treated in clinical trials within the recommended dose range, cyclosporine therapy was discontinued in 5.3% of the patients because of hypertension and in 7% of the patients because of increased creatinine. These changes are usually reversible with timely dose decrease or drug discontinuation. The frequency and severity of serum creatinine elevations increase with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced without dose reduction or discontinuation.

The following adverse events occurred in controlled clinical trials:

Cyclosporine (MODIFIED)/Cyclosporine (NON-MODIFIED) Rheumatoid Arthritis
Percentage of Patients with Adverse Events ≥3% in any Cyclosporine Treated Group

		Studies [illegible]	Study [illegible]	Study [illegible]	Study [illegible]	Study [illegible]	Studies [illegible]
Body System	Preferred Term	Cyclosporine (NON-MODIFIED)	Cyclosporine (NON-MODIFIED)	Methotrexate & Cyclosporine (NON-MODIFIED)	Methotrexate & Placebo	Cyclosporine (MODIFIED)	Placebo
Autonomic Nervous System Disorders	Flushing	2%	2%	3%	0%	3%	2%
Body as a Whole - General Disorders	Accidental Trauma	0%	1%	10%	4%	4%	0%
	Edema NOS*	5%	14%	12%	4%	10%	<1%
	Fatigue	6%	3%	8%	12%	3%	7%
	Fever	2%	3%	0%	0%	2%	4%
	Influenza-like Symptoms	<1%	6%	1%	0%	3%	2%
	Pain	6%	9%	10%	15%	13%	4%
	Rigors	1%	1%	4%	0%	3%	1%
Cardiovascular Disorders	Arrhythmia	2%	5%	5%	6%	2%	1%
	Chest Pain	4%	5%	1%	1%	6%	1%
	Hypertension	8%	26%	16%	12%	25%	2%
Central and Peripheral Nervous System Disorders	Dizziness	8%	6%	7%	3%	8%	3%
	Headache	17%	23%	22%	11%	25%	9%
	Migraine	2%	3%	0%	0%	3%	1%
	Paresthesia	8%	7%	8%	4%	11%	1%
	Tremor	8%	7%	7%	3%	13%	4%
Gastrointestinal System Disorders	Abdominal Pain	15%	15%	15%	7%	15%	10%
	Anorexia	3%	3%	1%	0%	3%	3%
	Diarrhea	12%	12%	18%	15%	13%	8%
	Dyspepsia	12%	12%	10%	8%	8%	4%
	Flatulence	5%	5%	5%	4%	4%	1%
	Gastrointestinal Disorder NOS*	0%	2%	1%	4%	4%	0%
	Gingivitis	4%	3%	0%	0%	0%	1%
	Gum Hyperplasia	2%	4%	1%	3%	4%	1%
	Nausea	23%	14%	24%	15%	18%	14%
	Rectal Hemorrhage	0%	3%	0%	0%	1%	1%
	Stomatitis	7%	5%	16%	12%	6%	8%
	Vomiting	9%	8%	14%	7%	6%	5%
Hearing and Vestibular Disorders	Ear Disorders NOS*	0%	5%	0%	0%	1%	0%
Metabolic and Nutritional Disorders	Hypomagnesemia	0%	4%	0%	0%	6%	0%
Musculo-Skeletal System Disorders	Arthropathy	0%	5%	0%	1%	4%	0%
	Leg Cramps/Involuntary Muscle Contractions	2%	11%	11%	3%	12%	1%
Psychiatric Disorders	Depression	3%	6%	3%	1%	1%	2%
	Insomnia	4%	1%	1%	0%	3%	2%
Renal Disorders	Creatinine Elevations ≥30%	43%	39%	55%	19%	48%	13%
	Creatinine Elevations ≥50%	24%	18%	26%	8%	18%	3%
Reproductive Disorders, Female	Leukorrhea	1%	0%	4%	0%	1%	0%
	Menstrual Disorder	3%	2%	1%	0%	1%	1%
Respiratory System Disorders	Bronchitis	1%	3%	1%	0%	1%	3%
	Coughing	5%	3%	5%	7%	4%	4%
	Dyspnea	5%	1%	3%	3%	1%	2%
	Infection NOS*	9%	5%	0%	7%	3%	10%
	Pharyngitis	3%	5%	5%	6%	4%	4%
	Pneumonia	1%	0%	4%	0%	1%	1%
	Rhinitis	0%	3%	11%	10%	1%	0%
	Sinusitis	4%	4%	8%	4%	3%	3%
	Upper Respiratory Tract	0%	14%	23%	15%	13%	0%
Skin and Appendages Disorders	Alopecia	3%	0%	1%	1%	4%	4%
	Bullous Eruption	1%	0%	4%	1%	1%	1%
	Hypertrichosis	19%	17%	12%	0%	15%	3%
	Rash	7%	12%	10%	7%	8%	10%
	Skin Ulceration	1%	1%	3%	4%	0%	2%
Urinary System Disorders	Dysuria	0%	0%	11%	3%	1%	2%
	Micturition Frequency	2%	4%	3%	1%	2%	2%
	NPN, Increased	0%	19%	12%	0%	18%	0%
	Urinary Tract Infection	0%	3%	3%	4%	3%	0%
Vascular (Extracardiac) Disorders	Purpura	3%	4%	1%	1%	2%	0%

† Includes patients in 2.5 mg/kg/day dose group only. *NOS = Not Otherwise Specified

In addition, the following adverse events have been reported in 1% to <3% of the rheumatoid arthritis patients in the cyclosporine treatment group in controlled clinical trials.

Autonomic Nervous System: dry mouth, increased sweating.
Body as a Whole: allergy, asthenia, hot flushes, malaise, overdose, procedure NOS*, tumor NOS*, weight decrease, weight increase.
Cardiovascular: abnormal heart sounds, cardiac failure, myocardial infarction, peripheral ischemia.
Central and Peripheral Nervous System: hypoesthesia, neuropathy, vertigo.
Endocrine: goiter.
Gastrointestinal: constipation, dysphagia, enanthema, eructation, esophagitis, gastric ulcer, gastritis, gastroenteritis, gingival bleeding, glossitis, peptic ulcer, salivary gland enlargement, tongue disorder, tooth disorder.
Infection: abscess, bacterial infection, cellulitis, folliculitis, fungal infection, herpes simplex, herpes zoster, renal abscess, moniliasis, tonsillitis, viral infection.
Hematologic: anemia, epistaxis, leukopenia, lymphadenopathy.
Liver and Biliary System: bilirubinemia.
Metabolic and Nutritional: diabetes mellitus, hyperkalemia, hyperuricemia, hypoglycemia.
Musculoskeletal System: arthralgia, bone fracture, bursitis, joint dislocation, myalgia, stiffness, synovial cyst, tendon disorder.
Neoplasms: breast fibroadenosis, carcinoma.
Psychiatric: anxiety, confusion, decreased libido, emotional lability, impaired concentration, increased libido, nervousness, paroniria, somnolence.
Reproductive (Female): breast pain, uterine hemorrhage.
Respiratory System: abnormal chest sounds, bronchospasm.
Skin and Appendages: abnormal pigmentation, angioedema, dermatitis, dry skin, eczema, nail disorder, pruritus, skin disorder, urticaria.
Special Senses: abnormal vision, cataract, conjunctivitis, deafness, eye pain, taste perversion, tinnitus, vestibular disorder.
Urinary System: abnormal urine, hematuria, increased BUN, micturition urgency, nocturia, polyuria, pyelonephritis, urinary incontinence.
*NOS = Not Otherwise Specified.

Psoriasis: The principal adverse reactions associated with the use of cyclosporine in patients with psoriasis are renal dysfunction, headache, hypertension, hypertriglyceridemia, hirsutism/hypertrichosis, paresthesia or hyperesthesia, influenza-like symptoms, nausea/vomiting, diarrhea, abdominal discomfort, lethargy, and musculoskeletal or joint pain.

In psoriasis patients treated in U.S. controlled clinical studies within the recommended dose range, cyclosporine therapy was discontinued in 1.0% of the patients because of hypertension and in 5.4% of the patients because of increased creatinine. In the majority of cases, these changes were reversible after dose reduction or discontinuation of cyclosporine.

There has been one reported death associated with the use of cyclosporine in psoriasis. A 27 year old male developed renal deterioration and was continued on cyclosporine. He had progressive renal failure leading to death.

Frequency and severity of serum creatinine increases with dose and duration of cyclosporine therapy. These elevations are likely to become more pronounced and may result in irreversible renal damage without dose reduction or discontinuation.

Adverse Events Occurring in 3% or More of Psoriasis Patients in Controlled Clinical Trials

Body System*	Preferred Term	Cyclosporine (MODIFIED) (N=182)	Cyclosporine (NON-MODIFIED) (N=185)
Infection or Potential Infection		24.7%	24.3%
	Influenza-like Symptoms	9.9%	8.1%
	Upper Respiratory Tract Infections	7.7%	11.3%
Cardiovascular System		28.0%	25.4%
	Hypertension**	27.5%	25.4%
Urinary System		24.2%	16.2%
	Increased Creatinine	19.8%	15.7%
Central and Peripheral Nervous System		26.4%	20.5%
	Headache	15.9%	14.0%
	Paresthesia	7.1%	4.8%
Musculoskeletal System		13.2%	8.7%
	Arthralgia	6.0%	1.1%
Body as a Whole - General		29.1%	22.2%
	Pain	4.4%	3.2%
Metabolic and Nutritional		9.3%	9.7%
Reproductive, Female		8.5% (4 of 47 females)	11.5% (6 of 52 females)
Resistance Mechanism		18.7%	21.1%
Skin and Appendages		17.6%	15.1%
	Hypertrichosis	6.6%	5.4%
Respiratory System		5.0%	6.5%
	Bronchospasm, Coughing, Dyspnea, Rhinitis	5.0%	4.9%
Psychiatric		5.0%	3.8%
Gastrointestinal System		19.8%	28.7%
	Abdominal Pain	2.7%	6.0%
	Diarrhea	5.0%	5.9%
	Dyspepsia	2.2%	3.2%
	Gum Hyperplasia	3.8%	6.0%
	Nausea	5.5%	5.9%
White Cell and RES		4.4%	2.7%

* Total percentage of events within the system
** Newly occurring hypertension = SBP ≥160 mm Hg and/or DBP ≥90 mm Hg

The following events occurred in 1% to less than 3% of psoriasis patients treated with cyclosporine:

Body as a Whole: fever, flushes, hot flushes; ***Cardiovascular:*** chest pain; ***Central and Peripheral Nervous System:*** appetite increased, insomnia, dizziness, nervousness, vertigo; ***Gastrointestinal:*** abdominal distention, constipation, gingival bleeding; ***Liver and Biliary System:*** hyperbilirubinemia; ***Neoplasms:*** skin malignancies [squamous cell (0.9%) and basal cell (0.4%) carcinomas]; ***Reticuloendothelial:*** platelet, bleeding, and clotting disorders, red blood cell disorder; ***Respiratory:*** infection, viral and other infection; ***Skin and Appendages:*** acne, folliculitis, keratosis, pruritus, rash, dry skin; ***Urinary System:*** micturition frequency; ***Vision:*** abnormal vision.

Mild hypomagnesemia and hyperkalemia may occur but are asymptomatic. Increases in uric acid may occur and attacks of gout have been rarely reported. A minor and dose related hyperbilirubinemia has been observed in the absence of hepatocellular damage. Cyclosporine therapy may be associated with a modest increase of serum triglycerides or cholesterol. Elevations of triglycerides (>750 mg/dL) occur in about 15% of psoriasis patients; elevations of cholesterol (>300 mg/dL) are observed in less than 3% of psoriasis patients. Generally these laboratory abnormalities are reversible upon dose reduction or discontinuation of cyclosporin.

OVERDOSAGE: There is a minimal experience with cyclosporine overdosage. Forced emesis can be of value up to 2 hours after administration of Gengraf™ (cyclosporine oral solution, USP [MODIFIED]). 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. Cyclosporine is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion. The oral dosage at which half of experimental animals are estimated to die is 31 times, 39 times and >54 times the human maintenance dose for transplant patients (6 mg/kg; corrections based on body surface area) in mice, rats, and rabbits.

DOSAGE AND ADMINISTRATION: Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) has increased bioavailability in comparison to Sandimmune®* (cyclosporine [NON-MODIFIED]). Gengraf™ and Sandimmune®* (cyclosporine [NON-MODIFIED]) are not bioequivalent and cannot be used interchangeably without physician supervision.

The daily dose of Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) should always be given in two divided doses (BID). It is recommended that Gengraf™ be administered on a consistent schedule with regard to time of day and relation to meals. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.

Newly Transplanted Patients: The initial oral dose of Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) can be given 4-12 hours prior to transplantation or be given postoperatively. The initial dose of Gengraf™ varies depending on the transplanted organ and the other immunosuppressive agents included in the immunosuppressive protocol. In newly transplanted patients, the initial oral dose of Gengraf™ is the same as the initial oral dose of cyclosporine (NON-MODIFIED). Suggested initial doses are available from the results of a 1994 survey of the use of cyclosporine (NON-MODIFIED) in U.S. transplant centers. The mean ± SD initial doses were 9±3 mg/kg/day for renal transplant patients (75 centers), 8±4 mg/kg/day for liver transplant patients (30 centers), and 7±3 mg/kg/day for heart transplant patients (24 centers). Total daily doses were divided into two equal daily doses. The Gengraf™ dose is subsequently adjusted to achieve a pre-defined cyclosporine blood concentration (see *DOSAGE and ADMINISTRATION, Blood Concentration Monitoring in Transplant Patients, below*). If cyclosporine trough blood concentrations are used, the target range is the same for Gengraf™ as for cyclosporine (NON-MODIFIED). Using the same trough concentration target range for Gengraf™ as for cyclosporine (NON-MODIFIED) results in greater cyclosporine exposure when Gengraf™ is administered (see *CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption*). Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower Gengraf™ doses may be sufficient as maintenance therapy.

Adjunct therapy with adrenal corticosteroids is recommended initially. Different tapering dosage schedules of prednisone appear to achieve similar results. A representative 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. Steroid doses may be further tapered on an individualized basis depending on status of patient and function of graft. Adjustments in dosage of prednisone must be made according to the clinical situation.

Conversion from Sandimmune®* (cyclosporine [NON-MODIFIED]) to Gengraf™ (cyclosporine oral solution, USP [MODIFIED]) in Transplant Patients: In transplanted patients who are considered for conversion to Gengraf™ from Sandimmune®* (cyclosporine [NON-MODIFIED]), Gengraf™ should be started with the same daily dose as was previously used with Sandimmune®* (cyclosporine [NON-MODIFIED]) (1:1 dose conversion). The Gengraf™ dose should subsequently be adjusted to attain the pre-conversion cyclosporine blood trough concentration. Using the same trough concentration target range for Gengraf™ as for Sandimmune®* (cyclosporine [NON-MODIFIED]) results in greater cyclosporine exposure when Gengraf™ is administered (see *CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption*). Patients with suspected poor absorption of
[NON-MODIFIED]

Psoriasis: The initial dose of Gengraf™ (cyclosporine oral solution, USP (MODIFIED)) should be 2.5 mg/kg/day. Gengraf™ should be taken twice daily, as a divided (1.25 mg/kg BID) oral dose. Patients should be kept at that dose for at least 4 weeks, barring adverse events. If significant clinical improvement has not occurred in patients by that time, the patient's dosage should be increased at 2 week intervals. Based on patient response, dose increases of approximately 0.5 mg/kg/day should be made to a maximum of 4.0 mg/kg/day.

Dose decreases by 25-50% should be made at any time to control adverse events, e.g., hypertension, elevations in serum creatinine (≥25% above the patient's pretreatment level), or clinically significant laboratory abnormalities. If dose reduction is not effective in controlling abnormalities, or if the adverse event or abnormality is severe, Gengraf™ should be discontinued (*see PRECAUTIONS, Special Monitoring of Psoriasis Patients*).

Patients generally show some improvement in the clinical manifestations of psoriasis in 2 weeks. Satisfactory control and stabilization of the disease may take 12-16 weeks to achieve. Results of a dose-titration clinical trial with Gengraf™ indicate that an improvement of psoriasis by 75% or more (based on PASI) was achieved in 51% of the patients after 8 weeks and in 79% of the patients after 12 weeks. Treatment should be discontinued if satisfactory response cannot be achieved after 6 weeks at 4 mg/kg/day or the patient's maximum tolerated dose. Once a patient is adequately controlled and appears stable the dose of Gengraf™ should be lowered, and the patient treated with the lowest dose that maintains an adequate response (this should not necessarily be total clearing of the patient). In clinical trials, cyclosporine doses at the lower end of the recommended dosage range were effective in maintaining a satisfactory response in 60% of the patients. Doses below 2.5 mg/kg/day may also be equally effective.

Upon stopping treatment with cyclosporine, relapse occurred in approximately six weeks (50% of the patients) to 16 weeks (75% of the patients). In the majority of patients rebound does not occur after cessation of treatment with cyclosporine. Thirteen cases of transformation of chronic plaque psoriasis to more severe forms of psoriasis have been reported. There were 9 cases of pustular and 4 cases of erythrodermic psoriasis. Long term experience with Gengraf™ in psoriasis patients is limited and continuous treatment for extended periods greater than one year is not recommended. Alternation with other forms of treatment should be considered in the long term management of patients with this life long disease.

Gengraf™ Oral Solution (cyclosporine oral solution, USP (MODIFIED)) - Recommendations for Administration: To make Gengraf™ more palatable, it should be diluted preferably with orange or apple juice that is at room temperature. Grapefruit juice affects metabolism of cyclosporine and should be avoided. The combination of Gengraf™ with milk can be unpalatable.

Take the prescribed amount of Gengraf™ from the container using the dosing syringe supplied, and transfer the solution to a glass of orange or apple juice. Stir well and drink at once. Do not allow diluted oral solution to stand before drinking. Use a glass container (not plastic). Rinse the glass with more diluents to ensure that the total dose is consumed. After use, dry the outside of the dosing syringe with a clean towel and store in a clean, dry place. Do not rinse the dosing syringe with water or other cleaning agents. If the syringe requires cleaning, it must be completely dry before resuming use.

Blood Concentration Monitoring in Transplant Patients: Transplant centers have found blood concentration monitoring of cyclosporine to be an essential component of patient management. Of importance to blood concentration analysis are the type of assay used, the transplanted organ, and other immunosuppressant agents being administered. While no fixed relationship has been established, blood concentration monitoring may assist in the clinical evaluation of rejection and toxicity, dose adjustments, and the assessment of compliance.

Various assays have been used to measure blood concentrations of cyclosporine. Older studies using a non-specific assay often cited concentrations that were roughly twice those of the specific assays. Therefore, comparison between concentrations in the published literature and an individual patient concentration using current assays must be made with detailed knowledge of the assay methods employed. Current assay results are also not interchangeable and their use should be guided by their approved labeling. A discussion of the different assay methods is contained in *Annals of Clinical Biochemistry* 1994;31:420-446. While several assays and assay matrices are available, there is a consensus that parent-compound-specific assays correlate best with clinical events. Of these, HPLC is the standard reference, but the monoclonal antibody RIAs and the monoclonal antibody FPIA offer sensitivity, reproducibility, and convenience. Most clinicians base their monitoring on trough cyclosporine concentrations. *Applied Pharmacokinetics, Principles of Therapeutic Drug Monitoring* (1992) contains a broad discussion of cyclosporine pharmacokinetics and drug monitoring techniques. Blood concentration monitoring is not a replacement for renal function monitoring or tissue biopsies.

HOW SUPPLIED:

Gengraf™ Oral Solution (cyclosporine oral solution, USP (MODIFIED)) A clear, colorless to yellow liquid supplied in 50 mL bottles containing 100 mg/mL with dispensing syringe. (NDC 0074-7269-50).

Store and Dispense: In the original container at controlled room temperature 59°-86°F (15° to 30°C) (See USP). Do not store in the refrigerator. Once opened, the contents must be used within two months. At temperatures below 68°F (20°C) the solution may gel; light flocculation or the formulation of a light sediment may also occur. There is no impact on product performance or dosing using the syringe provided. Allow to warm to room temperature 59°-86°F (15° to 30°C) (See USP) to reverse these changes.

*Sandimmune® is a registered trademark of Novartis Pharmaceuticals Corporation.

Revised: November, 1999

ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.A.

APPROVED
FEB 24 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-025

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. #2

2. ANDA #65-025

3. NAME AND ADDRESS OF APPLICANT

Abbott Laboratories
Attention: Rebecca A. Welch
D-491/AP6B
100 Abbott Park Road
Abbott Park, IL 60064-3500

Phone: 847-937-8971
Fax: 847-937-8002

4. LEGAL BASIS FOR SUBMISSION

Reference listed drug: Neoral® Oral Solution for microemulsion by Sandoz (now Novartis Pharmaceuticals) NDA #50716, approved 7/14/95.

Abbott states (page 12) that no exclusivity and no petition apply to this application. See also statement on page 13.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

Gengraf® Oral Solution

7. NONPROPRIETARY NAME

Cyclosporine Oral Solution, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original application: 8/14/98
Amendment 10/23/98 for Refuse to File 9/24/98
FDA acknowledgment: 11/27/98
Amendment 7/15/99 to N/A letter (MINOR) 6/9/99
Amendment 12/7/99: Revised labeling

10. PHARMACOLOGICAL CATEGORY
Immunosuppressive agent for the prophylaxis of organ rejection in allogeneic transplants.

11. Rx or OTC Rx

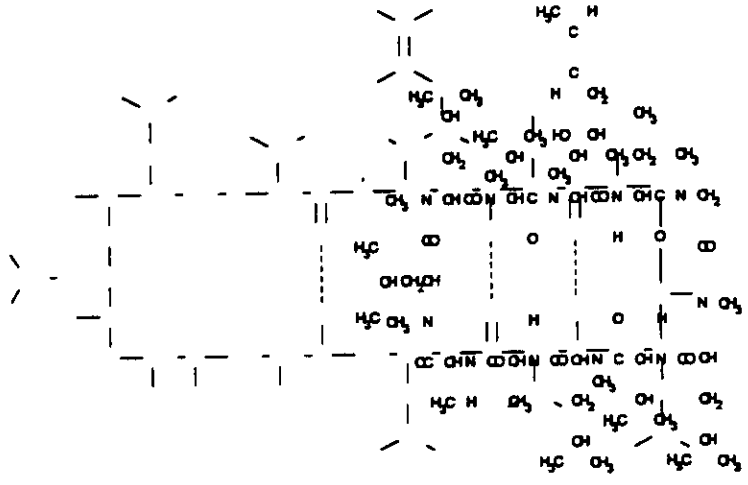
12. RELATED IND/NDA/DMF(s)
See under #37 DMF CHECKLIST

13. DOSAGE FORM
Oral Solution

14. POTENCY 100 mg/mL

15. CHEMICAL NAME AND STRUCTURE

Cyclosporine USP; $C_{62}H_{111}N_{11}O_{12}$; M.W. = 1202.64



[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). CAS [59865-13-3].

16. RECORDS AND REPORTS N/A

17. COMMENTS

The innovator has two formulations of cyclosporine, Neoral® and Sandimmune®, which are not bioequivalent. This application references Neoral® as the reference listed drug. In terms of chemistry, the only difference between Neoral® and Sandimmune® is the formulation. Both products are solutions in bottles when they are marketed. Neoral® contains emulsifiers not present in the Sandimmune® formulation.

Specifications for SangStat/Lilly's Cyclosporine Oral Solution (#64-195, approved 10/31/98) is attached in CR #1.

Page(s) 2

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #2

9/21/99

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended.

19. REVIEWER: Maria C. Shih

DATE COMPLETED: 9/21/99 (12/17/99)

Page(s) 9

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

JUN 9 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 65-025 **APPLICANT:** Abbott Laboratories

DRUG PRODUCT: Cyclosporine Oral Solution, USP (Modified), 100 mg/mL

The deficiencies presented below represent MINOR deficiencies.

A. Chemistry Deficiencies:

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following in your response:

1. Safety data relative to use of and have been sent on consult to the Division of Antiinfective Drug Products (HFD-520). Comments, if any, will be forwarded to you when the consult is returned.

2. A satisfactory compliance evaluation of firms referenced in the ANDA is required prior to approval.

Sincerely yours,

/S/

Florence S. Fang
for Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-025

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-025 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Cyclosporine Oral Solution, 100 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-025 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Cyclosporine Oral Solution, 100 mg/mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #65-025 SPONSOR: Abbott Laboratories
DRUG: Cyclosporine Oral Solution
DOSAGE FORM: Oral Solution
STRENGTHS/(s): 100 mg/mL
TYPE OF STUDY: Single-Dose, Fasting and Non-Fasting
STUDY SITE:
CLINICAL:
ANALYTICAL:

STUDY SUMMARY: The fasting and non-fasting studies are acceptable.

DISSOLUTION: The dissolution testing is not required for this drug product because this is an oral solution.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: /S/ DATE 12/29/98

BRANCH CHIEF: Shrinivas Nerurkar, Ph.D., BRANCH: II

INITIAL: /S/ DATE 1/11/1999

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: /S/ DATE 1/28/99

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL:_____ DATE_____

Cyclosporine Oral Solution, USP
100 mg/mL
ANDA #65-025
Reviewer: Kuldeep R. Dhariwal
File name: 65025S.O98

Abbott Laboratories
100 Abbott Park Road
Abbott Park
Illinois 60064-3500
Submission Date:
October 23, 1998

Review of Fasting and Non-Fasting Bioequivalence Studies

The firm has submitted fasting and non-fasting bioequivalence studies comparing its cyclosporine oral solution, 100 mg/mL with Neoral® oral solution for microemulsion, 100 mg/mL (Novartis).

Introduction:

It is a potent immunosuppressive agent. Following oral administration of Neoral®, the T_{max} ranged from 1.5-2.0 hours. The administration of food decreases AUC and C_{max}. Neoral® is available as soft gelatin capsules (25 mg, 100 mg) and as oral solution (100 mg/mL). Cyclosporine oral solution is also marketed by Sandoz as Sandimmune® oral solution, 100 mg/mL. Sandimmune® and Neoral® are not bioequivalent.

Bioequivalent Study Under Fasting Conditions:

A. Study Information:

Protocol#:	M97-721
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Analytical Site:	
Principal Investigator:	
Study Dates:	Group 1 (Subjects 1-28) Period I September 16, 1997 Period II September 23, 1997 Group 2 (Subjects 29-56) Period I September 19, 1997 Period II September 26, 1997
Analysis Dates:	October 1 to October 29, 1997
Study Design:	Randomized, two-way crossover design with a wash-out period of 7 days

Randomization Scheme:

AB: 2,4,6,8,9,11,13,15,17,20,21,
23,26,28,30,32,34,35,38,39,
42,44,46,48,50,51,53,56

BA: 1,3,5,7,10,12,14,16,18,19,22,
24,25,27,29,31,33,36,37,40,41,
43,45,47,49,52,54,55

Treatments:

A= Cyclosporine Oral Solution, 3 mLx100 mg/mL; Abbott; Batch #30-735-AR-05; Batch size: .iters; Manufacture Date: August 19, 1997; Assay: 100.7%

B= Neoral®, 3 mLx100 mg/mL; Novartis; Batch #203x0498; Expiry Date: November 1, 1998; Assay: 99.8%

Formulation of Test Product: Table 1

Subjects: 56 subjects (39 males, 17 females) were enrolled according to the criteria specified in the protocol

Housing: From the evening before dosing until after the 48 hour blood draw

Dosing: Subjects were dosed after an overnight fast. Three mL of cyclosporine oral solution were placed in an amber bottle and volume was made up to 45 mL with orange juice. After the subjects consumed this solution, the bottle was rinsed three times each time using 45 mL orange juice. The subjects this way consumed a total of 180 mL orange juice.

Sample Collection: Blood samples (7 mL) were collected at predose (0 h) and at following times after dosing:0.25,0.5,0.75,1,1.5,2,2.5, 3,4,6,8,10,12,15,18,24,30,36 and 48 hours.

B. Study Results:

1. Clinical:

Drop-outs: Subject #40 was withdrawn after dosing in period I (reference product) due to vasovagal reactions (vomiting, syncope, faintness, dizziness, pallor, nausea, headache etc.). Fifty-five subjects completed the study. Subject #17

experienced emesis within 70 minutes of dosing in both periods but he completed the study. His samples were analyzed but not included in statistical analysis.

Adverse Events: Some subjects experienced nausea, headache, vasodilation etc. The events were comparable on test and reference drugs. Subject #17 vomited 1 hour after dosing in period I as well as period II. Subject #19 vomited 5.47 hours after dosing in period I (test drug) and #40 vomited 1 minute after dosing in period I (test drug).

Protocol Deviations: There were a few sampling time deviations of less than 5 minutes. Two samples were drawn 11 and 9 minutes late. Since the deviations were of less than 10% of designated times, no adjustments were made in pharmacokinetic calculations. Some subjects took medications during the study.

2. Analytical: **NOT TO BE RELEASED UNDER FOI**

Method:

Internal Standard:

Linearity: Standard curve range
1.00 to 1000 ng/mL
QC Samples
2.70, 270.0, 771.00 ng/mL
Correlation coefficients were greater than 0.9963.

Regression: $1/(\text{concentration})^2$, linear

Accuracy: Standards 98.3-104%
QC samples 94.4-95.8%

Precision: Standards 1.4-4.2%
QC samples 6.3-7.2%

Reassays: Following samples were reassayed for reasons shown against them:

Processing error	8
Pharmacokinetic outlier	6

The firm has provided following pre-study method validation results:

Linearity: Standard curve range
1.00 to 1000 ng/mL

	QC Samples 2.70, 270, 771 ng/mL Correlation coefficients were greater than 0.9968
Accuracy:	Inter-day: Standards 98.1-103.7% QC samples 98.0-101.4% Intra-day: Standards 98.0-103.5% QC samples 95.5-102.3%
Precision:	Inter-day: Standards 0.91-9.3% QC samples 2.8-8.8% Intra-day: Standards 0.48-8.8% QC samples 1.4-13%
Recovery:	2.70 ng/mL 103.2% (34% CV) 771 ng/mL 79.5% (26% CV) Internal Standard 92.1% (30% CV) Note: Extracted as well as unextracted samples have high %CV.
Stability:	a) pre-extraction: stable at room temperature for 24 h before extraction b) autosampler: stable for 24 h c) after extraction: stable at 4°C for 139 h d) freeze-thaw: stable over 3 cycles e) long-term: stability was compared in samples stored in containers and in presence of two anticoagulants: Cyclosporine was stable for at least 30 days in tubes containing for 40 days in glass tubes containing and for 75 days in glass tubes containing No differences were observed in the results between samples stored in vs containers and also EDTA vs heparin. The reviewer will therefore extrapolate the results and presume that the study samples which were stored in tubes and is anticoagulant were stable for the maximum storage period of 44 days.

3. Pharmacokinetics/Statistics:

Mean Plasma Concentrations:	Table 2 and Figure 1	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	$LAUC_{0-t}$	93.91-99.55%
	$LAUC_{0-inf}$	93.90-99.59%
	LC_{max}	94.97-100.46%
Test/Reference Ratio:	AUC_{0-t}	0.98 (0.78-1.98)
	AUC_{0-inf}	0.98 (0.75-2.01)
	C_{max}	0.98 (0.72-1.35)
AUC_{0-t}/AUC_{0-inf} Ratio:	Test	0.95 (0.90-0.98)
	Reference	0.95 (0.90-0.97)

Comments:

1. No subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug concentration as C_{max}.
2. **NOT TO BE RELEASED UNDER FOI:** Majority of subjects (46 out of

a.

b.

c.

d.

e.

3

4.

5.

6

Bioavailability of Cyclosporine Oral Solution, 100 mg/mL Under Non-Fasting Conditions:

A. Study Information:

Protocol#:	M96-570
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Analytical Site:	
Principal Investigator:	
Study Dates:	Group 3 (Subject 24) Period I October 2, 1997 Period II October 9, 1997 Period III October 30, 1997 Group 2 (Subject #5,13,18) Period I October 9, 1997 Period II October 23, 1997 Period III October 30, 1997 Group 1 (remaining subjects) Period I October 2, 1997 Period II October 9, 1997 Period III October 23, 1997
Analysis Dates:	October 29 to November 8, 1997

Study Design: Randomized, three-way crossover design with a wash-out period of at least 7 days

Randomization Scheme:
ABC: 6,9,17,18,21
BCA: 3,12,23
ACB: 1,8,15,22
CBA: 7,14,24
CAB: 2,10,13,19
BAC: 4,5,11,16,20

Treatments:

A= Cyclosporine Oral Solution, 3x100 mg/mL; Abbott; Batch #30-735-AR-05; administered after a 10 hour fast

B= Cyclosporine Oral Solution, 3x100 mg/mL; Abbott; Batch #30-735-AR-05; administered after a standard breakfast

C= Neoral®, 3x100 mg/mL; Novartis; Batch #203x0498; administered after a standard breakfast

Lot numbers of drug products administered in this study are the same as those for the fasting study.

Subjects: 24 subjects (10 male, 14 female) were enrolled according to inclusion/exclusion criteria specified in the protocol

Dosing: Treatments B and C: Subjects were given OGD approved standardized breakfast 30 minutes before dosing after a fast lasting about 10 hours. The dose was given with 180 mL of orange juice. Treatment A: Subjects were given a single oral dose of the assigned formulation with 180 mL of orange juice after a 10 hour fast.

Sample Collection: Blood samples (5 mL) were collected at predose (0 h) and at following times after dosing: 0.25,0.5,0.75,1,1.5,2, 2.5,3,4,6,8,9,10,12,15,18,24,30,36, and 48 hours.

Housing: From the evening before dosing until after the 48 hour blood draw

B. Study Results:

1. Clinical:

Drop-outs: Subject #3 was withdrawn from the study after period II due to pharyngitis.

Adverse Events: Some subjects experienced nausea, headache, vasodilation etc. The events were comparable on test and reference drugs. Some subjects experienced diarrhea. Subject #12 vomited 50 minutes after dosing in period III (test fasting).

Protocol Deviations: There was one sampling time deviation of more than 5 minutes. Some subjects took concurrent medications.

2. Analytical:

Method: - - - - -

Internal Standard: - - - -

Linearity: Standard curve range
1.00 to 1000 ng/mL
QC Samples
2.70, 270.0, 771.00 ng/mL
Correlation coefficients were greater than 0.9956.

Regression: $1/(\text{concentration})^2$, linear

Accuracy: Standards 98.9-101.6%
QC samples 99.9-102.9%

Precision: Standards 0.8-5.2%
QC samples 2.7-4.8%

Reassays: Twelve samples were reassayed for pharmacokinetic reasons.

3. Pharmacokinetics/Statistics:

Mean Plasma Concentrations: Table 3, Figure 2

Pharmacokinetic Parameters: Table 4

AUC_{0-t}/AUC_{0-inf} Ratios:	Test Fasting	0.95	(0.91-0.97)
	Test Non-fasting	0.95	(0.91-0.97)
	Ref. Non-fasting	0.95	(0.91-0.97)
Test non-fasting/Ref. non-fasting:	AUC_{0-t}	0.99	(0.90-1.05)
	AUC_{0-inf}	0.99	(0.69-1.19)
	C_{max}	1.04	(0.71-1.46)

Comments:

1. The reviewer recalculated the pharmacokinetic parameters and ratios of means. The reported values are in good agreement with those obtained by the reviewer.
2. No subjects with first scheduled post-dose time point as C_{max}, and no subjects with first measurable drug concentration as C_{max}.
3. **NOT TO BE RELEASED UNDER FOI:** Majority of subjects had
   m
   h
   d
   s
   b
   above).
4. Subject #3 was withdrawn after period II without completing test fasting treatment. The data from this subject were included in the analysis because this study mainly compares test and reference products under non-fasting conditions. The data from subject #12 were not omitted from analysis for the same reason though the subject vomited 50 minutes after dosing in period III (test fasting).
5. Ratios of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test non-fasting and reference non-fasting are within acceptable limits. The non-fasting study is acceptable.
6. There was some confusion about the labeling of sample tubes for subjects 5,13, and 18. Ratios of means for AUC and C_{max} remain within acceptable limits after omitting these subjects.
7. Food decreased AUC and C_{max} consistent with the labeling of the reference listed drug.

In Vitro Dissolution Testing:

The drug product is a solution and therefore dissolution testing is not required.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Abbott on its cyclosporine oral solution, 100 mg/mL, lot #30-735-AR-05, comparing it to the reference product Neoral® oral solution 100 mg/mL, lot #203x0498 manufactured by Novartis has been found acceptable by the Division of Bioequivalence. The study demonstrates that Abbott's cyclosporine oral solution 100 mg/mL is bioequivalent to the reference

product, Neoral® oral solution 100 mg/mL manufactured by Novartis.

2. The bioequivalence study conducted under fed conditions by Abbott on its cyclosporine oral solution 100 mg/mL, lot #30-735-AR-05, comparing it to the reference product Neoral® oral solution 100 mg/mL, lot #203x0498 manufactured by Novartis has been found acceptable by the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of Abbott's cyclosporine oral solution 100 mg/mL is similar to that of the reference product Neoral® oral solution 100 mg/mL manufactured by Novartis.

3. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and the application is acceptable.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

/S/ Date 1/11/1999

Concur: /S/ Date 1/28/99
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

Table 1

Quantitative Composition of Cyclosporine Oral Solution

Ingredient	mg/mL
Cyclosporine	100
Propylene Glycol	
Polyoxyl 40 Hydrogenated Castor Oil	
Sorbitan Monooleate	

Table 2

MEAN BLOOD CYCLOSPORINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS
IN FASTING STUDY, N= 54

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	1.12	1.34	0.84	1.24	1.34
0.25	78.98	65.05	61.33	49.66	1.29
0.5	470.79	263.68	434.33	242.44	1.08
0.75	889.36	340.11	876.76	336.76	1.01
1	1149.72	300.13	1135.19	325.50	1.01
1.5	1211.21	248.75	1241.89	282.09	0.98
2	1100.36	229.69	1149.70	232.27	0.96
2.5	933.55	208.99	958.54	230.05	0.97
3	760.95	189.44	809.80	230.51	0.94
4	526.23	150.66	563.99	173.57	0.93
6	296.11	72.68	309.74	77.28	0.96
8	189.75	47.69	195.94	60.23	0.97
10	135.50	37.86	139.45	38.30	0.97
12	93.12	27.26	97.02	28.14	0.96
15	62.71	16.77	65.72	17.97	0.95
18	48.29	12.63	50.15	12.91	0.96
24	30.73	8.12	32.00	9.01	0.96
30	20.21	5.72	20.82	5.96	0.97
36	15.89	4.76	16.46	4.95	0.97
48	11.75	3.74	12.17	3.88	0.97

UNIT: BLOOD LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	6496.30	1249.83	6723.42	1310.75	0.97
AUCT	6173.78	1149.10	6390.98	1201.80	0.97
CMAX	1295.38	223.93	1326.15	222.48	0.98
KE	0.04	0.01	0.04	0.01	1.00
LAUCI	6379.88	0.19	6603.21	0.19	0.97
LAUCT	6070.18	0.19	6283.32	0.19	0.97
LCMAX	1277.33	0.17	1307.99	0.17	0.98
THALF	18.41	3.64	18.40	3.45	1.00
TMAX	1.45	0.54	1.56	0.58	0.93

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	6501.19	6721.99	0.97	94.02	99.41
AUCT	6178.23	6389.96	0.97	94.05	99.32
CMAX	1295.04	1325.49	0.98	94.95	100.45
LAUCI	6384.21	6601.83	0.97	93.90	99.59
LAUCT	6074.28	6282.30	0.97	93.91	99.55
LCMAX	1276.98	1307.34	0.98	94.97	100.46

Table 3

MEAN BLOOD CYCLOSPORINE LEVELS (ng/mL) FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY, N=24

	MEAN1*	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.65	0.78	1.17	1.84	1.00	1.47	0.56
0.25	96.66	59.19	26.84	22.52	29.14	24.62	3.60
0.5	534.86	234.21	165.11	125.53	164.72	120.48	3.24
0.75	959.46	370.53	336.40	224.60	317.05	188.15	2.85
1	1115.65	380.11	496.52	273.65	470.10	239.69	2.25
1.5	1148.66	365.60	654.54	217.27	664.38	192.60	1.75
2	1055.60	287.36	717.89	173.74	736.80	149.13	1.47
2.5	917.13	265.34	716.56	138.96	736.29	124.61	1.28
3	780.24	261.89	700.51	118.47	711.28	171.77	1.11
4	567.20	153.91	607.90	127.99	622.47	157.38	0.93
6	305.61	87.02	435.78	151.39	444.77	120.41	0.70
8	186.54	42.53	235.85	72.24	239.42	55.13	0.79
10	128.30	27.43	159.81	49.54	160.34	41.37	0.80
12	93.42	19.88	116.58	36.75	117.79	33.93	0.80
15	62.08	13.22	71.39	18.55	73.08	18.06	0.87
18	47.86	9.64	53.60	16.23	53.31	13.65	0.89
24	31.78	6.51	34.25	9.46	33.34	10.42	0.93
30	20.83	5.27	20.79	6.00	20.65	6.38	1.00
36	17.03	4.42	15.92	4.92	16.05	5.09	1.07
48	12.75	3.66	11.56	3.84	11.83	4.06	1.10

(CONTINUED)

* n=23

	RMEAN13	RMEAN23
TIME HR		
0	0.65	1.17
0.25	3.32	0.92
0.5	3.25	1.00
0.75	3.03	1.06
1	2.37	1.06
1.5	1.73	0.99
2	1.43	0.97
2.5	1.25	0.97
3	1.10	0.98
4	0.91	0.98
6	0.69	0.98
8	0.78	0.99
10	0.80	1.00
12	0.79	0.99
15	0.85	0.98
18	0.90	1.01
24	0.95	1.03
30	1.01	1.01
36	1.06	0.99
48	1.08	0.98

1=TEST FASTING
2=TEST NON-FASTING
3=REF. NON-FASTING

Table 4

CYCLOSPORINE ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY, N=24

	MEAN1*	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	6603.06	1236.15	6032.36	1095.07	6119.90	1104.92	1.09
AUCT	6234.31	1122.15	5752.72	995.65	5822.03	1016.88	1.08
CMAX	1275.75	251.56	822.10	123.58	804.08	173.93	1.55
KE	0.04	0.01	0.04	0.01	0.04	0.01	0.85
LAUCI	6492.73	0.19	5941.18	0.18	6025.46	0.18	1.09
LAUCT	6138.34	0.18	5672.18	0.17	5737.14	0.18	1.08
LCMAX	1252.63	0.20	812.93	0.15	788.19	0.20	1.54
THALF	19.41	3.44	16.38	2.78	17.06	2.56	1.19
TMAX	1.43	0.68	2.38	0.92	2.29	0.74	0.60

* n=23

(CONTINUED)

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
ARITHMETIC MEANS AND RATIOS

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.08	0.99
AUCT	1.07	0.99
CMAX	1.59	1.02
KE	0.89	1.05
LAUCI	1.08	0.99
LAUCT	1.07	0.99
LCMAX	1.59	1.03
THALF	1.14	0.96
TMAX	0.63	1.04

LSMEANS AND RATIOS

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	6661.24	6036.42	6112.01	1.10	1.09	0.99
AUCT	6290.72	5759.14	5819.55	1.09	1.08	0.99
CMAX	1301.43	827.21	804.88	1.57	1.62	1.03
LAUCI	6549.53	5945.20	6019.26	1.10	1.09	0.99
LAUCT	6191.85	5677.53	5734.93	1.09	1.08	0.99
LCMAX	1282.72	815.55	787.61	1.57	1.63	1.04

1= TEST FASTING
2= TEST NON-FASTING
3= REF. NON-FASTING

FIG 1. BLOOD CYCLOSPORINE LEVELS

CYCLOSPORINE ORAL SOLUTION, 100 MG/ML, ANDA #65-025
UNDER FASTING CONDITIONS
DOSE=3 X 100 MG/ML

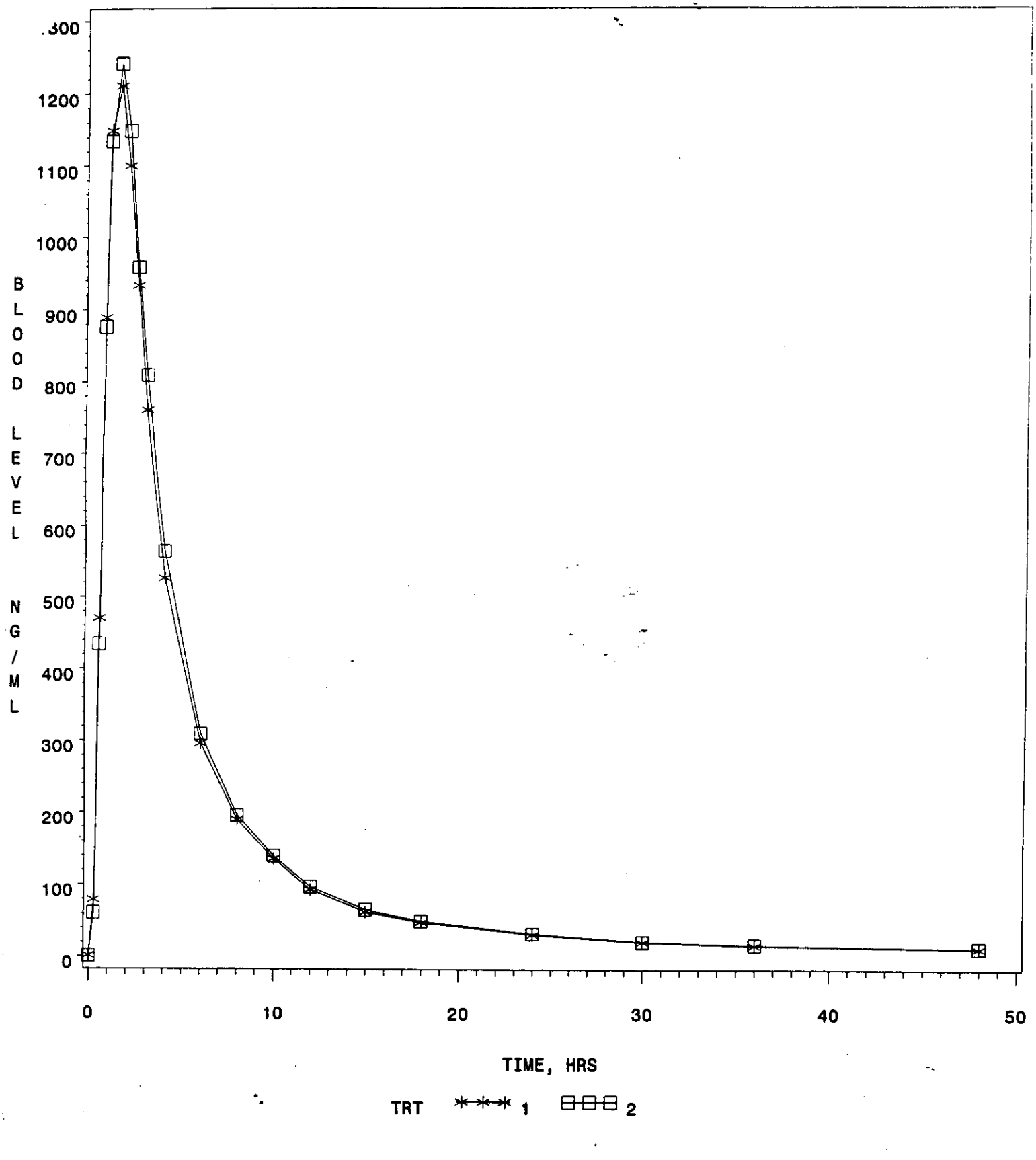
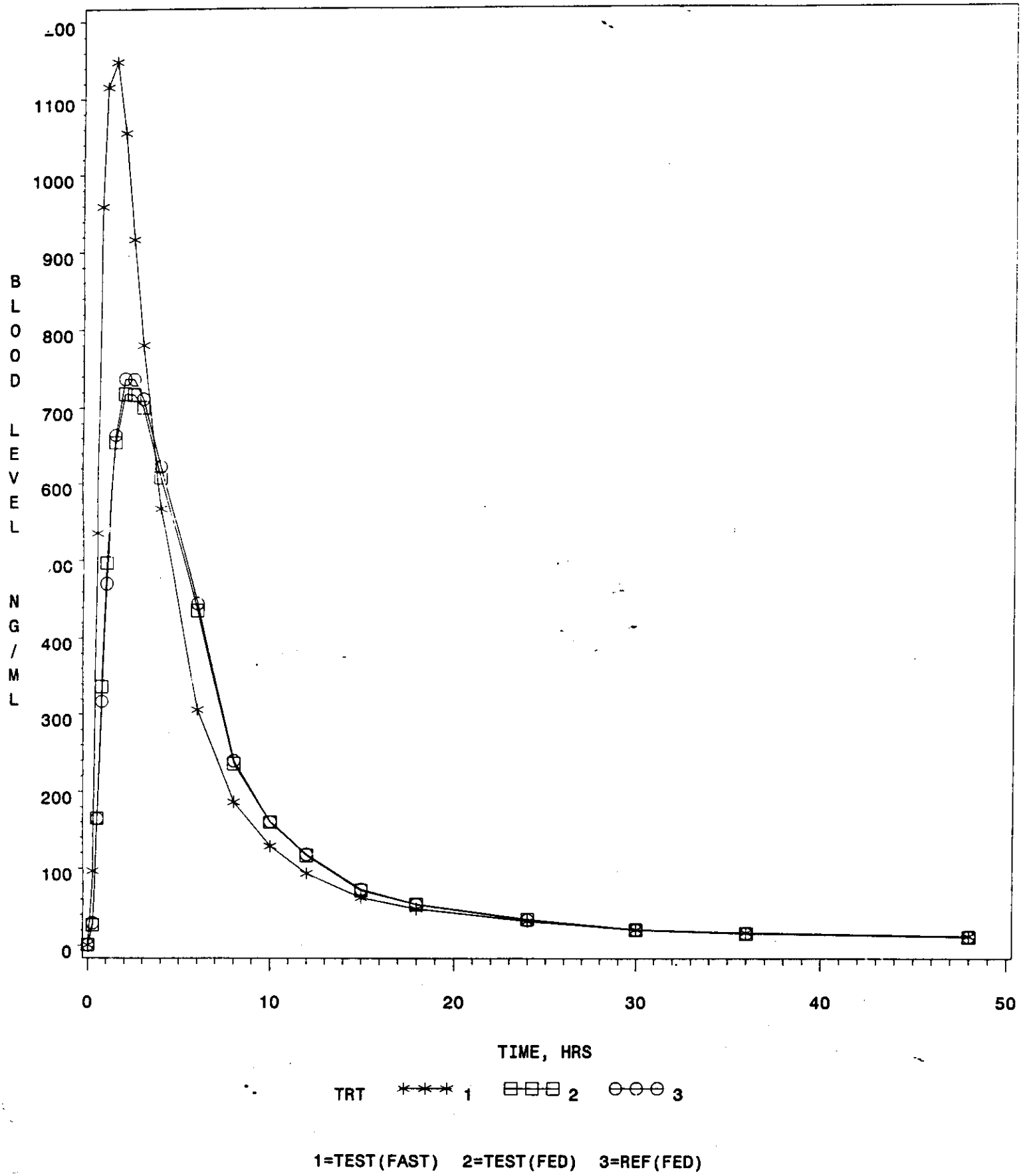


FIG 2. BLOOD CYCLOSPORINE LEVELS

CYCLOSPORINE ORAL SOLUTION, 100 MG/ML, ANDA #65-025
UNDER FASTING/NONFASTING CONDITIONS
DOSE=3 X 100 MG/ML



CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-025

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA #: 65-025 **FIRM:** Abbott Laboratories

DRUG PRODUCT: Cyclosporine Oral Solution, USP

DOSAGE: Oral Solution **STRENGTH:** 100 mg/mL

CAMP STATEMENT/EIR UPDATE STATUS: Acceptable (8/24/99)

BIO STUDY: Acceptable (1/28/99)

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Not requested (USP drug)

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION): The container/closure system used in the stability is the same as those described in the container section.

LABELING: Acceptable (12/16/99)

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): See below

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
An exhibit lot (Lot #30-735-AR-05) of was manufactured in support of the L maximum production size. An attempt was made to package an equal amount of both amber glass bottles and TET bottles (1000 each), actually glass bottles and ET bottles were filled.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): See above

Specifications for active ingredient: Under #23A

Specifications for the finished product: Under #28 and #29

CHEMIST: Maria C. Shih /S/ 12/17/99 **DATE:** 9/21/99

SUPERVISOR: R. Adams /S/ **DATE:** 12/17/99

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-025 Date of Submission: August 14, 1998 and October 23, 1998

Applicant's Name: Abbott Laboratories

Established Name: Cyclosporine Oral Solution USP (**MODIFIED**), 100 mg/mL

Labeling Deficiencies:

1. GENERAL COMMENTS:

   a. We acknowledge your proposal for a combined package insert for your separate applications for cyclosporine oral solution and capsules. Please note that these applications must be approved at the same time, or further revisions may be necessary prior to approval.

   b. The Nomenclature Committee has found your proposed proprietary name "Gengraf™" acceptable.

   c. Please note that the comments in this review supersede the ones appearing in the Agency's labeling deficiency letter for your application ANDA 65-003 submitted August 14, 1998.

   d. We acknowledge your comments regarding the established name (Cyclosporine oral solution, USP). Although this is the accurate established name for this product, we ask that you distinguish your product from the non-modified formulation by revising your product's established name to read "Cyclosporine Oral Solution, USP (**MODIFIED**)" throughout your labels and labeling.

2. CONTAINER - 50 mL (Glass & PET bottle)

   a. See general comments, as applicable.

   b. Include "USUAL DOSAGE" prior to the text "See enclosed...".

c. Revise the "Store and dispense" requirement to read "... 68° to 77°F (20° to 25°C). Do not... two months. See package insert for further information.".

d. Include the statement "*Sandimmune® is a registered trademark of Novartis Pharmaceuticals Corporation".

3. CARTON

a. See comments (a), (b) & (d) under CONTAINER.

b. Revise the storage requirement to read "temperature 68° to 77°F (20° to 25°C). Use...".

c. We encourage you to increase the prominence of the statement "Do not rinse syringe before use." using bold face and upper case letters.

4. INSERT

a. GENERAL

i. See general comments, as applicable.

ii. Please assure that the requirements of 21 CFR 201.10(g) are met throughout the text. The established name must appear in certain sections in association with the proprietary name. Please revise your labeling accordingly.

iii. Include your proprietary name "Gengraf™" in place of Neoral® appearing in the reference listed drug labeling where applicable.

iv. We ask you to include the term "non-modified" when expressing the established name for Sandimmune® to read "cyclosporine, (non-modified)" where Sandimmune® appears in the insert labeling of the reference listed drug. However, please retain the innovator's proprietary name "Sandimmune®" {i.e., Sandimmune® (cyclosporine [non-modified])} where it appears when making comparison to or substitution of your product for Sandimmune®. In addition, add asterisk to read "*Sandimmune®" in order to acknowledge that "*Sandimmune® is a registered trademark of

Novartis Pharmaceuticals Corporation".

v. Due to the difficulty in determining the dosage form of the reference listed drug utilized during **clinical studies** (oral solution or capsule), we ask that you assure the following wording appears throughout the insert (including the tables):

Where "Neoral®" appears in the innovator's package insert labeling without reference to specific dosage form, revise to read "cyclosporine (**MODIFIED**)".

Likewise, where "Sandimmune®" appears in the innovator's insert labeling without reference to specific dosage form, revise to read "cyclosporine (non-modified)".

vi. It is preferable to use the term "to" rather than a hyphen when expressing a range.

b. BOXED WARNING

i. First box - First sentence:

... transplant recipients should... [rather than "patients"]

ii. Second box

Delete the first sentence.

c. DESCRIPTION

i. We note that the innovator describes their product as forming a microemulsion in an aqueous environment. Please describe in the first paragraph how your drug product is modified in the same condition.

ii. We ask that you include the alcohol content of your product in terms of percent volume (v/v) of absolute alcohol. You may add the alcohol content on a w/w basis as well, if you prefer. You are referred to section 502(e) of the Act and 21 CFR 201.10(d)(2) for guidance.

iii. We note that you have indicated "other ingredients". Please note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure. Please respond accordingly by correctly noting all the inactive ingredients present in this product. If you elect not to mention an inactive ingredient because it is a trade secret and decide to retain the phrase "and other ingredients", provide supporting data concerning the "trade secret".

iv. Include the following as the second paragraph in this section.

NOTE: The nomenclature "Cyclosporine Oral Suspension for Microemulsion" has been changed throughout the insert to read "Cyclosporine Oral Solution, USP (**MODIFIED**)".

v. Please include the structural formula, molecular weight, and molecular formula of your drug products.

d. CLINICAL PHARMACOLOGY

i. Pharmacokinetics - Eighth sentence [Gengraf Capsules ... for microemulsion)].

Revise to read as follows:

Gengraf™ capsules (cyclosporine capsules, [**MODIFIED**]) are bioequivalent to Gengraf™ oral solution (cyclosporine oral solution, [**MODIFIED**]).

ii. Absorption

A) Delete the second sentence "Gengraf is ... for microemulsion).".

B) Second paragraph:

We have determined that kinetics information appearing in the labeling of reference listed drug can be used in the labeling of all generic drug

applications. Please revise to cite studies of the reference listed drug. Also, we note that you have made comparisons regarding kinetics which do not appear in the labeling of the reference listed drug and should be deleted.

e. CLINICAL TRIALS (Rheumatoid Arthritis) - Table:

i. Please assure that the bars representing different regimens are distinguished properly.

ii. Revise to read "columns" at the top of the graph. [spelling]

iii. Replace Neoral with "CsA(**MODIFIED**)[1]".

iv. Include the legend to read "1 Cyclosporine (**MODIFIED**)".

f. INDICATIONS AND USAGE - Revise the last sentence to read as follows:

Cyclosporine (**MODIFIED**) has been ... corticosteroids".

g. WARNINGS

Revise to read "dL" rather than "dl" throughout this section.

h. PRECAUTIONS

i. General

A) Special Monitoring of Rheumatoid Arthritis Patients - Third sentence:

... after an increase of the...

B) Special Monitoring for Psoriasis Patients - Fourth paragraph, fourth sentence:

If at **any time** the serum... [note "bold face"]

ii. Information for Patients - Second paragraph, first sentence:

... receiving cyclosporine.

iii. Drug Interactions (Drugs That May Potentiate Renal Dysfunction):

"sulidac" rather than "sulindrec".

iv. Pediatric Use - Last sentence:

... treatment in pediatric patients with...

i. ADVERSE REACTIONS

i. Rheumatoid Arthritis - Table:

A) Replace "Cyclosporine for Microemulsion" with "Cyclosporine **(MODIFIED)**". [2 places]

B) Please rewrite headings of the table on each page when you prepare final print.

ii. Psoriasis

A) Second paragraph, first sentence:

... with U.S. controlled clinical studies...

B) Replace "Cyclosporine for Microemulsion" with "Cyclosporine **(MODIFIED)**".

j. DOSAGE AND ADMINISTRATION

a. First paragraph:

Delete the first sentence.

b. Include the section headings wherever a reference is made to a subsection in the text throughout this section. [e.g., "(see CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption)"]

c. Rheumatoid Arthritis - Second paragraph:

... (See WARNINGS...) [plural]

k. HOW SUPPLIED

a. Gengraf Oral Solution

... 100 mg/mL with dispensing syringe (NDC...).

b. Revise the last statement to read as follows:

*Sandimmune® is registered trademark of Novartis Pharmaceuticals Corporation.

Please revise your labels and labeling, as instructed above, and submit in draft or in final print, if you prefer.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed innovator's labeling with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 65-025

CORRESPONDENCE

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

July 15, 1999

NDA ORIG AMENDMENT

N/A

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Attention: Mark Anderson, Project Manager

Re: ANDA 65-025
Cyclosporine Oral Solution, USP (modified)

MINOR AMENDMENT

Dear Sir:

The sponsor is providing this correspondence to address the deficiencies identified in the letter dated June 9, 1999.

The CMC issues identified as "Chemistry Deficiencies, Item 1-5, are addressed in the following attachments.

The issue regarding the safety of the and s similar to the discussion regarding the Cyclosporine capsule under At that time it was felt the data held in the suppliers DMF was adequate to support the use of the associated inactives. In the case of the Cyclosporine Oral Solution the inactive ingredient, is filed under DMF held by Although there is no DMF for the his inactive is also used in the Cyclosporine capsule formulation in approximately the same concentration (ie.

capsule).

Regarding the compliance evaluation of the Abbott Laboratories North Chicago manufacturing site, a follow up meeting was held between the sponsor and the Chicago

District on June 25, 1999 to discuss the audit findings. Based on that meeting and subsequent discussions, it is the sponsor's belief that a recommendation for approval of the Cyclosporine Oral Solution will be made by the second week of August.

The comments from the Labeling Review Branch have been also been addressed. Four copies of the updated package insert and bottle/carton labels are included in this submission.

If you have any questions regarding this information, please call at the number provided below.

Sincerely,

Rebecca A Welch

Rebecca A. Welch
Associate Director
Dept. 491, PPD Regulatory Affairs
100 Abbott Park Rd.
Abbott Park IL 60064-6108
847-937-8971

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-6108

December 7, 1999

NDA ONLY AMENDMENT
N/AF

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Division of Chemistry II
Document Control Room, Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

ttention: Mr. Mark Anderson.

e: **ANDA 65-025**
Gengraf™ Oral Solution
(cyclosporine oral solution, USP [MODIFIED])

Labeling Fax Amendment

r Sir:

sponsor is providing this amendment to address the deficiencies identified in the letter d October 21, 1999. The letter included comments on the labeling for ANDA 65-025.

esponses to the labeling comments are provided. The FPL for the bottle, carton and ge insert are provided as references 1, 2 and 3. The review copy has 12 mounted copies of or each label. The archival copy includes one copy of each label. In addition, the ted labeling is provided behind the last tab, "Annotated Labels". In order to perform a side comparison, a copy of the innovator bottle label, carton and insert are included. notated package insert is provided on a side by side label format, where any changes to ovator text has been reflected in the right hand column. This format has been cause it provides a high quality copy and is easier to review.

t version of the innovator insert (June '97) is also provided for the reviewer, however quality is poor due to the original package insert being printed in blue and oversized. eing provided as an aid to the reviewer and is not expected to be used for the review.

The Gengraf package insert has been provided on disk in Word '97 and is included in the archival copy. This label has been verified to be an exact copy of the FPL but is in an 81/2 x 11" format. This is being provided as a reviewer aid.

This submission consists of one volume. Two copies (archival and review copies) are being provided to the Office of Generic Drugs.

Thank you for your attention to this matter. Please contact me at the number provided below if you have any questions or concerns regarding this information.

Sincerely,

Rebecca A Welch

Rebecca A. Welch
Regulatory Affairs
D491, Building AP6B
Pharmaceutical Products Division
Abbott Laboratories
(847) 937-8971

ANDA 65-025

Abbott Laboratories
Attention: Rebecca A. Welch
D-491/AP6B-1
100 Abbott Park Road
Abbott Park, IL 60064-3500

NOV 27 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our "Refuse to File" letter dated September 24, 1998 and your amendment dated October 23, 1998.

NAME OF DRUG: Cyclosporine Oral Solution USP, 100 mg/mL

DATE OF APPLICATION: August 14, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 26, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

October 23, 1998

NDA ORIG AMENDMENT
N/Ac

505(b)(2) CK
11/13/98

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Jerry Phillips
Division of Labeling and Program Support
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Re: ANDA 65-025
Cyclosporine Oral Solution USP (modified)
Amendment

Dear Sir:

The sponsor is submitting this amendment under Section 505 (j) of the Federal Food, Drug and Cosmetic Act and CFR 314.96 for Cyclosporine Oral Solution USP, 100 mg/mL. This submission is being made in response to a Refuse to File letter dated September 24, 1998 and signed by Mr. Jerry Phillips, Director, Division of Labeling and Program Support.

The Office of Generic Drugs has refused to file the ANDA for Cyclosporine Oral Solution for the reasons stated in the referenced letter. The sponsor, Abbott Laboratories, is responding to the concerns and amending the application within 30 days from the date of the letter.

If you have any comments regarding this information, please contact me at the number provided below.

Thank you for your attention to this matter.

Sincerely,
Rebecca A Welch

Rebecca A. Welch
Regulatory Affairs
D491, Building AP6B
Pharmaceutical Products Division
Abbott Laboratories
847-937-8971

RECEIVED
OCT 2 0 1998
GENERIC DRUG

ANDA 65-025

Abbott Laboratories
Attention: Rebecca A. Welch
D-491/AP6B-1
100 Abbott Park Road
Abbott Park, IL 60064-3500

SEP 24 1998

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated August 14, 1998, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Cyclosporine Oral Solution USP, 100 mg/mL.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(2) for the following reasons:

You have failed to provide data on the active drug substance lot used in the manufacture of your test batch. Please provide this data.

You have failed to provide a letter of authorization from the AADA applicant for the approved bulk antibiotic cyclosporine, which would permit the FDA to refer to the approved application to support the approval of your application for Cyclosporine Oral Solution USP, 100 mg/mL. Please provide this authorization from the applicant of the approved antibiotic application for cyclosporine.

You have failed to provide complete blank master batch records for your proposed production batch. These blank batch records must show the maximum batch size proposed as well as packaging records and labeling reconciliation records.

Your proposed labeling as well as the summary of the container/closure system indicate that your proposed product will be packaged in 2 oz. bottles but page 4540 refers to

2 oz. bottles and 5 mL syringes. Please explain this discrepancy.

The application lacks side-by-side comparisons of the proposed labeling versus the labeling for the reference listed drug with all of the differences annotated and explained. Labeling is defined in the regulations to include both container labels and package insert labeling. Please provide this comparison with all differences annotated and explained as per 21 CFR 314.94(a)(8)(iv).

Your form FDA 356h does not contain an original signature. Please provide a new form with an original signature.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Gregory S. Davis
Project Manager
(301) 827-5862

Sincerely yours,

/S/

Jerry Phillips 9/24/98
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
100 Abbott Park Road
D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

RTF 9/21/98
Gregory S. Davis

August 14, 1998

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

Re: Gengraf™
Cyclosporine Oral Solution, USP
ANDA

Original Submission

Dear Madam or Sir:

The sponsor, Abbott Laboratories, submits the following information under the provision of section 505 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94. This information consists of Chemistry, Manufacturing and Controls information and two bioequivalence studies comparing Abbott Gengraf™ (Cyclosporine Oral Solution, USP) to the innovator product, Neoral® Oral Solution.

This submission consists of 15 volumes. A complete set of the volumes has been provided as the archival copy (blue). Sections I-VII are being provided for bioavailability/bioequivalence review (orange). Sections I-V and VII-XXI are being provided for chemistry review (red). In addition, a complete copy of the chemistry, manufacturing and controls sections, Sections I-V and VII-XXI, have been provided as the field copy to the FDA Chicago District Office as required in 21 CFR 314.70 (burgundy).

Two additional copies of the Methods Validation (Section XVI) information are included. Although the product is a USP monograph item, the HPLC test methods have been modified in order to assure the degradants are separated from the Cyclosporine A main peak. Abbott Gengraf™ (Cyclosporine Oral Solution, USP) does meet the USP monograph requirements for Cyclosporine Oral Solution, USP.

A complete list of the available samples is included in section XIX. The actual samples of the drug substance and drug product are not included in this submission, but will be provided upon request.

This application meets the requirements for a categorical exclusion for an environmental assessment, under 21 CFR 25.24 because the formulation will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect.

There are no user fees associated with this application.

As always, should you have any questions regarding this information, please call me at the number provided below.

Rebecca A Welch

Rebecca A. Welch
Sr. Administrator, PPD Regulatory Affairs
Abbott Laboratories
Dept. 491, Bldg. AP6B-1
(847) 937-8971
100 Abbott Park Road
Abbott Park, IL 60064