CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

65-040

Generic Name: Cyclosporine Capsules, USP

Sponsor: Apotex Corporation

Approval Date: May 9, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
65-040

CONTENTS

Reviews / Information Included in this ANDA Review.	
Approval Letter	X
Tentative Approval Letter	X
ANDAs	
Approvable Letter	
Final Printed Labeling	X
Medical Review(s)	
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Reviews	
Bioequivalence Review(s)	X
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-040

APPROVAL LETTER

ANDA 65-040

May 9, 2002

Apotex Corporation
Attention: Marcy Macdonald
U.S. Agent for: TorPharm Inc.
50 Lakeview Parkway, Suite #127
Vernon Hills, IL 60061

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated January 11, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cyclosporine Capsules USP, 25 mg and 100 mg. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated June 9, and September 30, 1999; April 12, 2000; May 18, September 24, and November 8, 2001; and February 7, and April 10, 2002.

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 Capsules USP, 25 mg and 100 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Sandimmune® Soft Gelatin Capsules, 25 mg and 100 mg, respectively, of Novartis Pharmaceuticals Corp.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

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 that 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 5/9/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

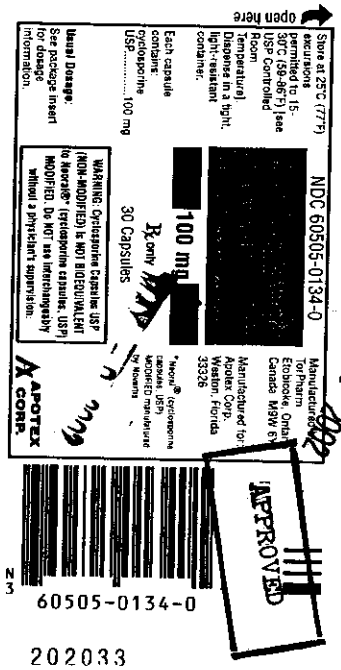
APPLICATION NUMBER:

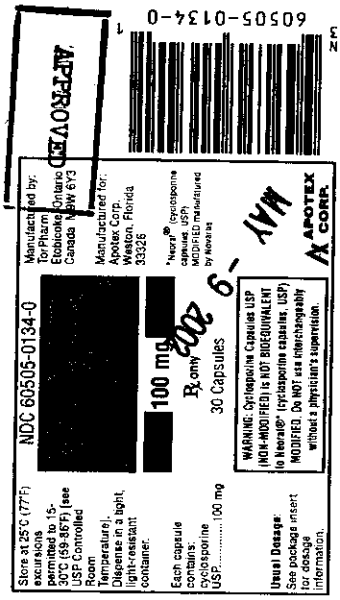
65-040

APPROVED FINAL LABELING

COVER
TORP6530

DOWN
TORP6530





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

Drug Interactions
All of the individual drugs cited below are well substantiated to interact with cyclosporine.

Drugs That Exhibit Nephrotoxic Synergy

gentamicin	amphotericin B	cimetidine	trimethoprim
tobramycin	ketoconazole	ranitidine	with sulfamethoxazole
vancomycin	melphalan	diclofenac	azapropazon

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

Drugs That Alter Cyclosporine Levels
Cyclosporine is extensively metabolized by the liver. Therefore, circulating cyclosporine levels may be influenced by drugs that affect hepatic microsomal enzymes, particularly the cytochrome P-450 system. Substances known to inhibit these enzymes will decrease hepatic metabolism and increase cyclosporine levels. Substances that are inducers of cytochrome P-450 activity will increase hepatic metabolism and decrease cyclosporine levels. Monitoring of circulating cyclosporine levels and appropriate cyclosporine dosage adjustment are essential when these drugs are used concomitantly (See **Blood Level Monitoring**).

Drugs That Increase Cyclosporine Levels

CYCLOSPORINE CAPSULES USP
25 mg and 100 mg

℞ only

WARNING

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Cyclosporine Capsules USP NON-MODIFIED. 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.

Cyclosporine Capsules USP NON-MODIFIED should be administered with adrenal corticosteroids but not with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.

Cyclosporine Soft Gelatin Capsules USP (NON-MODIFIED) have decreased bioavailability in comparison to Neoral®* (cyclosporine capsules, USP) MODIFIED.

Cyclosporine Capsules USP (NON-MODIFIED) and Neoral®* (cyclosporine capsules, USP) MODIFIED are not bioequivalent and cannot be used

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

Drug Interactions
All of the individual drugs cited below are well substantiated to interact with cyclosporine.

Drugs That Exhibit Nephrotoxic Synergy

gentamicin	amphotericin B	cimetidine	trimethoprim
tobramycin	ketoconazole	ranitidine	with sulfamethoxazole
vancomycin	melphalan	diclofenac	azapropazon

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

Drugs That Alter Cyclosporine Levels
Cyclosporine is extensively metabolized by the liver. Therefore, circulating cyclosporine levels may be influenced by drugs that affect hepatic microsomal enzymes, particularly the cytochrome P-450 system. Substances known to inhibit these enzymes will decrease hepatic metabolism and increase cyclosporine levels. Substances that are inducers of cytochrome P-450 activity will increase hepatic metabolism and decrease cyclosporine levels. Monitoring of circulating cyclosporine levels and appropriate cyclosporine dosage adjustment are essential when these drugs are used concomitantly (See **Blood Level Monitoring**)

Drugs That Increase Cyclosporine Levels

diltiazem	ketoconazole	danazol	erythromycin
nicardipine	fluconazole	bromocriptine	methylprednisolone
verapamil	itraconazole	metoclopramide	

Drugs That Decrease Cyclosporine Levels

rifampin	phenytoin	phenobarbital	carbamazepine

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 Capsules USP, vaccination may be less effective; and 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.

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

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

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

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

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

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

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

The following data represent the reported outcomes of 116 pregnancies in women receiving cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period. Since most of the patients were not prospectively identified, the results are likely to be biased toward negative outcomes. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. It is not possible to separate the effects of cyclosporine on these pregnancies from the effects of the other immunosuppressants, the underlying maternal disorders, or other aspects of the transplantation milieu. Sixteen fetal losses occurred. Most of the pregnancies (65 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%. In a report of 23 children followed up to 4 years, postnatal development was said to be normal.

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

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

ADVERSE REACTIONS

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

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

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

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

	Randomized Kidney Patients		All Cyclosporine Patients		
Body System/ Adverse Reactions	Cyclosporine (N=227) %	Azathioprine (N=229) %	Kidney (N=705) %	Heart (N=112) %	Liver (N=75) %
Genitourinary					
Renal Dysfunction	32	6	25	38	37
Cardiovascular					
Hypertension	26	16	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	1	0	0	5	16

CYCLOSPORINE CAPSULES USP
25 mg and 100 mg

℞ only

WARNING

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Cyclosporine Capsules USP NON-MODIFIED. 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.

Cyclosporine Capsules USP NON-MODIFIED should be administered with adrenal corticosteroids but not with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.

Cyclosporine Soft Gelatin Capsules USP (NON-MODIFIED) have decreased bioavailability in comparison to Neoral® (cyclosporine capsules, USP) MODIFIED.

Cyclosporine Capsules USP (NON-MODIFIED) and Neoral® (cyclosporine capsules, USP) MODIFIED are not bioequivalent and cannot be used interchangeably without physician supervision.

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

DESCRIPTION

Cyclosporine, the active principle in Cyclosporine Capsules USP is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Tolypocladium inflatum Gams*.

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).

Cyclosporine Capsules USP are provided as hard shell capsules. The hard shell capsules do not contain a solution of cyclosporine in a suitable vehicle. The capsules contain cyclosporine in the form of dry granules.

Cyclosporine Capsules USP are available in 25 mg and 100 mg strengths.

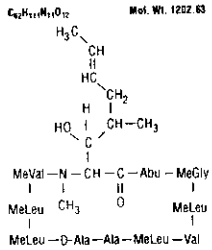
Each 25 mg capsule contains:
cyclosporine USP ..... 25 mg

Each 100 mg capsule contains
cyclosporine USP ..... 100 mg

Each capsule contains the following inactive ingredients: methanol, purified water, sodium lauryl sulfate and talc. The 25 mg and the 100 mg capsule shell contains gelatin, red iron oxide and titanium dioxide. The 25 mg and 100 mg capsule black imprinting ink contains the following inactive ingredients: n-butyl alcohol, D&C yellow #10 aluminum lake, FD&C blue #1 aluminum lake, FD&C blue #2 aluminum lake, FD&C red #40 aluminum lake, pharmaceutical glaze, propylene glycol, SDA-3A alcohol and synthetic black iron oxide.

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

$C_{62}H_{111}N_{11}O_{12}$ Mol. Wt. 1202.63



CLINICAL PHARMACOLOGY

Cyclosporine is a potent immunosuppressive agent which in animals prolongs survival of allogeneic transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine, and lung. Cyclosporine has been demonstrated to suppress some humoral immunity and to a greater extent, cell-mediated reactions such as allograft rejection, delayed hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, and graft vs. host disease in many animal species for a variety of organs.

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

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

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

The absorption of cyclosporine from the gastrointestinal tract is incomplete and variable. Peak concentrations (C_{max}) in blood and plasma are achieved at about 3.5 hours. C_{max} and area under the plasma or blood concentration/time curve (AUC) increase with the administered dose, for blood the relationship is curvilinear (parabolic) between 0 and 1400 mg of dose. As determined by a specific assay, C_{max} is approximately 1.0 ng/mL/mg of dose for plasma and 2.7-1.4 ng/mL/mg of dose for blood (for low to high doses).

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Cyclosporine Capsules are contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

WARNINGS

(See boxed **WARNINGs**)

Cyclosporine Capsules USP NON-MODIFIED, when used in high doses, can cause hepatotoxicity and nephrotoxicity.

Cardiovascular					
Hypertension	26	18	13	53	27
Cramps	4	<1	2	<1	0
Skin					
Hirsutism	21	<1	21	28	45
Acne	6	8	2	2	1
Central Nervous System					
Tremor	12	0	21	31	55
Convulsions	3	1	1	4	5
Headache	2	<1	2	15	4
Gastrointestinal					
Gum Hyperplasia	4	0	9	5	16
Diarrhea	3	<1	3	4	8
Nausea/Vomiting	2	<1	4	10	4
Hepatotoxicity	<1	<1	4	7	4
Abdominal Discomfort	<1	0	<1	7	0
Autonomic Nervous System					
Paresthesia	3	0	1	2	1
Flushing	<1	0	4	0	4
Hematopoietic					
Leukopenia	2	19	<1	6	0
Lymphoma	<1	0	1	6	1
Respiratory					
Sinusitis	<1	0	4	3	7
Miscellaneous					
Gynecomastia	<1	0	<1	4	3

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

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

Renal Transplant Patients in Whom Therapy Was Discontinued

Reason for Discontinuation	Randomized Patients Cyclosporine (N=227) %	Randomized Patients Azathioprine (N=228) %	All Cyclosporine Patients (N=705) %
Renal Toxicity	5 7	0	5 4
Infection	0	0 4	0 9
Lack of Efficacy	2 8	0 9	1.4
Acute Tubular Necrosis	2 6	0	1 0
Lymphoma/ Lymphoproliferative Disease	0 4	0	0.3
Hypertension	0	0	0.3
Hematological Abnormalities	0	0 4	0
Other	0	0	0 7

Cyclosporine was discontinued on a temporary basis and then restarted in 18 additional patients.

Infectious Complications in the Randomized Renal Transplant Patients

Complication	Cyclosporine Treatment (N=227) % of Complications	Standard Treatment* (N=228) % 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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Cyclosporine Capsules USP NON-MODIFIED

Cyclosporine Capsules USP (NON-MODIFIED) have decreased bioavailability in comparison to Neoral®* (cyclosporine capsules, USP) MODIFIED. Cyclosporine Capsules USP (NON MODIFIED) and Neoral®* (cyclosporine capsules, USP) MODIFIED are not bioequivalent and cannot be used interchangeably without physician supervision.

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

(See **Blood Level Monitoring** below)

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

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

[illegible] USP NON-MODIFIED should be administered on a [illegible] with regard to time of day and relation to meals.

Blood Level Monitoring

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

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

(CYC/C-VA 01-APK-B-K-R04-280102)

HOW SUPPLIED

Cyclosporine Capsules USP

25 mg
Hard gelatin capsules with a pale reddish brown opaque body and a pale reddish brown opaque cap. "APO" over "133" and "25" are imprinted on each capsule in black ink, supplied in bottles of 30 (NDC 60505-0133-0) and in bottles of 1000 (NDC 60505-0133-1).

100 mg
Hard gelatin capsules with a reddish brown opaque body and a reddish brown opaque cap. "APO" over "134" and "100" are imprinted on each capsule in black ink; supplied in bottles of 30 (NDC 60505-0134-0) and in bottles of 1000 (NDC 60505-0134-1).

Store and Dispense
Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container. [see USP].

CONTRAINDICATIONS

Cyclosporine Capsules are contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

WARNINGS

(See boxed **WARNINGs**)

Cyclosporine Capsules USP NON-MODIFIED, when used in high doses, can cause hepatotoxicity and nephrotoxicity.

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

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

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

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

Nephrotoxicity vs Rejection

Parameter	Nephrotoxicity	Rejection
History	Donor > 50 years old or hypotensive Prolonged kidney preservation Prolonged anastomosis time Concomitant nephrotoxic drugs	Antidonor immune response Retransplant patient
Clinical	Often > 6 weeks postop[b] Prolonged initial nonfunction (acute tubular necrosis)	Often < 4 weeks postop[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	CyA serum trough level < 150 ng/mL
	Gradual rise in Cr (< 0.15 mg/dL/day)[a]	Rapid rise in Cr (> 0.3 mg/dL/day)[a]
	Cr plateau < 25% above baseline	Cr > 25% above baseline
	BUN/Cr ≥ 20	BUN/Cr < 20
Biopsy	Arteriolopathy (medial hypertrophy[a], hyalinosis, nodular deposits, intimal thickening, endothelial vacuolization, progressive scarring)	Endovasculitis[c] (proliferation[a], intimal arteritis[b], necrosis, sclerosis)
	Tubular atrophy, isometric vacuolization, isolated calcifications	Tubulitis with RBC[b] and WBC[b] casts, some irregular vacuolization
	Minimal edema	Interstitial edema[c] and hemorrhage[b]
	Mild focal infiltrates[c]	Diffuse moderate to severe mononuclear infiltrates[d]
	Diffuse interstitial fibrosis, often striped form	Glomerulitis (mononuclear cells)[c]
Aspiration Cytology	CyA deposits in tubular and endothelial cells Fine isometric vacuolization of tubular cells	Inflammatory infiltrate with mononuclear phagocytes, macrophages, lymphoblastoid cells, and activated T-cells
		These strongly express HLA-DR antigens
Urine Cytology	Tubular cells with vacuolization and granularization	Degenerative tubular cells, plasma cells, and lymphocyturia > 20% of sediment
Manometry	Intracapsular pressure < 40 mm Hg[c]	Intracapsular pressure > 40 mm Hg[b]
Ultrasonography	Unchanged graft cross sectional area	Increase in graft cross sectional area AP diameter ≥ Transverse diameter
Magnetic Resonance Imagery	Normal appearance	Loss of distinct corticomedullary junction, swelling, image intensity of parachyma approaching that of psoas, loss of hilar fat
Radionuclide Scan	Normal or generally decreased perfusion	Patchy arterial flow
	Decrease in tubular function	Decrease in perfusion > decrease in tubular function
	(^{131}I hippuran) > decrease in perfusion (^{99m}Tc DTPA)	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]$p < 0.0001$

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

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

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

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of cyclosporine and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans. (See **ADVERSE REACTIONS**)

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

Hepatotoxicity has been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of 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

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.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Cyclosporine Capsules USP NON-MODIFIED
Cyclosporine Capsules USP (NON-MODIFIED) have decreased bioavailability in comparison to Neoral®* (cyclosporine capsules, USP) MODIFIED. Cyclosporine Capsules USP (NON-MODIFIED) and Neoral®* (cyclosporine capsules, USP) MODIFIED are not bioequivalent and cannot be used interchangeably without physician supervision.

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

(See Blood Level Monitoring below)

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

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

Cyclosporine Capsules USP NON-MODIFIED should be administered on a consistent schedule with regard to time of day and relation to meals.

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

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

(CYC/C-VA-01-APX-B-K-R04-280102)

HOW SUPPLIED

Cyclosporine Capsules USP

25 mg
Hard gelatin capsules with a pale reddish brown opaque body and a pale reddish brown opaque cap. "APO" over "133" and "25" are imprinted on each capsule in black ink; supplied in bottles of 30 (NDC 60505-0133-0) and in bottles of 1000 (NDC 60505-0133-1).

100 mg
Hard gelatin capsules with a reddish brown opaque body and a reddish brown opaque cap. "APO" over "134" and "100" are imprinted on each capsule in black ink, supplied in bottles of 30 (NDC 60505-0134-0) and in bottles of 1000 (NDC 60505-0134-1).

Store and Dispense
Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container [see USP].

TORPHARM
CYCLOSPORINE CAPSULES USP
25 mg and 100 mg

Manufactured by:	Manufactured for:
TorPharm	Apotex Corp.
Etobicoke, Ontario	Weston, Florida
Canada M9W 6Y3	33326

Revised: January 2002

202033

*Neoral® (cyclosporine capsules, USP) MODIFIED manufactured by Novartis

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

$^{a}p < 0.05$, $^{b}p < 0.01$, $^{c}p < 0.001$, $^{d}p < 0.0001$

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

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

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

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of cyclosporine and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans. (See **ADVERSE REACTIONS**)

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

Hepatotoxicity has been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of 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, which can also increase susceptibility to infection, Cyclosporine Capsules USP should not be administered with other immunosuppressive agents except adrenal corticosteroids. The efficacy and safety of cyclosporine in combination with other immunosuppressive agents have not been determined.

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

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

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

Because Cyclosporine Capsules USP (NON-MODIFIED) are not bioequivalent to Neoral®* (cyclosporine capsules, USP) MODIFIED, conversion from Neoral®* (cyclosporine capsules, USP) MODIFIED to Cyclosporine Capsules USP (NON-MODIFIED) using a 1:1 ratio (mg/kg/day) may result in a lower cyclosporine blood concentration. Conversion from Neoral®* (cyclosporine capsules, USP) MODIFIED to Cyclosporine Capsules (NON-MODIFIED) should be made with increased blood concentration monitoring to avoid the potential of underdosing.

PRECAUTIONS

General
Patients with malabsorption may have difficulty in achieving therapeutic levels with cyclosporine.

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

During treatment with Cyclosporine Capsules USP NON-MODIFIED, vaccination may be less effective; and the use of live attenuated vaccines should be avoided.

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

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

APPROVED
MAY - 9 2002

Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature.] Dispense in a tight, light-resistant container.

Each capsule contains: cyclosporine USP.....100 mg

Usual Dosage: See package insert for dosage information.

NDC 60505-0134-1

[redacted]

[redacted] **100 mg** [redacted]

℞ only

1000 Capsules

WARNING:Cyclosporine Capsules USP (NON-MODIFIED) is NOT BIOEQUIVALENT to Neoral®* (cyclosporine capsules, USP) MODIFIED. Do NOT use interchangeably without a physician's supervision.

Manufactured by:
TorPharm
Etobicoke, Ontario
Canada M9W 6Y3

MAY - 9 2002

Manufactured for:
Apotex Corp.
Weston, Florida
33326

*Neoral® (cyclosporine capsules, USP) MODIFIED manufactured by Novartis

APPROVED

APOTEX CORP.

60505-0134-1

202035

Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature.] Dispense in a tight, light-resistant container.

Each capsule contains: cyclosporine USP.....100 mg

Usual Dosage: See package insert for dosage information.

NDC 60505-0134-1

[redacted] **100 mg** [redacted]

℞ only

1000 Capsules

WARNING:Cyclosporine Capsules USP (NON-MODIFIED) is NOT BIOEQUIVALENT to Neoral® (cyclosporine capsules, USP) MODIFIED. Do NOT use interchangeably without a physician's supervision.

Manufactured by:
TorPharm
Etobicoke, Ontario
Canada M9W 6Y3

MAY - 9 2002

Manufactured for:
Apotex Corp.
Weston, Florida
33326

*Neoral® (cyclosporine capsules, USP) MODIFIED manufactured by Novartis

APPROVED

APOTEX CORP.

60505-0134-1

60505-0134-1

Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature.] Dispense in a tight, light-resistant container.

Each capsule contains: cyclosporine USP..........100 mg

Usual Dosage: See package insert for dosage information.

NDC 60505-0134-1

[redacted]

100 mg

℞ only

1000 Capsules

WARNING: Cyclosporine Capsules USP (NON-MODIFIED) is NOT BIOEQUIVALENT to Neoral® (cyclosporine capsules, USP) MODIFIED. Do NOT use interchangeably without a physician's supervision.

Manufactured by:
TorPharm
Etobicoke, Ontario
Canada M9W 6Y3

Manufactured for:
Apotex Corp.
Weston, Florida
33326

*Neoral® (cyclosporine capsules, USP) MODIFIED manufactured by Novartis

APOTEX CORP.

APPROVED MAY - 9 200

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

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

Drug Interactions
All of the individual drugs cited below are well substantiated to interact with cyclosporine.

Drugs That Exhibit Nephrotoxic Synergy

gentamicin	amphotericin B	cimetidine	trimethoprim
tobramycin	ketoconazole	ranitidine	with sulfamethoxazole
vancomycin	melphalan	diclofenac	azapropazon

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

Drugs That Alter Cyclosporine Levels
Cyclosporine is extensively metabolized by the liver. Therefore, circulating cyclosporine levels may be influenced by drugs that affect hepatic microsomal enzymes, particularly the cytochrome P-450 system. Substances known to inhibit these enzymes will decrease hepatic metabolism and increase cyclosporine levels. Substances that are inducers of cytochrome P-450 activity will increase hepatic metabolism and decrease cyclosporine levels. Monitoring of circulating cyclosporine levels and appropriate cyclosporine dosage adjustment are essential when these drugs are used concomitantly (See **Blood Level Monitoring**).

Drugs That Increase Cyclosporine Levels

diltiazem	ketoconazole	danazol	erythromycin
nicardipine	fluconazole	bromocriptine	methylprednisolone
verapamil	itraconazole	metoclopramide	

Drugs That Decrease Cyclosporine Levels

rifampin	phenytoin	phenobarbital	carbamazepine

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 Capsules USP, vaccination may be less effective; and 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.

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

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

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

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

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

Pregnancy
Pregnancy Category C.
Cyclosporine Oral Solution, USP has been shown to be embryo- and fetotoxic in rats and rabbits when

CYCLOSPORINE CAPSULES USP

25 mg and 100 mg

℞ only

WARNING

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Cyclosporine Capsules USP NON-MODIFIED. 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.

Cyclosporine Capsules USP NON-MODIFIED should be administered with adrenal corticosteroids but not with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.

Cyclosporine Soft Gelatin Capsules USP (NON-MODIFIED) have decreased bioavailability in comparison to Neoral®* (cyclosporine capsules, USP) MODIFIED.

Cyclosporine Capsules USP (NON-MODIFIED) and Neoral®* (cyclosporine capsules, USP) MODIFIED are not bioequivalent and cannot be used interchangeably without physician supervision.

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

DESCRIPTION

Cyclosporine, the active principle in Cyclosporine Capsules USP is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Tolypocladium inflatum Gams*.

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).

Cyclosporine Capsules USP are provided as hard shell capsules. The hard shell capsules do not contain a solution of cyclosporine in a suitable vehicle. The capsules contain cyclosporine in the form of dry granules.

Cyclosporine Capsules USP are available in 25 mg and 100 mg strengths.

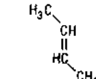
Each 25 mg capsule contains:
cyclosporine USP..25 mg

Each 100 mg capsule contains:
cyclosporine USP..100 mg

Each capsule contains the following inactive ingredients: methanol, purified water, sodium lauryl sulfate and talc. The 25 mg and the 100 mg capsule shell contains gelatin, red iron oxide and titanium dioxide. The 25 mg and 100 mg capsule black imprinting ink contains the following inactive ingredients: n-butyl alcohol, D&C yellow #10 aluminum lake, FD&C blue #1 aluminum lake, FD&C blue #2 aluminum lake, FD&C red #40 aluminum lake, pharmaceutical glaze, propylene glycol, SDA-3A alcohol and synthetic black iron oxide.

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

$C_{62}H_{111}N_{11}O_{12}$ **Mol. Wt. 1202.63**



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

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

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

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

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

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

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

The following data represent the reported outcomes of 116 pregnancies in women receiving cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period. Since most of the patients were not prospectively identified, the results are likely to be biased toward negative outcomes. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. It is not possible to separate the effects of cyclosporine on these pregnancies from the effects of the other immunosuppressants, the underlying maternal disorders, or other aspects of the transplantation milieu. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, 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%. In a report of 23 children followed up to 4 years, postnatal development was said to be normal.

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

Renal Transplant Patients in Whom Therapy Was Discontinued

	Randomized Patients		All Cyclosporine Patients
Reason for Discontinuation	**Cyclosporine (N=227) %**	**Azathioprine (N=228) %**	**(N=705) %**
Renal Toxicity	5.7	0	5.4
Infection	0	0.4	0.9
Lack of Efficacy	2.6	0.9	1.4

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).

Cyclosporine Capsules USP are provided as hard shell capsules. The hard shell capsules do not contain a solution of cyclosporine in a suitable vehicle. The capsules contain cyclosporine in the form of dry granules.

Cyclosporine Capsules USP are available in 25 mg and 100 mg strengths.

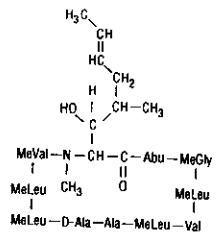
Each 25 mg capsule contains:
cyclosporine USP.....25 mg

Each 100 mg capsule contains:
cyclosporine USP.....100 mg

Each capsule contains the following inactive ingredients: methanol, purified water, sodium lauryl sulfate and talc. The 25 mg and the 100 mg capsule shell contains gelatin, red iron oxide and titanium dioxide. The 25 mg and 100 mg capsule black imprinting ink contains the following inactive ingredients: n-butyl alcohol, D&C yellow #10 aluminum lake, FD&C blue #1 aluminum lake, FD&C blue #2 aluminum lake, FD&C red #40 aluminum lake, pharmaceutical glaze, propylene glycol, SDA-3A alcohol and synthetic black iron oxide.

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

$C_{62}H_{111}N_{11}O_{12}$ **Mol. Wt. 1202.63**



CLINICAL PHARMACOLOGY

Cyclosporine is a potent immunosuppressive agent which in animals prolongs survival of allogeneic transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine, and lung. Cyclosporine has been demonstrated to suppress some humoral immunity and to a greater extent, cell-mediated reactions such as allograft rejection, delayed hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, and graft vs. host disease in many animal species for a variety of organs.

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

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

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

The absorption of cyclosporine from the gastrointestinal tract is incomplete and variable. Peak concentrations (C_{max}) in blood and plasma are achieved at about 3.5 hours. C_{max} and area under the plasma or blood concentration/time curve (AUC) increase with the administered dose; for blood the relationship is curvilinear (parabolic) between 0 and 1400 mg. As determined by a specific assay, C_{max} is approximately 1.0 ng/mL/mg of dose for plasma and 2.7-1.4 ng/mL/mg of dose for blood (for low to high doses).

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Cyclosporine Capsules are contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

WARNINGS

(See boxed **WARNINGs**)

Cyclosporine Capsules USP NON-MODIFIED, when used in high doses, can cause hepatotoxicity and nephrotoxicity.

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

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

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

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

	Nephrotoxicity vs Rejection	
Parameter	**Nephrotoxicity**	**Rejection**
History	Donor > 50 years old or hypotensive	Antidonor immune response
	Prolonged kidney preservation	Retransplant patient
	Profonged anastomosis time	
	Concomitant nephrotoxic drugs	
Clinical	Often > 6 weeks postop[b]	Often < 4 weeks postop[b]
	Prolonged initial nonfunction (acute tubular necrosis)	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	CyA serum trough level

Skin					
Hirsutism	21	<1	21	28	45
Acne	6	8	2	2	1
Central Nervous System					
Tremor	12	0	21	31	55
Convulsions	3	1	1	4	5
Headache	2	<1	2	15	4
Gastrointestinal					
Gum Hyperplasia	4	0	9	5	16
Diarrhea	3	<1	3	4	8
Nausea/Vomiting	2	<1	4	10	4
Hepatotoxicity	<1	<1	4	7	4
Abdominal Discomfort	<1	0	<1	7	0
Autonomic Nervous System					
Paresthesia	3	0	1	2	1
Flushing	<1	0	4	0	4
Hematopoietic					
Leukopenia	2	19	<1	6	0
Lymphoma	<1	0	1	6	1
Respiratory					
Sinusitis	<1	0	4	3	7
Miscellaneous					
Gynecomastia	<1	0	<1	4	3

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

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

Renal Transplant Patients in Whom Therapy Was Discontinued

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

Cyclosporine was discontinued on a temporary basis and then restarted in 18 additional patients.

Infectious Complications in the Randomized Renal Transplant Patients

Complication	Cyclosporine Treatment (N=227) % of Complications	Standard Treatment* (N=228) % 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.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Cyclosporine Capsules USP NON-MODIFIED

Cyclosporine Capsules USP (NON-MODIFIED) have decreased bioavailability in comparison to Neoral®* (cyclosporine capsules, USP) MODIFIED. Cyclosporine Capsules USP (NON-MODIFIED) and Neoral®* (cyclosporine capsules, USP) MODIFIED are not bioequivalent and cannot be used interchangeably without physician supervision.

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

(See **Blood Level Monitoring** below)

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

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

Cyclosporine Capsules USP NON-MODIFIED should be administered on a consistent schedule with regard to time of day and relation to meals.

Blood Level Monitoring

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

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

(CYC/C-VA-01-APX-D-K-R02-290102)

HOW SUPPLIED

Cyclosporine Capsules USP

25 mg

(See boxed **WARNINGs**)

Cyclosporine Capsules USP NON-MODIFIED, when used in high doses, can cause hepatotoxicity and nephrotoxicity.

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

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

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

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

Nephrotoxicity vs Rejection

Parameter	Nephrotoxicity	Rejection
History	Donor > 50 years old or hypotensive	Antidonor immune response
	Prolonged kidney preservation	Retransplant patient
	Prolonged anastomosis time	
	Concomitant nephrotoxic drugs	
Clinical	Often > 6 weeks postop[b]	Often < 4 weeks postop[b]
	Prolonged initial nonfunction (acute tubular necrosis)	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	CyA serum trough level < 150 ng/mL
	Gradual rise in Cr (< 0.15 mg/dL/day)[a]	Rapid rise in Cr (> 0.3 mg/dL/day)[a]
	Cr plateau < 25% above baseline	Cr > 25% above baseline
	BUN/Cr ≥ 20	BUN/Cr < 20
Biopsy	Arteriolopathy (medial hypertrophy[a], hyalinosis, nodular deposits, intimal thickening, endothelial vacuolization, progressive scarring)	Endovasculitis[c] (proliferation[a], intimal arteritis[b], necrosis, sclerosis)
	Tubular atrophy, isometric vacuolization, isolated calcifications	Tubulitis with RBC[b] and WBC[b] casts, some irregular vacuolization
	Minimal edema	Interstitial edema[c] and hemorrhage[b]
	Mild focal infiltrates[c]	Diffuse moderate to severe mononuclear infiltrates[d]
	Diffuse interstitial fibrosis, often striped form	Glomerulitis (mononuclear cells)[c]
Aspiration Cytology	CyA deposits in tubular and endothelial cells Fine isometric vacuolization of tubular cells	Inflammatory infiltrate with mononuclear phagocytes, macrophages, lymphoblastoid cells, and activated T-cells
		These strongly express HLA-DR antigens
Urine Cytology	Tubular cells with vacuolization and granularization	Degenerative tubular cells, plasma cells, and lymphocyturia > 20% of sediment
Manometry	Intracapsular pressure < 40 mm Hg[b]	Intracapsular pressure > 40 mm Hg[b]
Ultrasonography	Unchanged graft cross sectional area	Increase in graft cross sectional area
		AP diameter ≥ Transverse diameter
Magnetic Resonance Imagery	Normal appearance	Loss of distinct corticomedullary junction, swelling, image intensity of parachyma approaching that of psoas, loss of hilar fat
Radionuclide Scan	Normal or generally decreased perfusion	Patchy arterial flow
	Decrease in tubular function	Decrease in perfusion > decrease in tubular function
	(^{131} I-hippuran) > decrease in perfusion (^{99m} Tc DTPA)	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]$p < 0.0001$

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

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

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

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic

ııovııus	4.8	12.3
al Infections	15.9	18.4
ract Infections	21.1	20.2
nd Skin Infections	7.0	10.1
ia	6.2	9.2

atients also received ALG.

OVERDOSAGE

minimal experience with overdosage. Because of the slow absorption of Cyclosporine Capsules J-MODIFIED, forced emesis would be of value up to 2 hours after administration. Transient kicity and nephrotoxicity may occur which should resolve following drug withdrawal. General ve measures and symptomatic treatment should be followed in all cases of overdosage. rine is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion. The . is 2329 mg/kg in mice, 1480 mg/kg in rats, and > 1000 mg/kg in rabbits. The I.V. LD_{50} is g in mice, 104 mg/kg in rats, and 46 mg/kg in rabbits.

DOSAGE AND ADMINISTRATION

rine Capsules USP NON-MODIFIED
rine Capsules USP (NON-MODIFIED) have decreased bioavailability in comparison to Neoral®* rine capsules, USP) MODIFIED. Cyclosporine Capsules USP (NON-MODIFIED) and Neoral®* rine capsules, USP) MODIFIED are not bioequivalent and cannot be used interchangeably without supervision.

oral dose of Cyclosporine Capsules USP NON-MODIFIED should be given 4-12 hours prior to tation as a single dose of 15 mg/kg. Although a daily single dose of 14 to 18 mg/kg was used linical trials, few centers continue to use the highest dose, most favoring the lower end of the ere is a trend towards use of even lower initial doses for renal transplantation in the ranges of mg/kg/day. The initial single daily dose is continued postoperatively for 1-2 weeks and then y 5% per week to a maintenance dose of 5 to 10 mg/kg/day. Some centers have successfully ne maintenance dose to as low as 3 mg/kg/day in selected *renal* transplant patients without an rise in rejection rate.

d Level Monitoring below)

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

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

ine Capsules USP NON-MODIFIED should be administered on a consistent schedule with regard day and relation to meals.

el Monitoring
udy centers have found blood level monitoring of cyclosporine useful in patient management. fixed relationships have yet been established, in one series of 375 consecutive cadaveric renal t recipients, dosage was adjusted to achieve specific whole blood 24-hour trough levels of 0 ng/mL as determined by high-pressure liquid chromatography (HPLC).

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

(CYC/C-VA-01-APX-D-K-R02-290102)

HOW SUPPLIED

ine Capsules USP

tin capsules with a pale reddish brown opaque body and a pale reddish brown opaque cap. er "133" and "25" are imprinted on each capsule in black ink; supplied in bottles of 30 (NDC 33-0) and in bottles of 1000 (NDC 60505-0133-1).

in capsules with a reddish brown opaque body and a reddish brown opaque cap. "APO" over "100" are imprinted on each capsule in black ink; supplied in bottles of 30 (NDC 60505-0134- bottles of 1000 (NDC 60505-0134-1).

Dispense
25ºC (77ºF) excursions permitted to 15-30ºC (59-86ºF). [see USP Controlled Room re]. Dispense in a tight, light-resistant container. [see USP].

M
DRINE CAPSULES USP
1 100 mg

red by:	Manufactured for:
	Apotex Corp.
Ontario	Weston, Florida
9W 6Y3	33326

anuary 2002

(cyclosporine capsules, USP) MODIFIED manufactured by Novartis

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

$^{a}p < 0.05$, $^{b}p < 0.01$, $^{c}p < 0.001$, $^{d}p < 0.0001$

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

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

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

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of cyclosporine and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans. (See **ADVERSE REACTIONS**)

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

Hepatotoxicity has been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of 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, which can also increase susceptibility to infection, Cyclosporine Capsules USP should not be administered with other immunosuppressive agents except adrenal corticosteroids. The efficacy and safety of cyclosporine in combination with other immunosuppressive agents have not been determined.

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

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

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

Because Cyclosporine Capsules USP (NON-MODIFIED) are not bioequivalent to Neoral®* (cyclosporine capsules, USP) MODIFIED, conversion from Neoral®* (cyclosporine capsules, USP) MODIFIED to Cyclosporine Capsules USP (NON-MODIFIED) using a 1:1 ratio (mg/kg/day) may result in a lower cyclosporine blood concentration. Conversion from Neoral®* (cyclosporine capsules, USP) MODIFIED to Cyclosporine Capsules (NON-MODIFIED) should be made with increased blood concentration monitoring to avoid the potential of underdosing.

PRECAUTIONS

General
Patients with malabsorption may have difficulty in achieving therapeutic levels with cyclosporine.

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

During treatment with Cyclosporine Capsules USP NON-MODIFIED, vaccination may be less effective; and the use of live attenuated vaccines should be avoided.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-040

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 65-040

3. NAME AND ADDRESS OF APPLICANT
TorPharm
50 Steinway Boulevard
Etobicoke, Ontario M9W 6Y3
Canada

AUTHORIZED U.S. AGENT
Marcy Macdonald
Apotex Corporation
50 Lakeview Parkway, Suite #127
Vernon Hills, Illinois 60061

Phone: (847) 573-9999
Fax: (847) 573-1001

4. LEGAL BASIS FOR SUBMISSION
The application is based on Sandimmune® Soft Gelatin Capsules manufactured by Novartis Pharmaceutical Corporation (NDA# 50-625). The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
APO-MUNE (Cyclosporine Capsules)

7. NONPROPRIETARY NAME
Cyclosporine Capsules

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

9. AMENDMENTS AND OTHER DATES:
Firm:
Original Submission: 1/11/99
Additional Information (Certificate of analysis for cap): 1/26/99
Additional Information (DMF number for [redacted] 2/16/99
Bioequivalence Amendment: 6/9/99

FDA:
Acceptance for filing: 2/16/99
Labeling review: 3/29/99
Division of Bioequivalence review: 3/30/99

10. PHARMACOLOGICAL CATEGORY
    1. Prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants.
    2. Treatment of chronic rejection in patients previously treated with other immunosuppressive agents.

11. Rx or OTC
    Rx

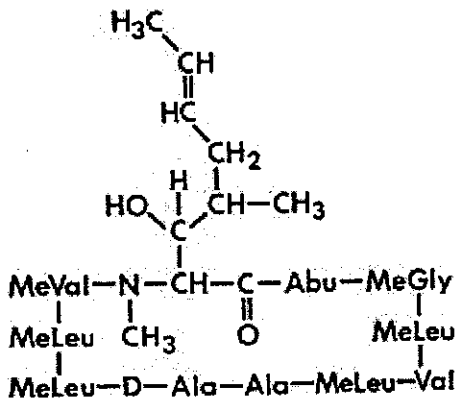
12. RELATED IND/NDA/DMF(s)
    NDA 50-625: Novartis Pharmaceutical Corporation
    DMF [redacted]
    DMF [redacted]
    DMF [redacted]
    DMF [redacted]
    DMF [redacted]

13. DOSAGE FORM
    Hard Gelatin Capsules

14. POTENCIES
    25 mg and 100 mg

15. CHEMICAL NAME AND STRUCTURE
    $C_{62}H_{111}N_{11}O_{12}$
    Mol. Wt. 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)



Redacted 22

pages of

trade secret and/or

confidential

commercial

information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 65-040

3. NAME AND ADDRESS OF APPLICANT

TorPharm
50 Steinway Boulevard
Etobicoke, Ontario M9W 6Y3
Canada

AUTHORIZED U.S. AGENT
Marcy Macdonald
Apotex Corporation
50 Lakeview Parkway, Suite #127
Vernon Hills, Illinois 60061

Phone: (847) 573-9999
Fax: (847) 573-1001

4. LEGAL BASIS FOR SUBMISSION

The application is based on Sandimmune® Soft Gelatin Capsules manufactured by Novartis Pharmaceutical Corporation (NDA# 50-625). The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

APO-MUNE (Cyclosporine Capsules)

7. NONPROPRIETARY NAME

Cyclosporine Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
Original Submission: 1/11/99
Additional Information: 1/26/99
Additional Information: 2/16/99
Bio Amendment: 6/9/99
Bio and Chemistry Correspondence: 9/30/99
Bio and Chemistry Amendment: 2/14/00
Bio Correspondence: 4/12/00

FDA:
Acceptance for Filing: 2/16/99
Labeling Review, deficient: 4/22/99
Bio Review, deficient: 3/30/99
Bio Review, deficient: 7/23/99
Chemistry Review, deficient: 9/13/99
Bio Review, acceptable: 11/23/99
Methods Validation, acceptable: 12/3/99
Bio Response to Correspondence: 5/25/00
Labeling Review, deficient: 7/7/00

10. PHARMACOLOGICAL CATEGORY
1. Prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants.
2. Treatment of chronic rejection in patients previously treated with other immunosuppressive agents.

11. Rx or OTC
Rx

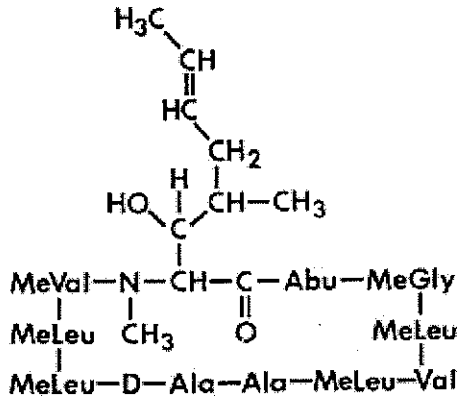
12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Hard Gelatin Capsules

14. POTENCIES
25 mg and 100 mg

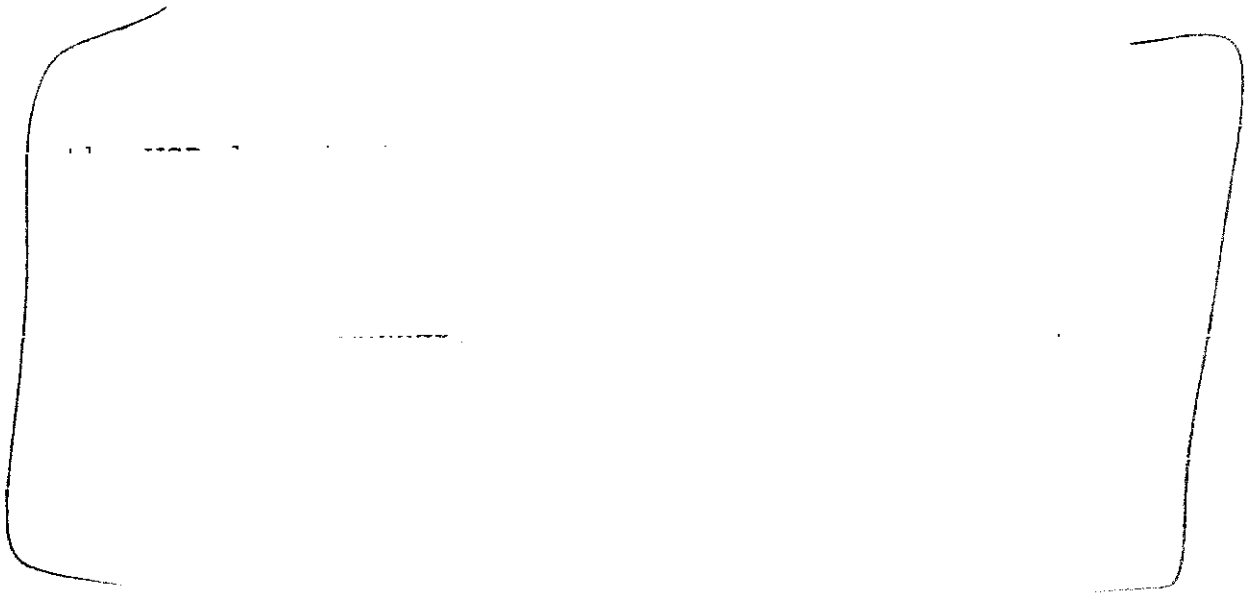
15. CHEMICAL NAME AND STRUCTURE
$C_{62}H_{111}N_{11}O_{12}$
Mol. Wt. 1202.64

[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)



16. RECORDS AND REPORTS
N/A

17. COMMENTS



18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable, Minor

19. REVIEWER: Ruth Ganunis

DATE COMPLETED: August 17, 2000

APPEARS THIS WAY
ON ORIGINAL

Redacted 22

pages of

trade secret and/or

confidential

commercial

information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 65-040

3. NAME AND ADDRESS OF APPLICANT
TorPharm, Inc.
50 Steinway Boulevard
Etobicoke, Ontario M9W 6Y3
Canada

AUTHORIZED U.S. AGENT
Marcy Macdonald
Apotex Corporation
50 Lakeview Parkway, Suite #127
Vernon Hills, Illinois 60061

Phone: (847) 573-9999
Fax: (847) 573-1001

4. LEGAL BASIS FOR SUBMISSION
The application is based on Sandimmune® Soft Gelatin Capsules manufactured by Novartis Pharmaceutical Corporation (NDA# 50-625). The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
APO-MUNE (Cyclosporine Capsules)

7. NONPROPRIETARY NAME
Cyclosporine Capsules

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

9. AMENDMENTS AND OTHER DATES:

Firm:
Original Submission: 1/11/99
Additional Information: 1/26/99
Additional Information: 2/16/99
Bio Amendment: 6/9/99
Bio and Chemistry Correspondence: 9/30/99
Bio and Chemistry Amendment: 2/14/00
Bio Correspondence: 4/12/00
Chemistry and Labeling Fax Amendment: 10/6/00

FDA:
Acceptance for Filing: 2/16/99
Labeling Review, deficient: 4/22/99
Bio Review, deficient: 3/12/99
Bio Review, deficient: 7/23/99
Chemistry Review, deficient: 9/13/99
Bio Review, acceptable: 11/23/99
Methods Validation, acceptable: 12/3/99
Bio Response to Correspondence: 5/25/00
Labeling Review, deficient: 7/7/00
Chemistry Review, deficient: 8/25/00

10. PHARMACOLOGICAL CATEGORY

1. Prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants.
2. Treatment of chronic rejection in patients previously treated with other immunosuppressive agents.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DM [redacted]
DMF [redacted]

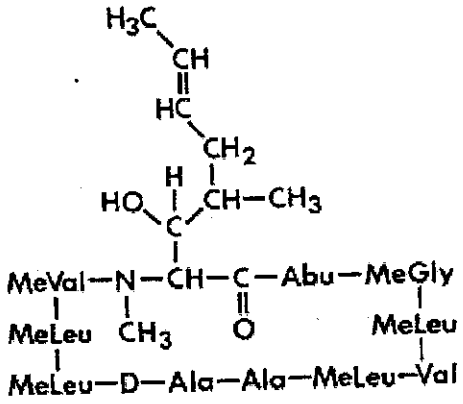
13. DOSAGE FORM

Hard Gelatin Capsules

14. POTENCIES
25 mg and 100 mg

15. CHEMICAL NAME AND STRUCTURE
$C_{62}H_{111}N_{11}O_{12}$
Mol. Wt. 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)



16. RECORDS AND REPORTS
N/A

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
Recommended for approval once the labeling and USP monograph issues are resolved.

19. REVIEWER:
Ruth Ganunis

DATE COMPLETED:
October 31, 2000;
January 16, 2001 (as revised)

Redacted 20

pages of

trade secret and/or

confidential

commercial

information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 65-040

3. NAME AND ADDRESS OF APPLICANT
TorPharm, Inc.
50 Steinway Boulevard
Etobicoke, Ontario M9W 6Y3
Canada

AUTHORIZED U.S. AGENT
Marcy Macdonald
Apotex Corporation
50 Lakeview Parkway, Suite #127
Vernon Hills, Illinois 60061

Phone: (847) 573-9999
Fax: (847) 573-1001

4. LEGAL BASIS FOR SUBMISSION
The application is based on Sandimmune® Soft Gelatin Capsules manufactured by Novartis Pharmaceutical Corporation (NDA# 50-625). The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
APO-MUNE (Cyclosporine Capsules)

7. NONPROPRIETARY NAME
Cyclosporine Capsules

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

9. AMENDMENTS AND OTHER DATES:

Firm:

Original Submission: 1/11/99
Additional Information: 1/26/99
Additional Information: 2/16/99
Bio Amendment: 6/9/99
Bio and Chemistry Correspondence: 9/30/99
Bio and Chemistry Amendment: 2/14/00
Bio Correspondence: 4/12/00
Chemistry and Labeling Fax Amendment: 10/6/00
Labeling Amendment: 12/13/00
Labeling Amendment: 1/2/01
Chemistry and Labeling Amendment: 5/3/01

FDA:

Acceptance for Filing: 2/16/99
Labeling Review, deficient: 4/22/99
Bio Review, deficient: 3/12/99
Bio Review, deficient: 7/23/99
Chemistry Review, deficient: 9/13/99
Bio Review, acceptable: 11/23/99
Methods Validation, acceptable: 12/3/99
Bio Response to Correspondence: 5/25/00
Labeling Review, deficient: 7/7/00
Chemistry Review, deficient: 8/25/00
Labeling Review, deficient: 11/2/00
Labeling Review, deficient: 12/27/00
Chemistry Review, deficient: 1/22/01
Labeling Review, deficient: 1/26/01

10. PHARMACOLOGICAL CATEGORY

1. Prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants.
2. Treatment of chronic rejection in patients previously treated with other immunosuppressive agents.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM

Hard Gelatin Capsules

14. POTENCIES

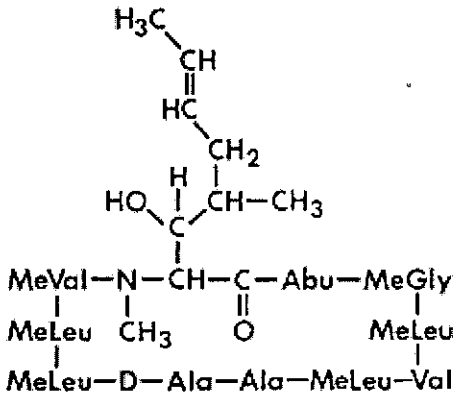
25 mg and 100 mg

15. CHEMICAL NAME AND STRUCTURE

$C_{62}H_{111}N_{11}O_{12}$

Mol. Wt. 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)



16. RECORDS AND REPORTS

N/A

17. COMMENTS

The reference listed drug for this application is Sandimmune® by Novartis, which is a soft gelatin capsule

Redacted 1

pages of

trade secret and/or

confidential

commercial

information

18. CONCLUSIONS AND RECOMMENDATIONS
Recommended for approval once the labeling and USP monograph issues are resolved.

19. REVIEWER: Ruth Ganunis

DATE COMPLETED: May 29, 2001

APPEARS THIS WAY
ON ORIGINAL

Redacted 20

pages of

trade secret and/or

confidential

commercial

information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 65-040

3. NAME AND ADDRESS OF APPLICANT
TorPharm, Inc.
50 Steinway Boulevard
Etobicoke, Ontario M9W 6Y3
Canada

APPEARS THIS WAY
ON ORIGINAL

AUTHORIZED U.S. AGENT
Marcy Macdonald
Apotex Corporation
50 Lakeview Parkway, Suite #127
Vernon Hills, Illinois 60061

Phone: (847) 573-9999
Fax: (847) 573-1001

4. LEGAL BASIS FOR SUBMISSION
The application is based on Sandimmune® Soft Gelatin Capsules manufactured by Novartis Pharmaceutical Corporation (NDA# 50-625). The firm states that no effective patents or exclusivity periods are in force for the referenced product.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
[redacted] (Cyclosporine Capsules)

7. NONPROPRIETARY NAME
Cyclosporine Capsules

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

APPEARS THIS WAY
ON ORIGINAL

9. AMENDMENTS AND OTHER DATES:

Firm:

Original Submission: 1/11/99
Additional Information: 1/26/99
Additional Information: 2/16/99
Bio Amendment: 6/9/99
Bio and Chemistry Correspondence: 9/30/99
Bio and Chemistry Amendment: 2/14/00
Bio Correspondence: 4/12/00
Chemistry and Labeling Fax Amendment: 10/6/00
Labeling Amendment: 12/13/00
Labeling Amendment: 1/2/01
Chemistry and Labeling Amendment: 5/3/01
Chemistry and Labeling Amendment: 11/8/01
Labeling Amendment: 2/7/02
Chemistry Amendment: 4/10/02

FDA:

Acceptance for Filing: 2/16/99
Labeling Review, deficient: 4/22/99
Bio Review, deficient: 3/12/99
Bio Review, deficient: 7/23/99
Chemistry Review, deficient: 9/13/99
Bio Review, acceptable: 11/23/99
Methods Validation, acceptable: 12/3/99
Bio Response to Correspondence: 5/25/00
Labeling Review, deficient: 7/7/00
Chemistry Review, deficient: 8/25/00
Labeling Review, deficient: 11/2/00
Labeling Review, deficient: 12/27/00
Chemistry Review, deficient: 1/22/01
Labeling Review, deficient: 1/26/01
Labeling Review, acceptable: 3/13/02
Chemistry Telephone Conference: 4/8/02

10. PHARMACOLOGICAL CATEGORY

1. Prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants.
2. Treatment of chronic rejection in patients previously treated with other immunosuppressive agents.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

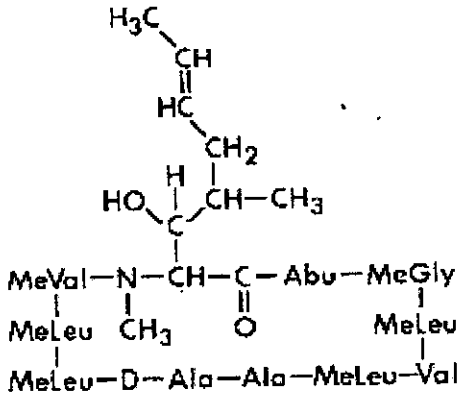
13. DOSAGE FORM
Hard Gelatin Capsules

14. POTENCIES
25 mg and 100 mg

15. CHEMICAL NAME AND STRUCTURE
$C_{62}H_{111}N_{11}O_{12}$
Mol. Wt. 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)

APPEARS THIS WAY
ON ORIGINAL



16. RECORDS AND REPORTS
N/A

Redacted 1

pages of

trade secret and/or

confidential

commercial

information

Summary:
First Generic
Labeling, acceptable: 3/13/02
Bio, acceptable: 11/23/99 (and 5/25/00)
Methods Validation, acceptable: 12/3/99
DMF for drug substance, acceptable: 8/16/00
EER, acceptable: 8/25/00

18. CONCLUSIONS AND RECOMMENDATIONS
Recommended for approval

19. REVIEWER:
Ruth Ganunis

DATE COMPLETED:
November 29, 2001;
March 14, 2002 (as revised);
April 11, 2002 (as revised)

Redacted 22

pages of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-040

BIOEQUIVALENCE REVIEW(S)

(6)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 65-040 SPONSOR : TorPharm, Inc.

DRUG AND DOSAGE FORM : Cyclosporine Hard Gelatin Capsule

STRENGTH(S): 25 mg and 100 mg

TYPES OF STUDIES : Fasting, non-fasting, and dissolution

III. A. STUDY FACILITIES

CLINICAL STUDY SITE(S)
Clinical Facility:
Principal Investigator:

ANALYTICAL SITE(S)
Analytical Facility:

STUDY SUMMARY : Single-dose fasting, and nonfasting studies on the 100 mg strength are acceptable.

DISSOLUTION : Dissolution studies are acceptable.

DSI INSPECTION STATUS

Inspection needed: **NO**	Inspection status:	Inspection results:
First Generic ___ New facility ___ For cause ___ Other ___	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : James Chaney, Ph.D. BRANCH : I
INITIAL : /S/ DATE : 10/15/99

TEAM LEADER : Yih Chain Huang, Ph.D. BRANCH : I
INITIAL : /S/ DATE : 10/15/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.
INITIAL : /S/ DATE : 11/4/99

ANDA: 65-040 APPLICANT: TorPharm, Inc.

DRUG PRODUCT: Cyclosporine Hard Gelatin Capsule, 25 mg and 100 mg

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

The dissolution testing method and specification recommended by the Division of Bioequivalence in its most recent correspondence (February 23, 2000) to you on your 25 mg and 100 mg cyclosporine hard gelatin capsules remain in effect.

The dissolution testing should be conducted in 1000 mL of 0.5% sodium lauryl sulphate in 0.1 N HCl at 37°C using USP 24 apparatus 1 (basket) at — rpm. The test product should meet the following specification:

> Not less than — (Q) of the labeled amount of cyclosporine in the dosage form is dissolved in 90 minutes.

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

CC: ANDA 65-040
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-652/ J. Chaney /S/ 5/24/00
HFD-652/ Y. Huang /S/ 5/24/2000
HFD-617/ J. Fan
HFD-650/ D. Conner /S/ 5/25/00

V:\FIRMSNZ\TORPHARM\LTRS&REV\65040a3.400

BIOEQUIVALENCY - ACCEPTABLE Submission Date:
April 12, 2000

STUDY AMENDMENT (STA) Strengths 25 mg and 100 mg
Outcome: NC

Outcome Decision: Acceptable

NOTE:
AC - Acceptable UN - Unacceptable
NC - No Action IC - Incomplete

WinBio Comments: The dissolution specification remains in 90 minutes.

Cyclosporine Hard Gelatin Capsule
100 mg and 25 mg
ANDA # 65-040
Reviewer: J. Chaney
V:\FIRMSNZ\TORPHARM\LTRS&REV\65040A3.400

TorPharm, Inc.
Ontario, Canada
Submission Dated:
April 12, 2000

AMENDMENT REQUESTING CLARIFICATION ON DISSOLUTION SPECIFICATIONS

BACKGROUND

TorPharm is confused as to whether the dissolution specification is Q= — or Q= — Their agent, Apotex Corporation, has requested verification of the correct method.

A history of correspondence between the Agency and the applicant regarding dissolution follows:

1/11/99. Original submission.
Firm's Dissolution Method: 0.5% SLS in 0.1N HCl
Firm's Specification: NLT — (Q) in 90 minutes.

3/30/99 FDA Response:
The dissolution testing used by TorPharm Inc. on its Cyclosporine Hard Gelatin Capsules, 100 mg and 25 mg was found unacceptable. The firm was advised to establish a dissolution test procedure for this product using the methodology in Method A of Pharmacopeial Forum, May-June 1998, Volume 24, No. 3, page 6155. The specification in the PF was —in 60 minutes. No specification was mentioned in the Agency's response letter of 3/30/99.

6/9/99. Firm's Response to the 3/30/99 Deficiency Letter:
In response to the 3/30/99 deficiency letter TorPharm reported that its cyclosporine capsules and the reference Sandimmune capsules failed the dissolution specification of —dissolved in 60 minutes as specified in the Pharmacopeial Forum.

8/16/99. FDA response to the 6/9/99 Amendment:
The firm was advised that the dissolution testing methodology used on its cyclosporine hard gelatin capsules was unacceptable and that it should establish a dissolution test procedure for this product using the following methodology:

Apparatus:	USP Paddle Method
RPM:	75 and 100 rpm

Medium: 0.1N HCl containing — of

— at 37°C

Volume: 1000 mL

Sampling: 15, 30, 45, 60 and 90 minutes.

Intentionally, no percent dissolved specification was provided in the response letter from the Agency.

9/30/99 Amendment in Response to 8/16/99 Agency Letter:
In this amendment TorPharm reported that the last recommended method (employing — did not work either. The firm stated that it planned to continue testing the product using the original method which it had validated and submitted in the original 1/11/99 application. The firm requested confirmation from the FDA of its agreement with this approach.

2/23/00 DBE Response to 9/30/99 Amendment:
The firm was advised that the original dissolution testing conducted on its 100 mg cyclosporine hard gelatin capsule was considered acceptable. The dissolution testing method recommended was that the testing should be conducted in 1000 mL of 0.5% sodium lauryl sulphate in 0.1 N HCl at 37°C using USP 23 apparatus 1 (basket) at — rpm. The test product should meet the following specifications:

> Not less than — (Q) of the labeled amount of cyclosporine in the dosage form is dissolved in 90 minutes.

RECOMMENDATION

The dissolution testing method and specification recommended by the Division of Bioequivalence in its most recent correspondence (February 23, 2000) to TorPharm Inc. on its 25 mg and 100 mg cyclosporine hard gelatin capsules remain in effect.

The dissolution testing should be conducted in 1000 mL of 0.5% sodium lauryl sulphate in 0.1 N HCl at 37°C using USP 24 apparatus 1 (basket) at — rpm. The test product should meet the following specification:

> Not less than — (Q) of the labeled amount of cyclosporine in the dosage form is dissolved in 90 minutes.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang

/S/ Date: 5/24/2000

Concur: /S/ Date 5/25/00

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/052200
V:\FIRMSNZ\TORPHARM\LTRS&REV\65040a3.400

Cyclosporine Hard Gelatin Capsule, 100 mg and 25 mg,

APPEARS THIS WAY
ON ORIGINAL

(6)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 65-040 SPONSOR : TorPharm, Inc.

DRUG AND DOSAGE FORM : Cyclosporine Hard Gelatin Capsule

STRENGTH(S): 25 mg and 100 mg

TYPES OF STUDIES : Fasting, non-fasting, and dissolution

III. A. STUDY FACILITIES

CLINICAL STUDY SITE(S)
Clinical Facility:
Principal Investigator:

ANALYTICAL SITE(S)
Analytical Facility:

STUDY SUMMARY : Single-dose fasting, and nonfasting studies on the 100 mg strength are acceptable.

DISSOLUTION : Dissolution studies are acceptable.

DSI INSPECTION STATUS

Inspection needed: **NO**	Inspection status:	Inspection results:
First Generic ___ New facility ___ For cause ___ Other ___	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : James Chaney, Ph.D. BRANCH : I
INITIAL : /S/ DATE : 10/15/99

TEAM LEADER : Yih Chain Huang, Ph.D. BRANCH : I
INITIAL : /S/ DATE : 10/15/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.
INITIAL : /S/ DATE : 11/4/99

ANDA: 65-040 APPLICANT: TorPharm, Inc.

DRUG PRODUCT: Cyclosporine Hard Gelatin Capsule, 25 mg and 100 mg

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

The following dissolution testing should be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 1000 mL of 0.5% sodium lauryl sulphate in 0.1 N HCl at 37°C using USP 23 apparatus 1 (basket) at — rpm. The test product should meet the following specifications:
>
> Not less than — (Q) of the labeled amount of cyclosporine in the dosage form is dissolved in 90 minutes.

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

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 65-040
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-652/ J. Chaney /S/ /S/ 10/15/99 & 10/15
HFD-652/ Y. Huang
HFD-617/ E. Hu
HFD-650/ D. Conner /S/ 11/23/99

V:\FIRMSNZ\TORPHARM\LTRS&REV\65040A2.999

BIOEQUIVALENCY - ACCEPTABLE Submission Date: September 30, 1999

STUDY AMENDMENT (STA) 01C Strengths 25 mg and 100 mg
Outcome: AC

Outcome Decision: Acceptable

NOTE:
AC - Acceptable UN - Unacceptable
NC - No Action IC - Incomplete

WinBio Comments: The fasting and fed biostudies and the dissolution testing are acceptable.

Cyclosporine Hard Gelatin Capsule
100 mg and 25 mg
ANDA # 65-040
Reviewer: J. Chaney
V:\FIRMSNZ\TORPHARM\LTRS&REV\65040A2.999

TorPharm, Inc.
Ontario, Canada
Submission Dated:
September 30, 1999

AMENDMENT TO FASTING AND FED BIOEQUIVALENCE STUDIES

BACKGROUND

In its original ANDA of January 11, 1999 TorPharm reported on *in vivo* bioequivalence studies under fasting and non-fasting conditions comparing its cyclosporine hard gelatin capsule, 100 mg, to the reference listed drug, Novartis' Sandimmune® (cyclosporine soft gelatin capsule), 100 mg.

The following dissolution testing methodology used by TorPharm Inc. on its cyclosporine hard gelatin capsule, 100 mg (lot # FD8040A), was unacceptable.

Basket Method: RPM: —
No. Units Tested: 12
Medium: 0.5% Sodium Lauryl Sulphate in 0.1 N HCl
Volume: 1000 mL
Specifications: NLT — (Q) in 90 minutes

In the deficiency letter of 3/30/99 the firm was advised to establish a dissolution test procedure for this product using the following methodology (Method A of Pharmacopeial Forum, May-June 1998, Volume 24, No. 3, page 6155):

Apparatus: USP Paddle
RPM: 75
Media, Volume:
25 mg capsules:
500 mL of 0.1N HCl containing — of — at 37°C
100 mg capsules:
1000 mL of 0.1N HCl containing — of — at 37°C
Sampling: 15, 30, 45, and 60 minutes.

In response to the 3/30/99 deficiency letter TorPharm reported in its 6/9/99 amendment that its test — and Sandimmune

Capsules failed the dissolution specification of — dissolved in 60 min) as stated in Pharmacopeial Forum, May-June 1998, Volume 24, Number 3 on page 6156 using either Method A or Method B.

The firm was then advised in the deficiency letter of 8/16/99 to establish a dissolution test procedure for this product using the following methodology:

Apparatus:	USP Paddle Method
RPM:	75 and 100 rpm
No. Units:	12
Medium:	0.1N HCl containing — of — at 37°C
Volume:	1000 mL
Sampling:	15, 30, 45, 60, 90 and 120 minutes.

In the current amendment (September 30, 1999) TorPharm has reported that the last recommended method does not work either. The firm plans to continue testing the product using the original method which it had validated and submitted in the original application. The dissolution testing results from this method are shown in Table 1. TorPharm has requested confirmation from the FDA of its agreement with this approach.

RECOMMENDATIONS

1. The in vivo bioequivalence studies conducted under fasting and non-fasting conditions by TorPharm Inc. on its cyclosporine hard gelatin capsule, 100 mg (lot # FD8040A), comparing it to the reference listed drug Novartis' Sandimmune® (cyclosporine soft gelatin capsule), 100 mg, has been found acceptable by the Division of Bioequivalence. The study results demonstrate that TorPharm's 100 mg cyclosporine hard gelatin capsule, is bioequivalent under fasting conditions to the reference product, Novartis' Sandimmune® (cyclosporine soft gelatin capsule), 100 mg.

2. The dissolution testing used by the firm on its cyclosporine hard gelatin capsule, 100 mg and 25 mg, lot numbers FD8040 and FD8039, respectively, is acceptable. The formulation for the 25 mg strength is proportionally similar to the 100

mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of *in vivo* bioequivalence study requirements for the 25 mg capsule of the test product may be granted. The Division of Bioequivalence deems cyclosporine hard gelatin capsule, 25 mg manufactured by TorPharm to be bioequivalent to Sandimmune® (Cyclosporine Soft Gelatin Capsule), 25 mg manufactured by Novartis.

3. The original dissolution testing conducted by TorPharm Inc. on its 100 mg cyclosporine hard gelatin capsule has been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.5% sodium lauryl sulphate in 0.1 N HCl at 37°C using USP 23 apparatus 1 (basket) at ___ rpm. The test product should meet the following specifications:

   Not less than — (Q) of the labeled amount of cyclosporine in the dosage form is dissolved in 90 minutes.

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

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date: 10/15/99

Concur: /S/ Date 11/4/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/101499

Table 14. In Vitro Dissolution Testing

Drug (Generic Name): Cyclosporine Hard Gelatin Capsules
Dose Strength: 25 & 100 mg
ANDA No.: 65-040
Firm: TorPharm, Inc.
Submission Date: January 11, 1999
File Name: 65040SDW.199

I. Conditions for Dissolution Testing: Sponsor's Method

Basket Method: RPM: —
No. Units Tested: 12
Medium: 0.5% Sodium Lauryl Sulphate in 0.1 N HCl
Volume: 1000 mL
Specifications: NLT — (Q) in 90 minutes
Reference Drug: Sandimmune® (Soft Gelatin Capsules), 100 mg (Novartis Pharmaceuticals).
Assay Methodology: —

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Min)	Test Product Lot # FD8039 Strength(mg) 25			Reference Product Lot # 22959 Strength(mg) 25		
	Mean %	Range	%CV	Mean %	Range	%CV
10	14	—	98	93	—	8
20	39	—	49	102	—	2
30	66	—	32	100	—	3
45	86	—	22	100	—	2
60	94	—	12	98	—	2
90	97	—	3	96	—	2
120	95	—	3	93	—	2
	Test Product Lot # FD8040 Strength(mg) 100			Reference Product Lot # 23923 Strength(mg) 100		
10	17	—	66	73	—	5
20	37	—	51	101	—	2
30	57	—	48	104	—	2
45	76	—	23	103	—	2
60	87	—	13	101	—	2
90	95	—	2	98	—	1
120	94	—	2	96	—	1

1/1 Adams, M

AUG 16 1999

ANDA: 65-040 APPLICANT: TorPharm, Inc.

DRUG PRODUCT: Cyclosporine Hard Gelatin Capsule, 25 mg and 100 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

The dissolution testing methodology used on your cyclosporine hard gelatin capsules, is unacceptable.

You should establish a dissolution test procedure for this product using the following recommended methodology:

Apparatus:	USP Paddle Method
RPM:	75 or 100 rpm
No. Units:	12
Medium:	0.1N HCl containing ——— of ——— at 37°C
Volume:	1000 mL
Sampling:	15, 30, 45, 60 and 90 minutes.

You should submit dissolution data from each of the recommended rotation speeds.

Sincerely yours,

(/S/

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

Cyclosporine Hard Gelatin Capsule
100 mg and 25 mg
ANDA # 65-040
Reviewer: J. Chaney

TorPharm, Inc.
Ontario, Canada
Submission Dated:
January 11, 1999
June 9, 1999

V:\FIRMSNZ\TORPHARM\LTRS&REV\65040A.699

AMENDMENT TO FASTING AND FED BIOEQUIVALENCE STUDIES

BACKGROUND

In its ANDA of January 11, 1999 TorPharm reported on the conduct of *in vivo* bioequivalence studies under fasting and non-fasting conditions comparing its Cyclosporine Hard Gelatin Capsule, 100 mg, to the reference listed drug, Novartis' Sandimmune® (Cyclosporine Soft Gelatin Capsule), 100 mg.

Deficiency
The in vivo bioequivalence studies conducted under fasting and non-fasting conditions by TorPharm Inc. on its Cyclosporine Hard Gelatin Capsule, 100 mg (lot # FD8040A), comparing it to the reference listed drug, Novartis' Sandimmune® (Cyclosporine Soft Gelatin Capsule), 100 mg was found incomplete per the dissolution deficiency.

The following dissolution testing methodology used by TorPharm Inc. on its Cyclosporine Hard Gelatin Capsule, 100 mg (lot # FD8040A), was unacceptable.

Basket Method: RPM: ⟶
No. Units Tested: 12
Medium: 0.5% Sodium Lauryl Sulphate in 0.1 N HCl
Volume: 1000 mL
Specifications: NLT ⟶ (Q) in 90 minutes

The firm was advised to establish a dissolution test procedure for this product using the following methodology (Method A of Pharmacopeial Forum, May-June 1998, Volume 24, No. 3, page 6155):

APPEARS THIS WAY
ON ORIGINAL

Apparatus: USP Paddle
RPM: 75
Media, Volume:
25 mg capsules:
500 mL of 0.1N HCl containing [redacted] of [redacted] at 37°C
100 mg capsules:
1000 mL of 0.1N HCl containing [redacted] of [redacted] at 37°C
Sampling: 15, 30, 45, and 60 minutes.

Firm's Response
In response to the deficiency letter TorPharm reported the following results from the above recommended method:

Method A was followed initially using twelve capsules per lot. Sandimmune Capsules 100 mg were found to dissolve at a faster rate (mean of 66% in 60 min, [redacted] range) than [redacted], (Cyclosporine Capsules) 100 mg (mean of 12% in 60 min, [redacted] range). A similar trend was observed for Sandimmune Capsules 25 mg (mean of 40%, [redacted] range) compared to [redacted] Capsules 25 mg (mean of 22% dissolved in 60 min, [redacted] range).

Method B (Same as Method A except 0.1N HCl medium was replaced with Gastric Fluid TS) was then investigated using three capsules from [redacted], Capsules 100 mg and three capsules from Sandimmune Capsules 100 mg. For 100 mg Sandimmune Capsules [redacted] was dissolved in 60 min and for 100 mg [redacted], [redacted] was dissolved in 60 min.

In conclusion, both [redacted] and Sandimmune Capsules failed the dissolution specification of [redacted] dissolved in 60 min) as stated in Pharmacopeial Forum, May-June 1998, Volume 24, Number 3 on page 6156 using either Method A or Method B.

Comments

1. In the review of March 1999, the RLD was mistakingly cited as Novartis' Neoral (Cyclosporine Soft Gelatin Capsule). In fact the reference was Novartis' Sandimmune® (Cyclosporine Soft Gelatin Capsule), 100 mg.

2. On May 20, 1998 and April 22, 1998, prior to starting the biostudies in June, 1998, Apotex Corporation (the U.S. agent

for TorPharm) had inquired relative to Cyclosporine Soft Gelatin Capsules in which Sandimmune was proposed as the RLD. There was no objection by the FDA to the use of Sandimmune as the RLD.

Recommendation

The firm's response to this deficiency is not acceptable.

The firm should establish a dissolution test procedure for this product using the following methodology:

Apparatus:	USP Paddle Method
RPM:	75 or 100 rpm
No. Units:	12
Medium:	0.1N HCl containing ——— of ——— at 37°C
Volume:	1000 mL
Sampling:	15, 30, 45, 60, 90 and 120 minutes.

The firm should submit dissolution data from each of the recommended rotation speeds.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang

/S/ Date: 7/21/99

Concur: /S/ Date 7/23/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
JEC/071499

ANDA: 65-040 APPLICANT: TorPharm, Inc.

DRUG PRODUCT: Cyclosporine Hard Gelatin Capsule, 25 mg and 100 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

The dissolution testing methodology used on your cyclosporine hard gelatin capsules, is unacceptable.

You should establish a dissolution test procedure for this product using the following recommended methodology:

Apparatus:	USP Paddle Method
RPM:	75 or 100 rpm
No. Units:	12
Medium:	0.1N HCl containing ~~~ of ~~~
	at 37°C
Volume:	1000 mL
Sampling:	15, 30, 45, 60 and 90 minutes.

You should submit dissolution data from each of the recommended rotation speeds.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 65-040
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-652/ J. Chane /S/ 7/21/99
HFD-652/ Y. Huang /S/ 7/21/99
HFD-617/ E. Hu /S/ 8/4/99
HFD-650/ D. Conner /S/ 7/23/99

V:\FIRMSNZ\TORPHARM\LTRS&REV\65040A.699

BIOEQUIVALENCY - INCOMPLETE

Submission Date: June 9, 1999

STUDY AMENDMENT (STA) 01

Strengths 25 mg and 100 mg
Outcome: IC

Outcome Decision: Incomplete

NOTE:
AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

WinBio Comments: Unacceptable dissolution data

APPEARS THIS WAY
ON ORIGINAL

Cyclosporine
100 mg Hard Gelatin Capsule
25 mg Hard Gelatin Capsule
ANDA # 65-040
Reviewer: J. Chaney

TorPharm, Inc.
Ontario, Canada
Submission Dated:
January 11, 1999

REVIEW OF TWO BIOEQUIVALENCE STUDIES, IN VITRO DISSOLUTION TESTING DATA AND A WAIVER REQUEST

I. OBJECTIVE:

TorPharm conducted *in vivo* bioequivalence studies under fasting and non-fasting conditions to compare its drug product Cyclosporine Hard Gelatin Capsule, 100 mg, to the reference listed drug, Novartis' Neoral® (Cyclosporine Soft Gelatin Capsule), 100 mg.

II. BACKGROUND:

Reference Drug Product:

Neoral® Soft Gelatin Capsules, 100 mg (Novartis Pharmaceuticals).

Indication:

Cyclosporine is a potent immunosuppressive agent and is indicated for the prophylaxis of organ rejection in kidney, liver, and heart transplants.

Metabolites:

Extensively metabolized but the immunosuppressive activity is primarily due to the parent drug.

Half Life:

The elimination of cyclosporine is primarily biphasic, with a terminal half-life of about 8.4 hors (range 5-18 hours).

Food Effect:

The administration of food with Neoral® decreases the cyclosporine AUC and Cmax.

Distribution:

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.

DBE Guidance: None

Recommended Dose:

Dependent on the transplanted organ and other immunosuppressive agents in the immunosuppressive protocol.

Absorption:

The extent of absorption of cyclosporine is dependent on the individual patient, the patient population, and the formulation.

III. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER FASTING FASTING CONDITIONS

III. A. STUDY FACILITIES

Clinical Facility: [redacted]
Principal Investigator: [redacted]
Analytical Facility: [redacted]

III. B. STUDY DESIGN

Open-label, randomized, single-dose 2-way crossover bioequivalence study.

III. C. STUDY DATES

Blood sampling started on June 27, 1998 and July 11, 1998 for periods 1 and 2, respectively. The study samples were analyzed between July 28, 1998 and August 11, 1998. (The maximum storage time was 45 days.)

III. D. TREATMENTS

Treatment A: 3 X 100 mg TorPharm's Cyclosporine Hard Gelatin Capsule, Lot # FD8040A, Batch size: [redacted] capsules, Content Uniformity, 101.4% (1.4%CV, 97.9-102.9%); Assay, 101.4%; manufacturing date: April 1998.

Treatment B: 3 X 100 mg Novartis' Neoral® (Cyclosporine Soft Gelatin), Lot # 23923, Content Uniformity, 100.0% (1.6%CV, 97.7-102.0%); Assay, 99.9%; expiration date: July 2000.

III. E. STUDY SCHEDULES:

Blood samples were collected in vacutainers tubes containing EDTA, before dosing (0 hour) and at 0.25, 0.50, 0.75, 1.00, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10, 12, 15, 18, 24, 30, 36, 42, 48, 60, and 72 hours post-dosing. The blood samples were stored frozen at -22°C until analysis.

III. F. ANALYTICAL

PRESTUDY VALIDATION

The analytical method employed [redacted].

Redacted _____

pages of trade secret and /or confidential commercial information

III. G. STATISTICAL ANALYSIS:

ANOVA was performed on each of the pharmacokinetic parameters using SAS® software. The ANOVA model contained factors for sequence, subjects within sequence, periods and products.

III. H. CLINICAL NOTES:

All subjects completed an acceptable medical history, clinical laboratory tests and a physical examination. A complete list of subject selection criteria can be found in the protocol in Vol. 1.1, pages 167-8. The study subjects were non-smoking adult males between the ages of 18 to 45. The washout period was 14 days. Of the 28 subjects who initiated the study, 27 successfully completed the study. Subject 07 elected to withdraw prior to Period II dose administration due to personal reasons. The subjects were monitored throughout the confinement portion of the study. None of the adverse events were considered serious.

III. I. RESULTS OF FASTING BIOEQUIVALENCE STUDY:

The mean whole blood concentrations of cyclosporine at each time point for each product and the arithmetic means of the pharmacokinetic parameters are shown in Table 3. A linear plot of the mean whole blood concentration for cyclosporine as a function of time is shown in Figure 1. The two curves are very similar.

Per protocol, data was analyzed from subjects 1-25 (excluding subject # 7).

Table 3. Arithmetic Mean Whole Blood Cyclosporine Concentrations and Pharmacokinetic Parameters, and Test/Reference Ratios Following an Oral Dose of 300 mg (3X100 mg Capsules) of Cyclosporine Under Fasting Conditions (N=24)

Whole Blood Levels (ng/mL)					
TIME (HRS)	TEST		REFERENCE		T/R
	MEAN	%CV	MEAN	%CV	
0	0	---	0	---	.
0.25	0	---	1.39	365	0
0.5	29.48	73	67.36	125	0.44
0.75	122.54	49	214.18	96	0.57
1	288.12	56	381.16	82	0.76
1.5	547.19	39	562.49	59	0.97
2	685.67	23	567.78	53	1.21
2.5	628.16	22	496.14	45	1.27
3	551.94	23	431.41	41	1.28
3.5	460.58	25	372.78	35	1.24
4	403.18	28	336.39	37	1.2
5	302.68	31	310.93	53	0.97
6	205.88	25	209.89	43	0.98
8	142.07	30	147.65	40	0.96
10	96.02	38	106.78	66	0.9
12	72.36	35	74.61	64	0.97
16	42.39	34	44.69	64	0.95
24	22.55	40	22.28	55	1.01
30	12.35	65	13.06	69	0.95
36	8.13	90	7.18	108	1.13
42	3.61	162	3.38	179	1.07
48	2.03	229	1.52	272	1.34
60	0.91	341	0		.
72	0	---	0	---	.

Pharmacokinetic Parameters					
PARAMETER	TEST		REFERENCE		T/R
	MEAN	%CV	MEAN	%CV	
AUCI	3887.38	23	3729.33	25	1.04
AUCT	3731.13	23	3574.46	26	1.04
CMAX	743.48	19	749.92	23	0.99
THALF	8.54	30	8.28	35	1.03
TMAX	2.19	24	2.56	79	0.85

Units: AUC, ng*hr/mL; CMAX, ng/mL; TMAX, hr

The comparison of LSmeans, geometric LSmeans and 90% confidence intervals for the pharmacokinetic parameters are shown in Table 4.

Table 4. LSMeans, Geometric LSMeans, T/R Ratios and 90% Confidence Intervals (C.I.) For Cyclosporine Pharmacokinetic Parameters in a Fasting Single-Dose Study

PARAMETER	TEST LSMEANS	REF LSMEANS	T/R	90% C.I.
AUCI	3887.38	3729.33	1.04	---
AUCT	3731.13	3574.46	1.04	---
CMAX	743.48	749.92	0.99	---
LAUCI*	3790.65	3622.92	1.05	96.3-113.7
LAUCT*	3636.51	3468.67	1.05	96.1-114.4
LCMAX*	730.04	727.72	1.00	90.6-111.1

Units: AUC, ng*hr/mL; CMAX, ng/mL. *Geometric Means

A summary of individual test/reference ratios of the pharmacokinetic parameters AUCL, AUCI, and Cmax, and individual AUCL/AUCI ratios for cyclosporine are shown in Table 5.

Table 5. Statistics on Individual Test/Reference Ratios and Individual AUCT/AUCI Ratios in Fasting Study

PARAMETER	N	MEAN	%CV	MINIMUM	MAXIMUM
AUCT T/R	24	1.08	29	0.70	2.02
AUCI T/R	24	1.08	27	0.71	1.98
CMAX T/R	24	1.04	29	0.57	1.79
AUCT/AUCI TEST	24	0.96	1.3	0.91	0.97
AUCT/AUCI REF	24	0.96	1.6	0.92	0.98

IV. SINGLE DOSE BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS

IV. A. STUDY FACILITIES

Same as for fasting study

IV. B. STUDY DESIGN

Open-label, randomized, three-way crossover, six sequence bioequivalence study under fed and fasting conditions.

IV. C. STUDY DATES

Blood sampling started on September 12, 1998, September 26, 1998 and October 10, 1998 for periods 1, 2 and 3, respectively. The study samples were analyzed between

October 18 and October 30, 1998. (The maximum storage time was 48 days.)

IV. D. TREATMENTS

Treatment A: Under fasting conditions, same product (test) and amount as in Part III. D. of review (Fasting Study)

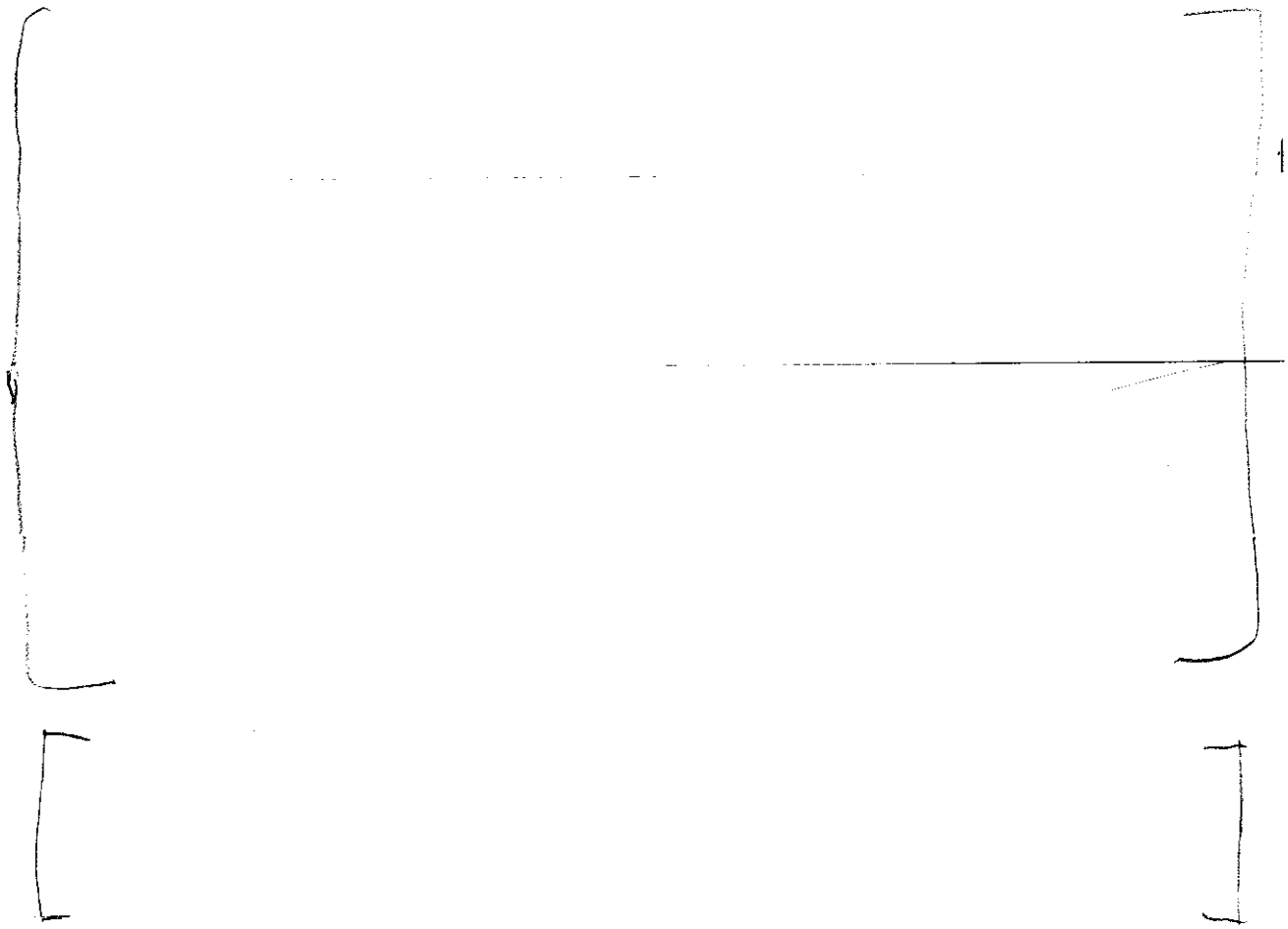
Treatment B: Under non-fasting conditions, same product and amount as in above Treatment A.

Treatment C: Under non-fasting conditions, same product (RLD) and amount as in Part III. D. of review (Fasting Study)

IV. E. STUDY SCHEDULES:

Same as fasting study

IV. F. ANALYTICAL



IV. H. CLINICAL NOTES:

All subjects completed an acceptable medical history, clinical laboratory tests and a physical examination. A complete list of subject selection criteria can be found in the protocol

in Vol. 1.4, pages 1541-2. The study subjects were non-smoking adult males between the ages of 18 to 45. The washout period was 14 days. Of the 18 subjects who initiated the study, 15 successfully completed the study. Subject 9 and 18 elected to withdraw prior to Period II dose administration due to personal reasons. Subject 14 elected to withdraw after his 10-hour blood draw in period 1 because he felt uncomfortable with side effects. The subjects were monitored throughout the confinement portion of the study. None of the adverse events were considered serious.

IV. I. RESULTS OF FED BIOEQUIVALENCE STUDY:

The mean whole blood concentrations of cyclosporine at each time point for each product and the arithmetic means of the pharmacokinetic parameters are shown in Table 7. A linear plot of the mean whole blood concentration for cyclosporine as a function of time is shown in Figure 2. The two curves are very similar.

Table 7. Arithmetic Mean Whole Blood Cyclosporine Concentrations and Pharmacokinetic Parameters, and Test/Reference Ratios Following an Oral Dose of 300 mg (3X100 mg Capsules) of Cyclosporine Under Fasted/Fed Conditions (N=15)

Whole Blood Levels (ng/mL)

TIME (HRS)	TEST FAST		TEST FED		REF FED		TEST FAST/ TEST FED	TEST FED/ REF FED
	MEAN	%CV	MEAN	%CV	MEAN	%CV		
0	0	---	0	---	0	---	.	.
0.25	0.73	385	0	---	0	---	.	.
0.5	56.23	46	0	---	15.36	258	.	0
0.75	223.28	50	0	---	57.57	230	.	0
1	379.05	48	7.73	158	87.01	224	49.02	0.09
1.5	631.39	33	74.19	126	113.6	233	8.51	0.65
2	641.53	32	195.95	107	139.59	169	3.27	1.40
2.5	599.94	30	290.93	84	182.62	132	2.06	1.59
3	521.94	27	340.45	57	248.39	103	1.53	1.37
3.5	417.01	24	405.73	52	308.89	90	1.03	1.31
4	329.79	27	454.51	50	345.75	74	0.73	1.31
5	247.44	35	610.5	36	521.15	50	0.41	1.17
6	177.89	43	530.26	40	478.06	53	0.34	1.11
8	114.83	40	271.79	39	359.95	48	0.42	0.76
10	80.79	41	174.55	36	265.17	44	0.46	0.66
12	57.77	40	118.25	32	185.38	60	0.49	0.64
16	34.45	40	65.9	36	87.81	50	0.52	0.75
24	17.02	56	31.95	42	43.7	50	0.53	0.73
30	6.86	114	16.66	57	22.41	47	0.41	0.74
36	2.94	213	10.4	70	13.41	76	0.28	0.78
42	1.23	386	6.76	115	9.99	83	0.18	0.68
48	0.87	386	2.62	209	3.82	179	0.33	0.69
60	0.98	388	0.69	390	0	---	1.41	.
72	0.89	385	0	---	0	---	.	.

Pharmacokinetic Parameters

PARA-METER	TEST FAST		TEST FED		REF FED		TEST FAST/ TEST FED	TEST FED/ REF FED
	MEAN	%CV	MEAN	%CV	MEAN	%CV		
AUCI	3501.93	36	4631.13	28	5112.33	27	0.76	0.91
AUCT	3312.2	33	4454.27	29	4935.27	27	0.74	0.90
CMAX	714.48	27	675.96	31	717.49	25	1.06	0.94
THALF	9.23	107	8.87	28	8.82	29	1.04	1.00
TMAX	1.87	24	4.43	28	5.2	50	0.42	0.85

Units: AUC, ng*hr/mL; CMAX, ng/mL; TMAX, hr

A comparison of LSMeans, geometric LSMeans and 90% confidence intervals for the pharmacokinetic parameters are shown in Table 8.

Table 8. LSMeans, Geometric LSMeans, and T/R Ratios For Cyclosporine Pharmacokinetic Parameters in Fasting/Fed Study

PARAMETER	TEST FASTED MEAN (A)	TEST FED MEAN (B)	REFERENCE FED MEAN (C)	A/B	B/C
AUCI	3468.75	4597.95	5079.15	0.75	0.91
AUCT	3279.99	4422.06	4903.06	0.74	0.90
CMAX	708.47	669.95	711.47	1.06	0.94
LAUCI*	3278.21	4418.82	4875.58	0.74	0.91
LAUCT*	3114.91	4247.2	4703.49	0.73	0.90
LCMAX*	678.18	640.86	688.4	1.06	0.93

Units: AUC, ng*hr/mL; CMAX, ng/mL. *Geometric Means

A summary of individual test/reference ratios of the pharmacokinetic parameters AUCL, AUCI, and Cmax, and individual AUCL/AUCI ratios for cyclosporine is shown in Table 9.

Table 9. Statistics on Individual Test Fed/Reference Fed Ratios and Individual AUCT/AUCI Ratios

PARAMETER	N	Mean	%CV
AUCT T/R	15	0.92	23
AUCI T/R	15	0.93	23
CMAX T/R	15	1.00	37
AUCT/AUCI TEST	15	0.96	1
AUCT/AUCI REF	15	0.96	1

V. DISSOLUTION

The reported methodology and results are shown in Table 14.

Table 14. In Vitro Dissolution Testing

Drug (Generic Name): Cyclosporine Hard Gelatin Capsules
Dose Strength: 25 & 100 mg
ANDA No.: 65-040
Firm: TorPharm, Inc.
Submission Date: January 11, 1999
File Name: 65040SDW.199

I. Conditions for Dissolution Testing: Sponsor's Method

Basket Method: RPM: ~~~
No. Units Tested: 12
Medium: 0.5% Sodium Lauryl Sulphate in 0.1 N HCl
Volume: 1000 mL
Specifications: NLT ~~ (Q) in 90 minutes
Reference Drug: Neoral® Soft Gelatin Capsules, 100 mg (Novartis Pharmaceuticals).
Assay Methodology: ~~~

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Min)	Test Product Lot # FD8039 Strength(mg) 25			Reference Product Lot # 22959 Strength(mg) 25		
	Mean %	Range	%CV	Mean %	Range	%CV
10	14		98	93		8
20	39		49	102		2
30	66		32	100		3
45	86		22	100		2
60	94		12	98		2
90	97		3	96		2
120	95		3	93		2
	Test Product Lot # FD8040 Strength(mg) 100			Reference Product Lot # 23923 Strength(mg) 100		
10	17		66	73		5
20	37		51	101		2
30	57		48	104		2
45	76		23	103		2
60	87		13	101		2
90	95		2	98		1
120	94		2	96		1

VI. Formulation Data

The following table summarizes the components and composition (mg/capsule) , (Cyclosporine Capsules) 25 mg and 100 mg.

Ingredient	**25 mg Capsule**	**100 Capsule mg**
Cyclosporine USP	25.0	100.0
Sodium Lauryl Sulfate NF		
Methanol NF*	---	---
Purified Water USP*	---	---
Total Weight		

VII. COMMENTS

1. The firm's single-dose bioequivalence studies under fasting and fasting/fed conditions on its cyclosporine hard gelatin capsules are acceptable.

2. The dissolution data is unacceptable.

3. The assayed potency and the content uniformity of the test and reference products are satisfactory.

4. The analytical data is acceptable.

5. Using SAS the reviewer checked the pharmacokinetic parameters and statistical analysis and the results were in agreement with what the firm reported.

6. The test product used for the biostudies and the dissolution studies were from the same batch.

IX. RECOMMENDATIONS:

1. The in vivo bioequivalence studies conducted under fasting and non-fasting conditions by TorPharm Inc. on its Cyclosporine Hard Gelatin Capsule, 100 mg (lot #28-687-AR-03), comparing it to the reference listed drug Novartis' Neoral® (Cyclosporine Soft Gelatin Capsule), 100 mg, has been found incomplete per the dissolution deficiency.

2. The dissolution testing methodology used by TorPharm Inc. on its Cyclosporine Hard Gelatin Capsule, 100 mg (lot #28-687-AR-03), is unacceptable.

The firm should establish a dissolution test procedure for this product using the following general parameters:

Apparatus:	USP Paddle
RPM:	75
Media, Volume	25 mg capsules: 500 mL of 0.1N HCl containing ~~~ of ~~~ at 37°C
	100 mg capsules: 1000 mL of 0.1N HCl containing ~~~ of ~~~ at 37°C
Sampling:	15, 30, 45, and 60 minutes.

The firm should be referred to the Pharmacopeial Forum, May-June 1998, Volume 24, No. 3, page 6155.

3. The waiver of the requirement for *in vivo* bioequivalence testing on the 25 mg strength may be granted pending receipt of a satisfactory response to the dissolution deficiency.

The firm should be informed of recommendation 2.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date: 3/12/99

Concur: /S/ Date 3/12/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/031199

CC: ANDA 65-040
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE
HFD-652/ J. Chaney /S/ 12/99
HFD-652/ Y. Huang /S/ 5/15/99
HFD-617/ E. Hu /S/ 5/12/99
HFD-650/ D. Conner /S/

V:\FIRMSNZ\TORPHARM\LTRS&REV\65040sdw.199

BIOEQUIVALENCY - ACCEPTABLE Submission Date: January 11, 1999

1. FASTING STUDY (STF) Strength: 100 mg
Clinical: [redacted] Outcome: IC

Analytical: [redacted]

2. FOOD STUDY (STP) Strength: 100 mg
Clinical: [redacted] Outcome: IC

Analytical: [redacted]

6. **WAIVER** (WAI) Strength: 25 mg
Outcome: IC

Outcome Decision: Incomplete

NOTE:
AC - Acceptable UN - Unacceptable
NC - No Action IC - Incomplete

WinBio Comments: Incomplete, pending acceptable dissolution data

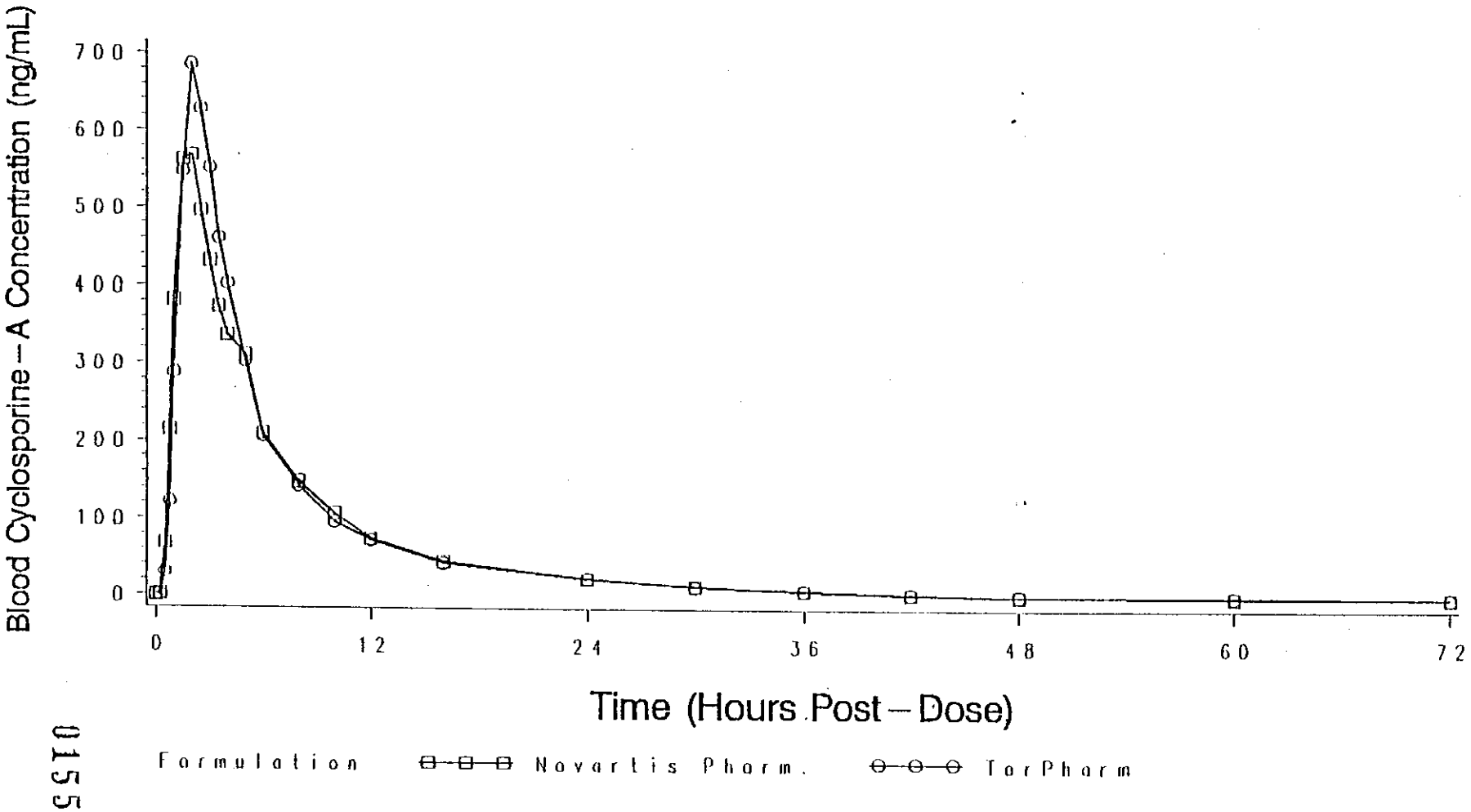
APPEARS THIS WAY
ON ORIGINAL

Figure 1

Project No. 981155

Mean Blood Cyclosporine – A Concentrations

(Linear Plot)



Pg 14

0155

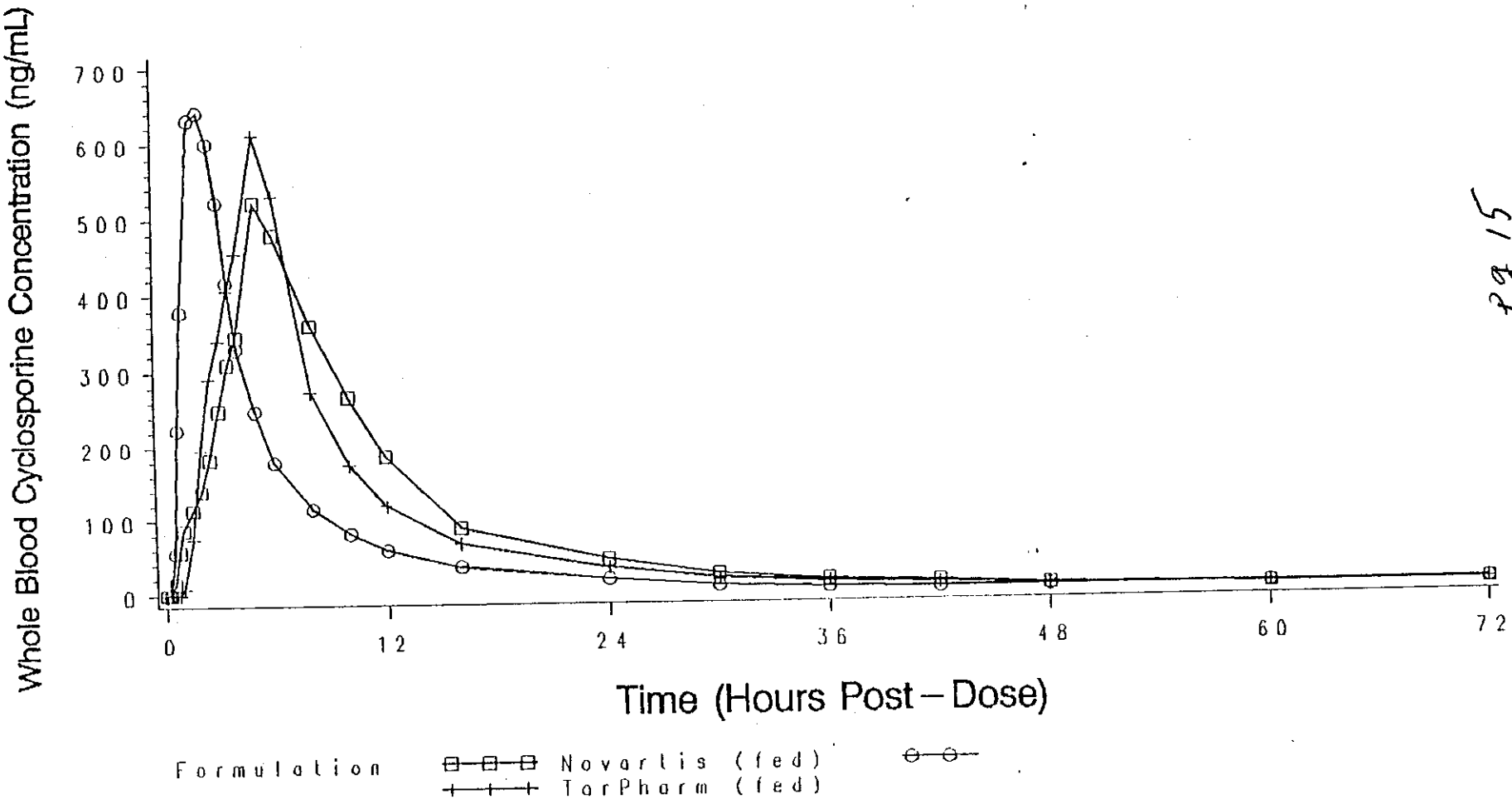
DEFAULT (10SEP98)

Figure 2

Project No. 981180

Mean Whole Blood Cyclosporine Concentrations

(Linear Plot)



1531

pg 15

DEFAULT (20NOV98)

ANDA: 65-040 APPLICANT: TorPharm, Inc.

DRUG PRODUCT: Cyclosporine Hard Gelatin Capsule, 25 mg and 100 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

You should establish a dissolution test procedure for this product using the following general parameters:

Apparatus: USP Paddle
RPM: 75
Media, Volume:
25 mg capsules:
500 mL of 0.1N HCl containing [redacted] of [redacted] at 37°C
100 mg capsules:
1000 mL of 0.1N HCl containing [redacted] of [redacted] at 37°C
Sampling: 15, 30, 45, and 60 minutes.

Please refer to the Pharmacopeial Forum, May-June 1998, Volume 24, No. 3, page 6155.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

ANDA: 65-040 APPLICANT: TorPharm, Inc.

DRUG PRODUCT: Cyclosporine Hard Gelatin Capsule, 25 mg and 100 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

You should establish a dissolution test procedure for this product using the following general parameters:

Apparatus: USP Paddle
RPM: 75
Media, Volume:
25 mg capsules:
500 mL of 0.1N HCl containing ——— of ——————— at 37°C
100 mg capsules:
1000 mL of 0.1N HCl containing ——— of ——————— at 37°C
Sampling: 15, 30, 45, and 60 minutes.

Please refer to the Pharmacopeial Forum, May-June 1998, Volume 24, No. 3, page 6155.

Sincerely yours,

/s/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-040

CORRESPONDENCE

Tor Pharm

ORIG AMENDMENT

N/AM

COVER LETTER

MINOR AMENDMENT

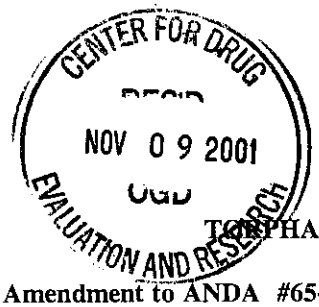
TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 65-040 for Cyclosporine Capsules USP 25 mg and 100 mg. The amendment is being submitted in response to the FDA Deficiency Letter dated July 20, 2001.

Samantha Law

Samantha Law
Supervisor, Regulatory Affairs

November 8, 2001

Date



TORPHARM
Amendment to ANDA #65-040
Cyclosporine Capsules USP
25 mg and 100 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

Tor Pharm Inc.

ONC AMENDMENT
N/AM

COVER LETTER

TELEPHONE AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 65-040 for Cyclosporine Capsules USP 25 mg and 100 mg. The amendment is being submitted in response to a FDA Telephone call from Ruth Ganunis to Marcy Macdonald on April 08, 2002.

L Chinn
Leanne Chinn
Supervisor, Regulatory Affairs

Apr 10/02
Date

RECEIVED
APR 1 1 2002
OGD / CDER

TORPHARM

Amendment to ANDA #65-040
Cyclosporine Capsules USP
25 mg and 100 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

Redacted 2

pages of trade secret and /or confidential commercial information

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

October 6, 2000

ORIG AMENDMENT
N/FA

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

FAX AMENDMENT

RE: ANDA 65-040
(Cyclosporine Capsules) 25 mg and 100 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, of Ontario, Canada, is hereby forwarding a fax amendment in response to the fax deficiency letter dated September 06, 2000.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 13 2000
OGD

Tor Pharm

NDA ORIG AMENDMENT

n/AP

COVER LETTER

LABELING AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 65-040 for Cyclosporine Capsules NON-25 mg and 100 mg. The amendment is being submitted in response to the FDA Deficiency Letter dated December 27, 2000.

Esther Barber
Manager, Regulatory Compliance

9 Jan 01
Date

TORPHARM
Amendment to ANDA 65-040
Cyclosporine Capsules
25 mg and 100 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

Tor Pharm

N/AM

ORIG AMENDMENT

COVER LETTER

MINOR AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 65-040 for Cyclosporine Capsules USP 25 mg and 100 mg. The amendment is being submitted in response to the FDA Deficiency Letter dated January 26, 2001.

Esther Barber
Esther Barber
Manager, Regulatory Compliance

May 3, 2001
Date

TORPHARM

Amendment to ANDA #65-040
Cyclosporine Capsules USP
25 mg and 100 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

Tor Pharm

COVER LETTER

ORIG AMENDMENT
N/A

LABELING AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 65-040 for Cyclosporine Capsules [redacted] 25 mg and 100 mg. The amendment is being submitted in response to the FDA Deficiency Letter dated November 3, 2000.

The proposed proprietary name has been revised due to comments from the Office of Post-marketing Drug Risk Assessment. Two proposed proprietary names are being submitted in this amendment for review:

1. [redacted]
2. [redacted]

Draft labeling has been generated for the proposed proprietary name [redacted]. No labeling for [redacted] has been generated as discussed in a telephone conversation with Charlie Hoppas on December 4, 2000. In that conversation Mr. Hoppas stated that TorPharm could submit complete labeling for one proposed proprietary name and propose an alternate name without the corresponding labeling.

Therefore for review of this amendment we request that " [redacted] be substituted with " [redacted] as an alternate naming option for the product.

Esther Barber

Esther Barber
Manager, Regulatory Compliance

13 Dec 00
Date

TORPHARM

Amendment to ANDA #65-040
Cyclosporine Capsules [redacted]
25 mg and 100 mg

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

NDA DRUG AMENDMENT
N/AB

APOTEX CORP.

25 YEARS OF CANADIAN SUCCESS

FACSIMILE

To:	Patty Nguyen	**Date:** April 12, 2000	
Company:	Div. of Bioequivalence	**Fax #**	301-594-0181
From:	Marcy Macdonald	**Pages** (including this page):	
Subject:	ANDA 65-040 Question concerning correct Dissolution Specifications		
cc:			

Patty:

As you may recall from our last telephone conversation of 3/23/00 concerning the above referenced ANDA, TorPharm wanted to confirm the dissolution specification for this product. There is some confusion as to whether the specification is Q= —. or Q- —. As you recommended, they have prepared a history of the communications they have had over this issue. This summary as well as the supporting documentation is attached for your ease of review.

Any assistance you could provide in verifying the correct dissolution specification would be greatly appreciated.

Thank you for your assistance in this matter.

Regards,

Marcy Macdonald

Marcy Macdonald

APPEARS THIS WAY ON ORIGINAL

Part 1 of 2 (15 pages)

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 14 2000
OGD

f. DOSAGE AND ADMINISTRATION

Delete the terminal "—" following the decimal point, [i.e., "1" instead of "—"].

Please revise your container labels and insert labeling, as instructed above, and submit draft labels and labeling. We will not request final print pending approval of your proposed proprietary name and issues regarding the established name of your drug product.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes,
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html.

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 your last submission with all differences annotated and explained.

/S/ for

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

February 14, 2000

NDA ORIG AMENDMENT
N/AC

Noted:
Bio already reviewed the identical information included in bio portion of this response as part of review of a separate bio submission dated 9/30/99. See Volume 1.1

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

MAJOR AMENDMENT

RE: ANDA 65-040
[redacted] (Cyclosporine Capsules) 25 mg and 100 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex Inc., of Ontario, Canada, is hereby forwarding a major amendment in response to the deficiency letters dated August 16, 1999 and September 14, 1999.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB 16 2000
OGD

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

June 9, 1999

NDA ORIG AMENDMENT
N/AB

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

RE: ANDA 65-040
[redacted] (Cyclosporine Capsules) 25 mg and 100 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex Inc., of Ontario, Canada, is hereby submitting a bioequivalency amendment in response to the deficiency letter dated March 30, 1999.

Apotex Corp. certifies that a true field copy of this amendment is also being submitted to the Office of Generic Drugs.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG
REC'D
JUN 14 1999
OGD
EVALUATION AND RESEARCH

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

February 16, 1999

APPEARS THIS WAY
ON ORIGINAL

NEW CORRESP
NC

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ADDITIONAL INFORMATION

RE: ANDA 65-040
[redacted] (Cyclosporine Capsules) 25 mg and 100 mg

To Whom It May Concern:

Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex Inc., of Ontario, Canada, is hereby submitting additional information to the above-referenced ANDA. We are enclosing an updated DMF letter of authorization that incorporates the assigned DMF number.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

RECEIVED
FEB 18 1999
GENERIC DRUGS

ANDA 65-040

APPEARS THIS WAY
ON ORIGINAL

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for TorPharm
50 Lakeview Parkway
Suite #127
Vernon Hills, IL 60061

FEB 16 1999

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.

NAME OF DRUG: ~~~~ (Cyclosporine Capsules, USP), 25 mg and 100 mg

X Product does not meet USP monograph.

/S/ 2/11/99

RLD=encapsulated solution

ANDA=encapsulated powder

DATE OF APPLICATION: January 11, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 13, 1999

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/

APPEARS THIS WAY
ON ORIGINAL

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

OIL /S/ 2/9/99

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

January 11, 1999

labeling review drafted 3/29/99 /S/

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

RE: ——— (Cyclosporine Capsules)
25 mg and 100 mg
Original Abbreviated New Drug Application

To Whom It May Concern:

Pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1994, Apotex Corp., as the U.S. agent for TorPharm, a Division of Apotex Inc. of Ontario, Canada, hereby submits an original abbreviated new drug application (ANDA) for ——— (Cyclosporine Capsules), 25 mg and 100 mg.

We are submitting an archival copy under blue cover, a chemistry review and two additional copies of the analytical methods section under red cover, and the bioavailability/bioequivalence review section under orange cover.

Apotex Corp. hereby certifies that in accordance with 21 CFR 314.94(d)(5), a true field copy of the technical sections of this submission under a burgundy cover is also included as a foreign applicant is submitting this ANDA.

We appreciate an expeditious review of this application. Please direct any inquiries regarding this application to me at the addresses listed above.

Sincerely,

RECEIVED
JAN 13 1999
GENERIC DRUGS

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-040

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA: 65-040

DRUG PRODUCT: Cyclosporine Capsules, USP

FIRM: TorPharm, Inc

DOSAGE FORM: Capsule **STRENGTH:** 25 mg and 100 mg

CGMP STATEMENT/EIR UPDATE STATUS: Signed cGMP certification provided on page 2817, Vol. 1.7. Acceptable EER dated 8/25/00.

BIO STUDY: The bio-study conducted on the applicant's product and Novartis's Sandimmune® 100 mg capsules, and the waiver for bio-study for the 25 mg capsules were found acceptable by the Division of Bioequivalence on 1/23/99.

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance is USP. Torpharm's product conforms to the revised monograph published in the Nov-Dec 2001 PF as an Interim Revision Announcement, which became official December 1, 2001. The analytical methods used to analyze the finished product were found acceptable 12/3/99.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?): Accelerated and room temperature stability data support the proposed 24 month expiration date. Containers used in the stability studies were identical to those described in the container section.

LABELING: See "Approval Summary" dated 3/13/02.

STERILIZATION VALIDATION (IF APPLICABLE): Not-applicable to this drug product.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): Exhibit batch #FD8040 (100 mg) used for stability and bio-studies and exhibit batch #FD8039 (25 mg) used for stability studies were manufactured with ——————. from ——————— The exhibit batch was —, from which —— 25 mg capsules (——————— and ——— 100 mg capsules ——————— were produced.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?): See above

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): The size of the proposed production batch is [redacted]. From that [redacted] 25 mg capsules ([redacted] and [redacted] 100 mg capsules ([redacted] will be produced. The manufacturing process described in the master production record is the same as that described in the exhibit batch record.

CHEMIST: Ruth Ganunis **DATE:** 11/29/01; 3/14/02
SUPERVISOR: Richard Adams /S/ **DATE:** 11/29/01 3/14/02

APPEARS THIS WAY
ON ORIGINAL

Redacted 3

pages of trade secret and /or confidential commercial information

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

ANDA Number: 65-040

Date of Submission: January 9, 2001

Applicant's Name: Torpharm

Established Name: Cyclosporine Capsules, USP 25 mg and 100 mg

Labeling Deficiencies:

1. General Comments

   a. Your proposed proprietary names, [redacted] [as an alternate] are still under review by the Office of Post-Marketing Drug Risk Assessment (OPDRA). We will notify you of their comments when available.

   b. [redacted]

2. Container: 25 mg and 100 mg (30s and 1000s)

   Delete [redacted] following "Cyclosporine Capsules".

3. Insert:

   Delete "[redacted]" following "Cyclosporine Capsules" in the TITLE, DESCRIPTION, INDICATIONS AND USAGE and HOW SUPPLIED sections.

Please revise your container labels and insert labeling, as instructed above, and submit draft labels and labeling. We will not request final print, pending the review of OPDRA regarding your proposed proprietary name and issues regarding the established name of your drug product.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

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 your previous submission with all differences annotated and explained.

/S/

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

ANDA Number: 65-040

Date of Submission: February 14, 2000

Applicant's Name: Torpharm

Established Name: Cyclosporine Capsules 25 mg and 100 mg

APPEARS THIS WAY ON ORIGINAL

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Use uppercase print for " [redacted] on your container labels and insert labeling.

   b. Following your proposed proprietary name " [redacted] add the text " [redacted] on your container labels and insert labeling. In addition, revise to read as follows:

   [redacted]

2. CONTAINER 25 mg and 100 mg (30s and 1000s)

   a. Print the "WARNING: ... supervision" statement in red print and enclose it in a black bordered box.

   b. Relocate the boxed warning statement to appear on the front panel.

3. INSERT

   a. General Comment

      See GENERAL COMMENT 1(b) above.

   b. WARNING BOX

      Second Box

      To be consistent with the insert labeling of the reference listed drug revise "Cyclosporine Capsules [redacted]" to read " [redacted]

   c. Italizize the first "*N*" in the chemical name.

   d. CONTRAINDICATIONS

      Cyclosporine capsules are contraindicated in patients with a hypersensitivity to cyclosporine or to any of the ingredients of the formulation.

   e. WARNINGS

      Fifteenth paragraph

      [redacted]

Esther Barber
Manager, Regulatory Affairs
TorPharm
50 Steinway Blvd.
Etobicoke, Ontario
M9W 6Y3 Canada
Tel: (416) 675-8394
Fax: (416) 675-0340

TorPharm

ORIG AMENDMENT
N/A/B

Fax

To:	Mark Anderson	**From:**	Esther Barber
Fax:	1-301-443-3839	**Pages:**	17
Phone:	1-301-827-5849	**Date:**	30/09/99
Re:	ANDA 65-040	**CC:**	N/A

☐ **Urgent** ☑ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Attached are the questions we discussed last week. I have included all of the attachments that you may need to refer to. Again, sorry for the delay and I hope to hear from you soon.

Please feel free to call me if you have any further questions.

Regards,

Esther Barber

Esther Barber

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
OCT 12 1999
OGD