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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 65-040

APPROVAL LETTER

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,

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

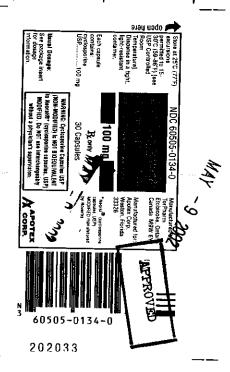
CENTER FOR DRUG EVALUATION AND RESEARCH

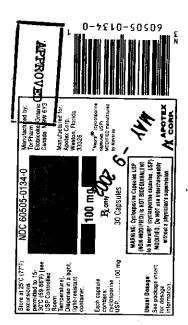
APPLICATION NUMBER: 65-040

APPROVED FINAL LABELING

COVER TORP6530

DOWN TORP6530





Laboratory Texts

Renal and fiver functions should be assessed repeatedly by measurement of BUN. serum creatings serum bilinging and liver enzymes.

Drug InteractionsAll of the individual drugs cited below are well substantiated to interact with cyclesporine.

Drugs That Exhibit Hapkrotaxic Synorgy

enlamicin ampholericin B cimelidine trimelinoprim obramycin ketoconazole ranitidine with sulfamethox ancomycin melphalan diciplenac azapropazon

Careful monitoring of rehal function should be practiced when cyclosporing is used with controlled draws.

Brags That After Cyclosporius Levels Cyclosporine is extensively metabolized by the liver. Therefore, circulatin, cyclosporine levels may be influenced by drugs that afted hepatic microroma promotes, particularly the cycloshorem P-450 system. Substances become in inhibit these enzymes will decrease hepatic metabolism and increase cyclosporine levels. Substances that are inducers of cytloshorem P-451 schirtly will increase hepatic metabolism and decrease cyclosponne levels decribing of circulating cyclosporine levels and appropriate cyclosporiate cyclosporiate cyclosporiate levels for the company of circulating cyclosporiate levels and appropriate cyclosporiate cyclosporiate cyclosporiate cyclosporiate for the cyclosporiate cyclosporia

ice Bland Lavel Monitoring).

CYCLOSPONING CAPSULES USP 25 mg alle 100 mg

R auk

Only physicians experienced in immunosuppressive thera management of organ transplant patients stroud prescribe Cyclo Capsules USP MON-MODIFED. Patients receiving the drug st managed in Facilities equipped and staffed with adequate laborat supportive medical resources. The physician responsible for mana-

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 bronchoms may result from the property of the control of the control

Cyclesporine Soft Gelatin Capsules USP (NON-MODIFIED) have decreased locavallability in comparison to Neoral ** (cyclosporine capsules, USP)

Cyclosporine Capsules USP (NON-MODIFIED) and Neoration (cyclosporine

Gregs Fhat Exhibit Meghroforic Synergy
gentamicin amphotoricin B circelidene totoramycin katoconazole razilistine with sulfamelhoazole vancomycin mejnhalan dictofenac azorropazon

Careful monitoring of renal function should be practiced when cyclosp is used with nephroloxic drugs.

is used with nephrotoxic drugs. Purps Tash Affer Declaporise Lerets Cyclosporine is citiesteely metabolised by the Rent. Therefore, circulating cyclosporine is citiesteely metabolised by the Rent. Therefore circulating cyclosporine is made in the inflamment by drugs. In all affect fepalit, microcomal productions and containing the cyclostrome P-450 system. Substances known to implementation cyclose with discharate hepatic metabolism and increase carbon tellulorism and increase activity will increase inspatic metabolism and decrease cyclosponitie levels. Mentiology of circulating cyclosponitie levels and appropriate cyclosponite declaps discharate are essential when these dirugs are used concomitantly (See Blood Level Monitoring).

Pruss Thei Incresse Opciosporine Levels
difficarem ketoconazole danazol
nicardipine ketoconazole bromocripine methylpradrusolone
verapernil draconazole metoclopramide

Orugs That <u>Occrease</u> Cyclosporine Levels
ritampin phenyluin phenobarbital carbamazepine

ditaining pheryton promounted to the control of the property o

Carcinogenesis, Mutagamenis, Impairment of Fertility Cyclosporine gave no evidence of mutagenic or teratogenic affects in appropriate test systems. Only all doce levels toxic lo dams, were adverse effects seen in reproduction studies in rats. (See Pregnamsy)

encus aum n reprocursiva doutes mi resu, very reginema). Carcinopenicity studies serie curred out in male and femba rats and mice. In the 78-week moarse bridy, all doses of 1, 4, and 16 mg/tg/city, evidence of a substicially significant in tent are second in symptomic by implement significantly exceeded to the patient of the patient of the patient in mid-desse makes significantly exceeded and the patient of the patient in mid-desse makes significantly exceeded and the patient of the patient

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

Cyclosporine has not been found mutagenic/genotosis in the Ames Test. No VY9-HOPRI Test, the microsundess test in mise and Chinese hamslers. The chromosome-aberization tests in Ohnese hamsler bote-marrier, the materials in the chromosome-aberization tests in Ohnese hamsler bote-marrier, the materials of command lethal design, and the following lethal test and provided in the chromosome-aberization study analyzing settle chromabil exchange (SCI) indication of a positive office of the chromosome of the chromosome

An increased incidence of malignancy is a necognized complication of minumosuppression in recipients of organ transplants. The most common forms of necipients are non-Hodgkin's symptomic and consciousness of the skin. The risk of milignancies in cyclopycomic recipients is higher than in the normal healthy produktion 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

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100

Programs: Programs: Calagory C. Programs: All Calagory C. Programs: Calagory C. Cyclospome Oral Solution, USP has been shown to be embryo- and letoloxic in rate and rabbits when given in doses 2.5 times the human dose. At tious closer (rate at 30 mg/kg/day and atbiblist at 100 mg/kg/day), Cyclospomero Oral Solution USP was embryo- and knotice to sinducide by increased pietand postband montally and reduced that weight together win instead selection returned programs and postband montally and reduced that weight together win instead selection returned and arbbits at less 0.50 mg/kg/day), Cyclospomiero Calagoria. Solution USP product to be without any embryolicital or ferallogenic effects.

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

inatives the potential risk to the fatur.

The following data represent the reported colorones of 116 pregnancies in women recruind cycloroprise during pregnancy, 60% of whom were worked recruind cycloroprise during pregnancy, 60% of whom were disconsistent of the patient were not prospectively reduced to the patient were not prospectively reduced the respective produced the respective produced the respective produced by the patients of abortomatily were prematute birth (postational period 28 to 8 beets) and now that weight for persistancial que, it is not possible to apparate the effects of cycloroprises on these pregnancies from the effects of the test immension appreciately decided to separate the effects of the test immension appreciately and deciders in other aspects to the birth (1901) were complicated by obsorbers inclined pure eclampsic externals present that of such patients of separated by the patients of the patients of the compatibility and electroparated by the patients of the patients and expects of feat loss. I wently-eight percent of the visitation are presented complications coursed in 27% in a report of 23 children followed up to 4 years, posmital derekipment was act to be normal.

Nersing Muthers Since cyclosperine is excreted in human milk, nursing should be avoided

Pediatric Use Allbough to 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, birsufism, hypertension, and gorn hyperplasia.

hypertension, which is usually mid to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients:

Gioneuta: capidary thrombosis has been found in patients treated with cyclosporine and may propers to quart failure. The pathologic changes resemble those sever are templetic-urrents synthem and include the patient of the patients are the patients of the beautiful patients and patients and afternat aerioles, wincreaployative beautiful patients and patients are the patients are the feddings have been observed when other minunosuppressives have been employed posttransplantation.

ih-pomagneserna has been reported in some but not all, patients exhibiting convolutions white on cyclosperine therapy. Although magnesium depletion studies in normal subjects suggest that hypomagnesima is associated with neurologic disciders, multiple tackors, including hypomagnesima is associated with reported in the control of the control including the control of the control o

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

	Randomized 9	Odney Patients	All Cyclosporine Patient			
Body System/ Advecse Reaction	(H=227)	Azathioprine (N=228)	Kiéney (N=705) %	Heart (H=112) %	Live (H=7)	
Genilourinary						
Renal Dysfunction	32	6	25	38	37	
Cardiovascular					_	
Hypertension	26	16	13	53	27	
Cramps	4	<1	2	<1	0	
Skan						
Hirsutism	21	<1	21	28	45	
Acne	6	8	2	2	- 1	
Central Nervous Sy	stem					
Tremni	12	0	21	31	55	
Convulsions	3	1	1	4	5	
Headache	2	<1	2	15	4	
Gastromtestinal						
Gum Hyperplasia	4	0	9	5	16	

CYCLOSPORINE CAPSULES USP 25 mg and 198 mg

B saty

WARNING

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Cyclosporne Capudes USP NON-MODIFIED. Patients receiving the drug should be managed in bacilities equipped and staffed with adequate aboratory and supportive medical recourses. The physician responsible for mantenance therapy should have complete information requisite for the follow-up of the patient.

inc purcons. Cyclosporine Capsules USP NON-MODIFED should be administered with administration orticosteroids but not with other minimosuppressive agents increased susceptibility to intection and the possible development of lymphoma may result from immonosuppression.

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

Cyclosponne Capsules USP (NON-MODIFIED) and Neoral** (cyclosponine capsules, USP) MODIFIED are not bioequivalent and cannot be used interchangeably without physician supervision

interclangably without physicians supervision. The absorption of cyclosporties during chronic administration of Cyclosporties during chronic administration of Cyclosporties Capitales USP ROM-MODIFED was found to be erable. Its commended that partients hallon Cyclosporties Capitales USP ROM-MODIFED over a period of time be monitored at repeated intervals for cyclosporties blood leeds and subsequent dose adsistments be made in order to avoid leading this in high levels and possible organ rejection due to few absorption of cyclosporties. Their is of special importance in their lamplants. Numerous assays are being developed to measure blood evers of cyclosporties. Comparison of levels in published Metrature to pallent levels under the comparison of the assay method employed. (See Blood Level Woorldong under OssaCE AND AUMINISTRATION)

DESCRIPTION

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

Chemically, cyclosporine is designated as $|R\{R^*,R^*,\ell^*\}|$ -cyclict_alony-lo-slamy-l-f-methy-l-t-slowy-l-f-methy-l-t-slowy-l-f-methy-l-t-slowy-l-f-methy-l-t-slowy-l-f-methy-l-t-slowy-l-f-methy-l-t-slowy-l-f-methy-l-t-methy-l

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

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

Each 25 mg capsule contains:

Each 100 mg capsule contains cyclosporine USP100 mg

Specia capsite some many the following inactive ingredients: methanol, purified water, sodorm laungt strillet and tale. The 25 mg and the 100 mg capouls shell containing special, not from onde and binative disords. The 25 mg and 100 mg capouls shell containing special, not for onde and binative disords. The 25 mg and 100 mg capouls shell remaining selection the followings and the followings are proposed by the followings and the followings are proposed by the followings and the followings are proposed by the followings and the followings are proprieted by the followings and the followings are proprieted by the fol

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

CLINICAL PHARMACOLOGY

Cyclosporine is a potent immunosoppressive agent which in animals prolongs survival of allogeness transplants involving stin heart suffery pancress. Done marrow small intelless, and wing Cyclosporine but been demonstrated to suppress some humoral immunoly and to a great or sub-cident excellent sections so that assigned in rection, delight of protection of involved reactions so that assigned in rection delight of protection protections and animal section of the protection of sections and craft virtual sections are many among topics for a carety of organs.

Successful killney, liver, and heart allogeness transplants have been performed in man using cyclosporine

The react mechanism of action of cyclosporine is not know. Experimental evidence suggests that the effectiveness of cyclosporine is due to specific and reversible elabilities of immunocomplentit tymohopyless at the Gy of Dy phase of the call cycle. Thymphocytes are preferentially mithold. The Tabetyr oil is the men lasted, although the T-supports or call register suppressed Cyclosporine also inhabits middless production and release including interfacilities or a to-dig cycles had only call of the middless and the call of the call of

monoring internations of incompanies (CCP). No functional effects on phagocytic (changes in earyme secrations not affered, chematicial impastion of granulocyties, macrophage migration, carbon clearance in vivo) or tumor cells (growth rate, metastasis) can be detected in animals. Cyclosponne does not cause bone marrow suppression in animal models or man.

The absorption of cyclosporine from the gastrombestmal tract is incomplete and variable. Peak consonitations (C_{mall} in blood and plasma are achieved alboid 1.5 boxes. C_{mall} and earload the plasma of blood concentration. C_{mall} and the plasma of blood concentration time curve (AUC) increase with the administered doss. For blood time curve (AUC) increase with the administered doss. For blood time curve (AUC) increase with the administered doss. For blood time curve (AUC) increase with the administered doss. For blood termined by a specific stage, C_{mall} is high procurately 1.0 and 0.0 doss for plasma and 2.7 i.4 agministry of dose for plasma and 2.7 i.4 agministry of dose for blood tile for to high doses.

Cyclosponne is distributed triggly activities the blood youthern in Mond the distribution is consentrated distribution state for blood the distribution is consentrated distribution for consentrated distribution for consentrated distribution for the distribution for the distribution for the distribution for the distribution of the distribution o

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

outry with only 5% of the dose excreted in the urine.

Cyclosporane of extensively metabolicate but there is no major metabolicate of the properties of the

INDICATIONS AND USAGE

Cyclosporine Capsules USP are indicated for the prophylazis of organ rejection in Midney, liver, and heart allogenic transplants. If a laways to be used with advertion confrontered by the drug may also based at the teatment of chronic rejection in patients previously treated with other immunosuppressive agents.

CONTRAINDICATIONS

Cyclosporine Capsules are contraindicated in patients with a hypersens to cyclosponne 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 mephrotoxicity

2 <1 <1	19 0 0	<1 1 4 <1	6 6 3	0 1 7 3
2 <1	19 0	1	6	1
2 <1	19 0	1	6	1
2	19			0 I
2	19			0
	-	-1	6	0
-1				
		1	ň	à
			2	1
<1	0	<1	,	
	_		7	8
<1	اه	4	r	•
				4
				4
4				10
				16
2	<1	2		•
				4
12				~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
n		•	24	55
	В	2	2	
21				1
			20	45
4	<1	2	< 1	U
26				2/
	4 21 6 6 n 12 3 2 4 3 2 c1 c1 3	4 <1 21	21	20

The following reactions occurred in 2% or less of patients: aflergic reactions, anemia, annexia, confusion conjunctivities, edema, fever, brittle fingernails, gastritis, hearing loss, thocups, hyperglyce muscle pain, peptic uteer: thrombocylopenia, hinnitus

The tollowing reactions occurred carely anxiety, chest pain constipation, depression, has breaking, hieraluria point pain thriaty, mouth sores, myocardial rifaction, night sweats pencreatitis, pruntus swallowing dirfacily, legiting, upper GI beeding, visual distributions.

Penal Transplant	of Patients in Whom Therapy Was Discontinued			
	Randomize Cyclosporine (M=227)	All Cyclesporin Palients (H=705)		
Reason for Discontinuali <u>en</u>	%	<u>%</u>	%	
	5.7	0	5 4	
Renal Toxicity	0	0.4	0.9	
Intection	2.6	0.9	1.4	
Lack of Efficacy Acute Tubular Necros		0	10	
Lymphoma/ Lymphoproliferative		0	0.3	
Disease Hypertension	0	0	0.3	
Hentalological	_		0	
Abnormalities	q	0.4	0.7	
Other	0	0	eis and then restar	

Cyclosporine was disc 18 additional patients.

callors in the Randomized Renal Transplant Patients

Complication	Cyclexperine Treatment (N=227) % of Complications	Standard Treatment (N=228) % of Complications
	5.3	4.8
Septicemia	4.4	5.3
Abscesses	2 2	3.9
Systemic Fungal Infection	7.5	9.6
Local Fungal Infection	4.8	12.3
Cytomegalovirus	15.9	18.4
Other Viral Intections	21.1	20.2
Urinary Tract Intections		10 I
Wound and Skin Intections	7.0 6.2	9.2
Pneumenia		

*Some patients also received ALG

OVERDOSAGE

There is a minimal experience, with overstosage. Because of the slow absorption of Cyclosporane Capsites USP MON-MODIFIED, fortand emersis would be of value us to 2 hours after administration. Transcent hepatitured and nephrotexority are occur with or both transcent and proportion of the production of the production

DOSAGE AND ADMINISTRATION

Disbase Capaties USP NM MODIFED
Cyclosporiae Capaties USP (NM MODIFED
Cyclosporiae Capaties USP (NM MODIFED to Nava discressed brianadability
an comparison Expenses USP (NM MODIFED) and Alexand Cyclosporiae
Capaties USP (NM MODIFED) and Notice USP (NM MODIFED)
Capaties USP) MODIFED are not be equivalent and cannot be used
interchangeably without physician supervision

interchangeably without physician supervision. The invols and does of Cyclosponee Capaties USP NON-MOUPTED should be given 4.12 billing prior to transplantion as a simple dose of 15 ma/kg, although a staffy simple dose of 1.4 to 1.8 ma/kg was used in most claimfall had been menter, consume to use the inhapest dose most because the disk few menters consume to use the inhapest dose most because the disk few menters consume to the inhapest dose most because the disk few menters and others for the staff. Enter is a trend lowards use of even forwer small doses for most because the staff of the staff o

(See Blood Lovel Monitoring below)

on 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.

roterated higher dorses than those used in adults.

Approx Thasays with arteral controlered is in recommended. Different trainering designs scheduled of predictions appear to achieve smaller results. A design scheduled hased on the patient's weight state twith 2 myllogistary for the steet 4 days bapered to 1 myllogistary by 1 week. 0.5 myllogistary by 7 months and 4 medical state of 1 myllogistary by 1 week. 0.5 myllogistary by 7 months and 4 medical state of 1 myllogistary by 1 week. 0.5 myllogistary by 2 months and 4 medical state of 1 myllogistary by 1 1 myllo

Band Lived Beathering
Benefit between the process of the parties of the process of the parties of the parties been been dead even monitoring of cycles-profite early in patient emergement. White no hand estationships have yet been creablease, in one series of 375 consecutive catalent result samplaint scapitatis, dosage was placed to achieve specific whole blood 24 hour trough herets of 100 to 200 inputs a determined by high-respects (quid chromatography (RPLC).

Of major importance to blood level analysis is the type of assay used. The above involved are profited to the parent operation in the control and cont

(CVC/C-VA 81-APX-8-K-R04-280102)

HOW SUPPLIED

Cyclosporine Capsules USP

25 mg Bard 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 int, supplied in bottles of 30 (NDC 60505-0133 0) and in bottles of 1000 (NDC 60505-0133-1).

100 mg Hard gelatin capsales with a reddish brown opeque body and a reddish brown copaque cap. "APO" over "134" and "100" are imprinted on sech capsale in buck mit, supplied an better of 30 (MDC 69505-9134-9) and in bottles of 1000 (MDC 69505-6194-1)

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 light, light-resistant container, [see USP].

CONTRAINDICATIONS

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

WARNINGS

(See baxed WARNINGs)

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

It is not unusual for sarum creatinine and 6UN levels to be elevated during cyclosponne therapy. These elevations or cenal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated before disage edisastment is initiated.

ossage adjustment is measure. Height obsocity has been noted in 25% of cases of innal transplantation, 38% of cases of learned transplantation, and 37% of cases of learned transplantation, and 37% of cases of learned transplantation, still dependently were presently inched 2.9 months later transplant and consisted of an arrest in the bill of the presponsative elevations of 9UN and creatings at a range of 35–54 maging and 20.6.25 months learned transplantation. These elevations were offere responsative glossage redination.

More over inephriotoxicity wasseen early after transplantation and was characterized by a tapidy rising BUM and creations. Since these events are similar to rejection episodes care must be taken to differentiate between them. This form of ephriotoxicity is usually responsive to cyclosporine dosage reduction.

Although specific diagnostic criteria, which reliably differentiate renal graft relection from drug forcitly have not been found a number of parameters have been riginiterantly associated to one or the other it should be noted however, that up to 20% of patients may have simultaneous nephrotoxicity and sear-from

Parameter	Nephrotoxicity vs Re Nephrotoxicity	Rejection
distory	Dongt > 50 years old	Antidonor immune
,	or hypotensive Prolonged kidney preservation Prolonged anastomosis time Concomutant rephrotoxic drug	s
Chimical	Often > 6 weeks postoph Prolonged initial nontunction (acute lubular necrosis)	Often < 4 weeks postopa Fever > 37.5 °C Weight gain > 0.5 kg Graff swelling and lenderness Decrease in daily unine volume > 500 mL (or 50%)
Laboratory	CyA semm 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)*
	Cr plateau < 25% above baseline	Cr > 25% above baseline
Biopsy	BUNCC: ≥ 20 Arterolopathy (medial hypertrophys, hyalinosts, nodular deposits, inthrial thickening, endolheliaf vacuolization, progressive scarring)	BUNICI < 20 Endovasculitiss (profileraliona, initimal arteritiss, necrosis, scierosis)
	Tubular atrophy, isometric vacuolization, isotated calgifications	Exhaulitis with RBCP and WBCP casts, some (regular vacuolization
-,	Minimal edema	interstitial edemac and hemorrhage ^b
	Mild focat infiltrates: Diffuse interstitial Whosis often strond form	Dittuse moderale to severe mononuclear infitrates ^d Glomerulitis (mononuclear cells is
Aspirate Cytologi	on CyA deposits in tubular and	Inflammatory infiltrale with mononuclear phagocytes,
		These strongly express HL DR antigens
Urine Cylolog	Tubular cells with y vacuolization and granularization	Degenerative tubular cells, ptasma cells, and tymphocytura > 20% of sediment
Manor	netry Intracapsular pressure < 40 mm Hg ^c	intracapsular pressure > 40 mm High
graphy graphy	no- Unchanged graft cross	increase in graft cross sectional area AP diameter ≥ Transverse diameter
Magne Reson Image	ance	Loss of distinct corticomedulary junction swelling, image intensity parachyma approaching of osoas loss of hilar fat
Radio nucled Scan		Patriny arterial flow
5541	Decrease in tubular fund	tion Decrease in perfusion > decrease in fubular function
	11-1 hippuran > decre- pertusion (⁹⁹ 11 To OTPA	gse on Indicased uptake of Indi 111 labeled platelets or To:99m in collect
Ther	apy Responds to decreased cyclosponee	Responds to increased steroids or antilymphoc globulin

*p < 0.05, *p < 0.01, *p < 0.001, *p < 0.0001

p < 0.05 kp < 0.01, sp < 0.01, sp < 0.001. pc < 0.0001

A form of otherwise progressive cycleoportria-associated nephrotesicity is chancied to be serial destroated in new function and morphologic changes in the kindery. From 59-15% of transplant recipient model that is a foreign to exclude the serial control of the serial control of the control of

progressive cyclosporine -associated naphrotoxicity 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 intersolval inforests and higher cumulative doves or persistently high circulating trough levels of cyclosponer. This is particularly frue duming the first of posttransplant months when the docage leads to be highest and when, in interpreting to the control of intersolated from the low control of the control of intersolated from the low the control of the control of intersolated from the low the control of the control of intersolated from the low the control of the control of intersolated from the low the control of the control of the control of intersolated from the low the control of the co

Impaired read function at any two requires close monitoring, and frequent decay adjustment may be indicated in patients with persistant high intervalsions of BWA and crashinine who are unexposure to dougle adjustments, consideration should be given to switching to other genomosphosewise therapy. In the event of several and interesting rection, in a preferable to allow the bedney transplant to be rejected and removed gamesting the properties of the properties

To assert the regional Constitution of the comboyropenia and microangingship hemolytic anemia which may result in graft feature. The vascilopability can cours in the absence of rejection and of a scompanied by avid glatelet consumption within the graft as demonstrated by inform 11 tabeled grabels studies. Netter the posthogenical root line management of this syndrome is clear. Though is solution has coursed after reliefs and control of the syndrome in the management of the syndrome is control of the syndrome in the control of the syndrome is control of the syndrome in the syndrome is control of the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome in the syndrome is sold to the syndrome in the syndrome in the syndrome is sold to the syndrome in the

Significant hyperkalemia (sometimes associated with hyperchloremic metapolic acidosis) and hyperunicemia have been seen occasionally in

Hepatoloxicity has been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of deer transplantation. The vast usually needed during in first amonth of therapy when high doses of cyclospentie were used and consisted of developing of hepatic enzymes and bioticin. The chemistry developing usually developed with a reduction in dose, and the contract of the contract

As in patients receiving offset immunosuppressants, those patients receiving cyclosponne are at increased risk for development of lymphomas and other malignancies, particularly those of the skin, the excased 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 Pneumonia	6.2	9.2

There is a minimal experience with overdosage. Because of the slow absorption of Oyclosporthe Capacides USP MON MODIFED, formed emessis would be of value up to 2 hours after administration. Transent hepstotocordy and empirications from your work of the properties of the properties

DOSAGE AND ADMINISTRATION

Cyclesperine Capalles USP ROM - MODIFED Devices on Capalles USP ROM - MODIFED Devices on Capalles USP (ROM - MODIFED) were decreased biocuralishing in comparison to Romanie (Cyclesportee capalles USP) (ROM - MODIFED) and Recust* (cyclesportee capalles USP) (MODIFED are not bioegarizent and cannot be used interchanges) without physician appearation.

almerbangeably without physicana supervision. The initial and does of Cyclesponter Capacides USP NON-MODIFED should be given 4-12 hours pint in transplantation as a single does of 15 mg/kg, 48 mg/kg does of 15 mg/k

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.

Identité higher doses flux flores used in adults.

Adjunct therapy with adversal cordiscosterods is recommended. Different placerang discage schedules of produtions appear to achieve similar results. A dossage schedules based on the patient's weight started with 2 moglacitary for the first 4 days tapeed to 1 mg/dayday by 1 week. 6.6 mg/dayday by 2 weeks. 0.3 mg/dayday by 1 morth, and 0.15 mg/dayday by 2 medits and beneather as a militarious doses. Another contributions with an initial dose of 200 mg tapeed by 40 mg/day well reaching 20 mg/day. After 2 months at this dose, a further reduction to 10 mg/day was made. Adjustments in doseage of predisiones must be made according to the clinical situation.

Contestin sciences, mercanical Model and Model and Model and Modeling Several study onthers have found blood tevel monitoring of cyclosporine useful in publish management. While no food debtanships have yet been established, in one retires of 375 consecutive castever formal transpart, established, in one retires of 375 consecutive scales for result anaptant established, some sets as better than the second of the second of the established and the second of the second of the established of the second of the second of the large density of 100 to 200 inpline, as determined by high-reservat regard circ ovalography (HPLC).

otromatography (FRLC).

Of major importance to blood level analysis is the type of assay used. The above levels are specific to the permit cyclooporine motionia and corrective directly to the one monocolomal specific radiomismoscopies (milk4-sp). Nemapoorine assays are not monocolomal specific radiomismoscopies (milk4-sp). Nemapoorine directed and access or an employed sevel and the permit compound methodal and access or an employed sevel and access which were roughly helds those of specific sessing, Austy and the rest access which were roughly helds those of specific sessing, Austy and the series of the second from which blood be guided by these agrowed belleding if plasma specimens are employed, levels will vary with the temporation at the time of separation from which blood. Plasma levels have range from 172-15 of whole blood levels. Refer to individual assay libering for complete instructions. In addition, Transpalantion Proceedings (plant 900) contains position papers and a broad consensus generated at the Cycleoporine-Transpack Chip (Ambrishing conference ball year. Blood level monotoning is not a replacement for reveal function monitoring or tissue blogoles.

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

HOW SUPPLED

Orciosporine Causates USP

25 mg Hard gelalin capsules with a pale recitish brown opaque body and a pale reddish brown opaque cap. "APO" over "133" and "25" are imprinted on each capsule in black int, supplied in bottles of 30 (NOC 60505-0133-4) and in bottles of 1000 (NDC 60505-0133-1).

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100 mg Hard gelatin capsules with a neddish brown opaque body and a reddish brown opaque cap "APO" over "134" and "100" are imprinted on each capsule in black mix, supplied in bottles of 39 (NDC 60505-0134-0) and in bottles of 1000 (NDC 60505-0134-1).

Nore 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 light, light-resistant container
[see USP].

TORPHARM CYCLOSPORINE CAPSULES USP 25 mg and 100 mg

Manufactured by TorPharm Etobicoke, Ontario Canada M9W 6Y3

Revised: January 2002

(cyclosporine capsules, USP) MODIFIED manufactured by Novariis



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enggeweggspromonon

umme moderate to severe monoreiclear insignates^a Glomerulitis (mononuclear cells)^c CyA deposits in tubular and endothelial cells -Fine isometric vacuolization Inflammatory inhitrate monunclear phagocy These strongly express HLA DR antigens Degenerative (ubular cells, plasma cells, and tymphocyturia > 20% of sediment intracapsular pressure > 40 mm Hg4 Increase in graff cross sectional area AP diameter ≥ Transverse diameter Loss of distinct corticomedullary junction swelling, image intensity parachyma approaching 8 of pseas, loss of hilar fat Increased uptake of inci 111 labeled platelets or Tc-99m in colloid

γp<0.005, γp<0.001, γp<0.0001, γp<0.00001

• y « 0.50, ½» « 0.01, ½» « 0.001, »» « 0.000.
A form of chronic progressive explosporise -sssociated apphratoxicity is characterized by sentil deterioration in must function and mosphologic charges in the biddings, "from Sx-15% of transplant explosition will fail to store education in a rising serum crashinite desoite a document or discontinuation of cyclosporise beneziny. Penal bioposite from these patients will demonstrate an interestinal filtrosis with tubular alrophy. In addition, fortic tubulopathy, persistants caraphar groups from a filtrosit introcis with tubular alrophy may be present. Though noise of filtrasi monthologic changes is entitiently penalic. a historic organized or former progressive cyclosporine-association imprintedirectly require sedence of filese.

to textual uncoron nava not yet open destrations.

Implicated most histolemant may be indicated. In patients with persistent high elevations of SUN and creatinine who are unresponsive to desage adjustiments, consideration should be given to switching to other minusoppressive therapy, in the event of severa and unrentilling rejection, it is preferable to allow the faither presuperation unrentilling rejection, it is preferable to allow the faither transplant to be registed and removed rather this increase the oydeoported dosage to a very high level in an attempt to creating the registerion.

to evenes the rejection

Coasinnally putlests have developed a syndrome of thrombocytopenia and microantification hemorytic anemia which may resett in grait faiture. The vasculopathy can occur in the absence of rejection and is accumpanied by and plateir coasimption within the grait as demonstrated by Indian 11 tabeled plateir studies. Hother the pathogenesis not the management of this syndrome a clear. Though resident has accurate able reduction or discontinuation of cyclosporties and 1) administration of steepfoliasses and hepatin of 2) plateinapheress, this appears to depend upon early detection with Indian 111 labeled plateiet scans. (See ADVERSE REACTIONS)

ceution. The chemistry envirance training observed with a moderate in decage. Also palletin foreign of their firmular properties of the properties and other manipular and other manipularities, particularly those of the 6th. The observed intelligence and other manipularities, particularly those of the 6th. The observed intelligence has present that to the intensity and duration of immunosuppression rather than to the use of specific genes. Books are first endough of oversuppression of the immunosuppression of the control of t

cyclosion in particularly in combination with high dear multi-hyperinactions. Encaphalography has been described both in post-marketing reports and in the filtrature. Manifestations include impared correctorances, convolutions, visual destructions (and the filtrature include impared correctorances, convolutions, visual destructions) and control of the control of

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

Frecusio (Mes).

Secure Cyclosporine Capsules USP (MOH MODIFIED) are not bioequivalent to Neoral** (cyclosporine capsules, USP) MODIFIED (convention from Neoral** (cyclosporine capsules, USP) MODIFIED is Cyclosporine Capsules, (NOM MODIFIED) strong to Capsules, USP) MODIFIED is Cyclosporine Capsules, (NOM MODIFIED) strong to Capsules, USP) MODIFIED is Cyclosporine Capsules, (NOM MODIFIED) strong to Capsules, USP) MODIFIED (Cyclosporine Capsules,

Hypertension is a common side effect of cyclosporine therapy. (See ADVERSE REACTIONS). Mald or moderate hypertension is more frequently encounteed than severe hypertension and the incidence decreases over time. Analysporinsis therapy may be required. Control of blood pressure can be accomplished with anyoff the common analysportensive agents, However, the common analysportensive agents.

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

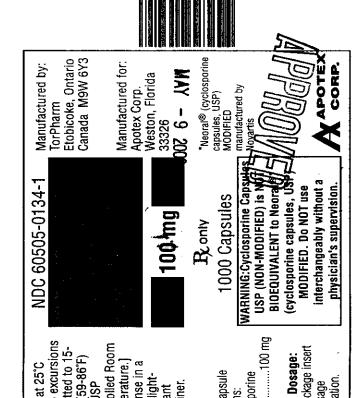
Information for Patients
Patients should be subsissed that any change of cyclosporine fermulation
should be made castiously and only under physician approximine because
it may result in the need for a change in decage.

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



permitted to 15-30°C (59-86°F) Store at 25°C (77°F) excursions cyclosporine USP.....100 mg contains: See package insert Each capsule for dosage container. tight, light-Dispense in a Controlled Room Jsual Dosage: resistant ntormation emperature.] see USP WARNING:Cyclosporine Capsules USP (NON-MODIFIED) is NOT (cyclosporine capsules, USP) BIOEQUIVALENT to Neoral®* NDC 60505-0134-1 interchangeably without a MODIFIED. Do NOT use physician's supervision 1000 Capsules 100 mg By only Novartis "Meoral® (cyclosporine cabsules, USP) manufactured by Manufactured for: Etobicoke, Ontario Canada M9W 6Y3 Manufactured by: MODIFIED Weston, Florida Apotex Corp. TorPharm APOTEX CORP.

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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 InteractionsAll of the individual drugs cited below are well substantiated to interact with cyclosporine.

All of the individual or ago.

**Drugs That Exhibit Nephrotoxic Synergy gentamicin amphotericin B theramycin ketoconazole synergy amphotenicin B theramycin amphotenicin B theramycin amphotenic between the synergy amph melphalan

cimetidine diclofenac

with sulfamethoxazoie azapropazon

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

Drugs That Atter 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 <u>Increase</u> Cyclosporine Levels

diltiazem nicardipine verapamil

ketoconazole fluconazole itraconazole

danazol bromocriptine metoclopramide

erythromycin methylprednisolone

Drugs That <u>Decrease</u> Cyclosporine Levels rifampin phenytoin

phenobarbitat

carbamazepine

Other Drug Interactions

Other Brug 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 potassisurparing diuretics because hyperkalernia can occur. During treatment with Cyclosporine displays 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 mifedipine, and convulsions with high dose methodreefuls alone.

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 ternales, 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 fow dose levet. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.

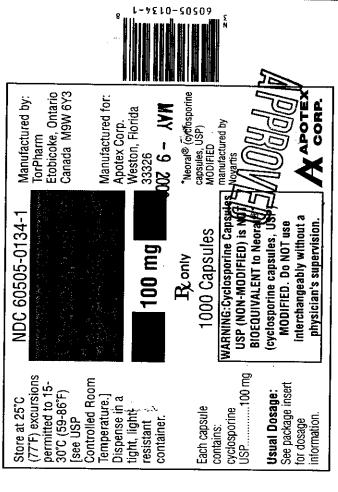
No impairment in fertility was demonstrated in studies in male and female rats.

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 cardinomas 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 letotoxic in rats and rabbits when



CYCLOSPORINE CAPSULES USP 25 mg and 100 mg

 $m I\!\!\!\!/
m e}$ 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 armino 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-M-methyl-L-leucyl-M-methyl-L-valyl-3-hydroxy-N-4-dimethyl-L-2-amino-6-octenoyl-L- α -amino-butyryl-M-methyl-L-leucyl-M-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

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

Each 25 mg capsule contains: cyclosporine USP..... 44-15

..25 ma

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

Each capsule contains the following inactive ingredients: methanot, purified water, sodium lauryl sulfate and tale. 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 #2 aluminum lake, FD&C blue #2 aluminum lake, FD&C blue #3 aluminum lake, pharmaceutical glaze, propylene glycol, SDA-3A alcohol and synthetic black into avide.

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

C₆₂H₁₁₁N₁₁O₁₂

Mol. Wt. 1202.63



Carcinogenesis. Mutagenesis, Impairment of Fertility
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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 retradations. 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.

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 blased 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 geal is not possible to separate the effects of cyclosporine on these pregnancies from the effects of the form immunosuppressants, the underlying maternal disorders, or other aspects of the transplantation militure. Sixteen tetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, pre-eclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rhincompatibity and fetoplacental dystinction. Preferre delivery occurred in 47%. Seven malformations were reported in 5 viable intants and in 2 cases refetal loss. Iwenty-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 negrenal. **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 gurn 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 renat microvasculature, with platelet-fibrin thrombi occluding glomerular capillaries and afterent arterioles, microanglopathic hemolytic anemia, thrombocytopenia, and decreased renal function. Similar findings have been observed when other immunosuppressives have been employed

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 hyperhension, 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,

	Randomized K	(idney Patients	All Cyc	losporine Pa	tients
Body System/ Adverse Reactions	Cyclesperine (N=227) %	Azathioprina (N=228) %	Kidney (N=705) %	Heart (N=112) %	Liver (N=75) %
Genitourinary					
Renal Dystunction Cardiovascular	32	6	25	38	37
Hypertension	26	18	13		
Cramps Skin	4	<1	2	53 <1	27 0
Hirsutism	21	<1	21	22	
Acne Central Nervous System	6	8	2	28 2	45 1
Tremor	12	^	21		
Convulsions	3	, O		31	55
Headache	3 2	≥Ì	1 2	.4	5 4
astrointestinal	-	<u> </u>	2	15	4
Gum Hyperplasia	4	0	•	-	
Diarrhea	3	<1	9 3	5 4	16
Nausea/Vomiting	4 3 2	<1	4	4	8
Hepatotoxicity	<1̄	<u><1</u>	4	10	4
Abdominal Discomfort	રો	ò	<1	7 7	4
utonomic Nervous System	••	U	<1	,	0
Paresthesia	3	0			
Flushing	<Ĭ	ŏ	4	2]
ematopoietic	••	v	4	U	4
Leukopenia	2	19	<1	c	_
Lymphoma	<1̄	ő	1	6 6	0
espiratory	••	•	1	О	1
Sinusitis	<1	0	4	3	,
liscellaneous	••	v	*	ა	7
Gynecomastia	<1	O	<1		3

less of patients: altergic reactions, anemia, anorexta, confusion, conjunctivitis, edema, fever, brittle fingernails, pastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic ulcer, thrombocytopenia, tinnitus.

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.

Renal Transplant Patients in Whom Therapy Was Discontinued

	Randomiza	d Patients	All Cyclosporine		
Reason for Discontinuation	Cyclosporine (N=227) %	Azathlopine (N=228) %	Patients (N=705)		
Renal Toxicity Infection Lack of Efficacy	5.7 0 2.6	0 0.4 0.9	5.4 0.9		

 $\frac{\alpha_{\text{CH}, \text{N}} - \alpha_{\text{CH}, \text{N}}}{\text{methyl-L-eucyl-L-valyl-3-nyoroxy-N, 4-dimethyl-L-2-amino-6-octenoyl-L-}\alpha_{\text{-}}}{\text{methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl}}.$

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

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

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

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

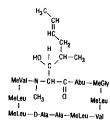
The state of the s

Each capsule contains the following inactive ingredients: methanol, purflied 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 take, FD&C blue #40 aluminum take, pharmaceutical glaze, propylene gyfool, SDA-3A alcohol and synthetic black

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

C62H111N11012

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-seell 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, metastasts) 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 Cycarbon of 2 of the leucine residues. Cn-carbon hydroxylation, and cyclic either formation (with exidation of the double bond) in the side chain of the amino acid 3-hydroxyl-M-4-dimethyl-L-2-amino-6-octenoic acid and M-demethylation of M-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 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

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 differ extentions.

Parameter	Nephrotoxicity ***Rejection	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 postopb Prolonged initial nonfunction (acute tubular necrosis)	Often < 4 weeks postopb Fever > 37.5 °C Weight gain > 0.5 kg
		Graft swelling and tenderness Decrease in daily urine volume > 500 mL (or 50%)
_aboratory	CyA serum trough level > 200 ng/mL	CyA serum trough level

The following reactions occurred in 2% or less of patients: allergic reactions, anemia, anorexia, confusion, conjunctivitis, edema, fever, brittle fingernalis, 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 Gl bleeding, visual disturbance, weakness, weight loss.

Renai Transplant Patients in Whom Therapy Was Discontinued

	Randor	nized f	Patients	All Cyclosporine
Reason for Discontinuation	Cyclosporine (N=227) %		Azathiopine (N=228) %	Patients (N=705) %
Renal Toxicity	5.7		0	5.4
Infection	0		0.4	0.9
Lack of Efficacy	2.6		. 0.9	1.3
Acute Tubular Necrosis	2.6	-	~ *0	1.0
Lymphoma/Lymphoproliferativ Disease	e 0.4		Ō	0.3
Hypertension	0	-	0	0.3
Hematological Abnormalities	Ō		0.4	0.0
Other	Ō	- 4	ŏ	0.7
Accelerate to the state of				

Cyclosporine was discontinued on a temporary basis and then restarted in 18 additional patients. Infectious Complications in the Rendomized Renal Transplant Patients

Complication	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
*Come nationts also serviced 45		

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 emests 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 overdosagne. Cyclosporine is not dialyzable to any great extent, nor is it cleared well by charcoal hemogerfusion. The oral LO₅₀ is 2329 mg/kg in mice, 1480 mg/kg in rats, and > 1000 mg/kg in rabbits. The I.V. LD₅₀ 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 Neorar® (Cyclosporine capsules, USP) MODIFIED. Cyclosporine Capsules USP (NON-MODIFIED) and Neorar® (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 tavoring the lower end of the scale. There is a trend lowards use of even lower initial doses for renal transplantation in the ranges of 10 to 14 mg/kg/dyay. 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 annarent use in rejection rate. 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, docage 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 blopsies. or tissue biopsies.

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

HOW SUPPLIED

Cyclosporine Capsules USP

(See boxed WARNINGs)

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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.

Parameter	Nephrotoxicity vs Rejection 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 postopb Prolonged initial nonfunction (acute tubular necrosis)	Often < 4 weeks postopb Fever > 37.5 °C Weight gain > 0.5 kg
		Graft swelling and tenderness Decrease in dally 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)² Cr piateau < 25% above baseline 8UN/Cr ≥ 20	Rapid rise in Cr {> 0.3 mg/dL/day}a Cr > 25% above baseline BUN/Cr < 20
Biopsy	Arteriolopathy (medial hypertrophys, hyalinosis, nodular deposits, intimal thickening, endothelial vacuolization, progressive scarring)	Endovasculitis ^a (proliferation), intimal arteritis ^b , necrosis, scienosis)
	Tubular atrophy, Isometric vacuolization, Isolated calcifications	Tubulitis with RBCb and WBCb casts, some irregular vacuolization
	Minimal edema	Interstitial edemas and hemorrhageb
	Mild focal infiltrates	Diffuse moderate to severe mononuclear infiltrates
	Diffuse interstitial fibrosis, often striped form	Glomerulitis (mononuclear cells):
Aspiration Cytology	CyA deposits in tubular and endothelial cells Fine Isometric vacuolization of tubular cells	Inflammatory infiltrate with mononuclear phagocytes, macrophages, lymphobiastoid cells, and activated T-cells
		These strongly express HLA- DR antigens
Jrine Cytology	Tubular cells with vacuolization and granularization	Degenerative tubular cells, plasma cells, and lymphocyturia > 20% of sediment
Vianometry	Intracapsular pressure < 40 mm Hgb	Intracapsular pressure > 40 mm Hgb
Jitrasono- Jraphy	Unchanged graft cross sectional area	Increase in graft cross sectional area AP diameter ≥ Transverse
	No. 1	diameter
Magnetic Resonance magery	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
herapy	Responds to decreased cyclosporine	Responds to increased steroids or antilymphocyte globulin

ap < 0.05, bp < 0.01, cp < 0.001, dp < 0.0001

A form of chronic progressive cyclosportne-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. Penal biopsies from these patients will demonstrate an interstital forsis with tubular atrophy. In addition, toxic tubulopathy, peritubular capillary congestion, arteriolopathy, and a striped form of interestital fibrosis with tubular atrophy and penaltic 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 posttransplant months when the dosage tends to be highest and when, in kindery recipients, he 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

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic

novinus	4.8	12.3
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(CYC/C-VA-01-APX-D-K-R02-290102)

HOW SUPPLIED

ine Causules USP

(in capsules with a paie reddish brown opaque body and a pale reddish brown opaque cap, ir "133" and "25" are imprinted on each capsule in black ink; supplied in bottles of 36 (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-ottles of 1000 (NDC 60505-0134-1).

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

DRINE CAPSULES USP

ired by:

Manufactured for: Apotex Corp. Weston, Florida

Ontario ISW 6Y3

anuary 2002

(cyclosperine capsules, USP) MODIFIED manufactured by Novartis



mononuclear infittrates^d Diffuse interstitial fibrosis, often striped form Glomerulitis (mononuclear cells)s Aspiration Cytology CyA deposits in tubular and Inflammatory infiltrate with mononuclear phagocytes, macrophages, lymphoblastoid cells, and endothelial cells Fine isometric vacualization of tubular cells activated T-cells These strongly express HLA-DR antigens Urine Cytology Tubular cells with vacuolization and Degenerative tubular cells, plasma cells, and lymphocyturia > 20% of granularization sediment Manometry Intracapsular pressure Intracapsular paessure > 40 mm Hgb ; < 40 mm Hnb Ultrasono-Unchanged graft cross sectional area Increase in graft cross graphy sectional area AP diameter ≥ Transverse Magnetic Normal appearance Loss of distinct corticomedulary junction, Resonance Imagery swelling, image intensity of parachyma approaching that of psoas, loss of hilar fat Radionuclide Normal or generally decreased Patchy arterial flow perfusion Decrease in perfusion > decrease in tubular function 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 Responds to increased cyclosporine steroids or antilymphocyte globulin

ap < 0.05, bp < 0.01, cp < 0.001, dp < 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 fall 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 interstital forsis with tubular atrophy. In addition, toxic tubulopathy, peritubular capillary congestion, arteriolopathy, and a striped form of intersitial 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 posttransplant months when the dosage tends to be highest and when, in kidney recipients, he 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 therapis. 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

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 patielet 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.

hyperuncernal have been seen deceasionary in internations, produced the seen of the seen of the seen of the seen of the sees of read 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), less 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 filequivalent 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 increasing 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 ADVERISE 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 discretics 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 desage.

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

- CHEMISTRY REVIEW NO. 1 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

- LEGAL BASIS FOR SUBMISSION 4. 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.
- SUPPLEMENT(s) 5. $\overline{N/A}$
- PROPRIETARY NAME 6. APO-MUNE (Cyclosporine Capsules)
- NONPROPRIETARY NAME 7. Cyclosporine Capsules
- SUPPLEMENT(s) PROVIDE(s) FOR: 8. \bar{N}/A
- AMENDMENTS AND OTHER DATES: 9. Firm:

Original Submission: 1/11/99

Additional Information (Certificate of analysis for cap):

1/26/99

Additional Information (DMF number for 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

- 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

12.	RELATED	IND/ND	A/DMF(s	;)

NDA 50-625: Novartis Pharmaceutical Corporation
DMF
DMF
DMF

DMF DMF

- 13. <u>DOSAGE FORM</u> 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

 $[R-\{R^*,R^*-(E)\}] Cyclic (L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L-\alpha-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl)$

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. <u>CHEMISTRY REVIEW NO. 2</u>
- 2. <u>ANDA</u> # 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. <u>LEGAL BASIS FOR SUBMISSION</u>

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. <u>SUPPLEMENT(s)</u> N/A
- 6. <u>PROPRIETARY NAME</u>
 APO-MUNE (Cyclosporine Capsules)
- 7. <u>NONPROPRIETARY NAME</u>
 Cyclosporine Capsules
- 8. <u>SUPPLEMENT(s) PROVIDE(s) FOR:</u> N/A

9. <u>AMENDMENTS AND OTHER DATES:</u>

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)

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13. DOSAGE FORM

Hard Gelatin Capsules

14. <u>POTENCIES</u> 25 mg and 100 mg

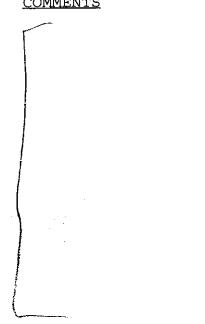
15. CHEMICAL NAME AND STRUCTURE

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

 $\begin{tabular}{ll} $[R-\{R^*,R^*-(E)\}]$ Cyclic (L-alanyl-D-alanyl-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) \end{tabular}$

16. <u>RECORDS AND REPORTS</u> N/A

17. COMMENTS





- 18. <u>CONCLUSIONS AND RECOMMENDATIONS</u>
 Not Approvable, Minor
- 19. <u>REVIEWER:</u> Ruth Ganunis

<u>DATE COMPLETED:</u> August 17, 2000

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ON ORIGINAL

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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. <u>LEGAL BASIS FOR SUBMISSION</u>
 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

- 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

12. RELATED IND/NDA/DMF(s)

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13. <u>DOSAGE FORM</u> Hard Gelatin Capsules

14. POTENCIES
25 mg and 100 mg

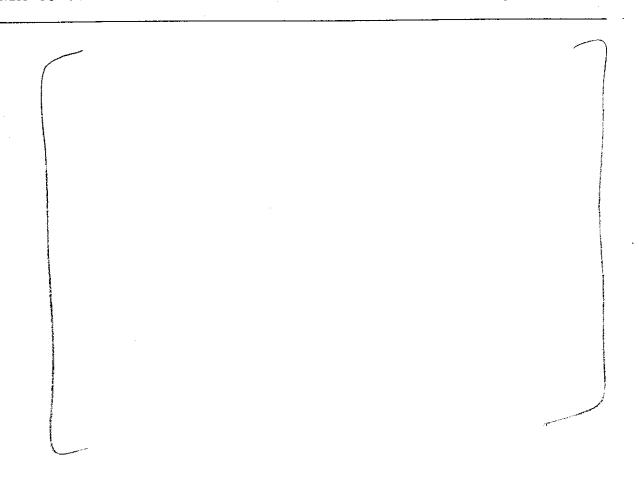
15. CHEMICAL NAME AND STRUCTURE

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

 $[R-\{R^*,R^*-(E)\}] \mbox{Cyclic} (L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L-\alpha-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl)$

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

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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. <u>PROPRIETARY NAME</u>
 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

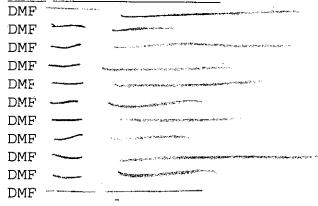
Labeling Review, deficient: 1/26/01

10. PHARMACOLOGICAL CATEGORY

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

11. Rx or OTC

12. RELATED IND/NDA/DMF(s)



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

 $\begin{tabular}{ll} $[R-\{R^*,R^*-(E)\}]$ 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) \end{tabular}$

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

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18. CONCLUSIONS AND RECOMMENDATIONS

Recommended for approval once the labeling and USP monograph issues are resolved.

19. <u>REVIEWER:</u> Ruth Ganunis

DATE COMPLETED:
May 29, 2001

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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 (Cyclosporine Capsules)
- 7. NONPROPRIETARY NAME
 Cyclosporine Capsules
- 8. SUPPLEMENT(s) PROVIDE(s) FOR:
 N/A

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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)

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- 13. <u>DOSAGE FORM</u> Hard Gelatin Capsules
- 14. POTENCIES
 25 mg and 100 mg
- 15. CHEMICAL NAME AND STRUCTURE C₆₂H₁₁₁N₁₁O₁₂ Mol. Wt. 1202.64

 $[R-\{R^*,R^*-(E)\}] Cyclic (L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L-\alpha-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl)$

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ON ORIGINAL

16. RECORDS AND REPORTS N/A

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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)

APPEARS THIS WAY ON ORIGINAL

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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 : TorP	harm, Inc.
DRUG AND DOSAGE FORM	: Cyclosporine Hard Gel	atin Capsule
STRENGTH(S): 25 mg and	l 100 mg	
TYPES OF STUDIES : Fa	asting, non-fasting, and	dissolution
III. A. STUDY FACI	LITIES	
CLINICAL STUDY SITE() Clinical Facility: Principal Investig		
ANALYTICAL SITE(S) Analytical Facilit	y:	
STUDY SUMMARY : Sing mg strength are acce		nfasting studies on the 100
DISCOLUTION . Discol	ution studies are accept	ahle
DISSOLUTION : DISSOI	acton scaarcs are accept	abic.
DISSOLUTION : DISSOI	DSI INSPECTION STA	TUS
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Inspection needed:	DSI INSPECTION STA Inspection status: Inspection requested: (date) Inspection completed:	TUS
Inspection needed: NO First Generic New facility For cause	DSI INSPECTION STA Inspection status: Inspection requested: (date)	TUS
Inspection needed: NO First Generic New facility	DSI INSPECTION STA Inspection status: Inspection requested: (date) Inspection completed:	TUS
Inspection needed: NO First Generic New facility For cause Other	DSI INSPECTION STA Inspection status: Inspection requested: (date) Inspection completed:	TUS
Inspection needed: NO First Generic New facility For cause Other PRIMARY REVITEWED . INITIAL : TEAM LEADER : Vih (INITIAL :	DSI INSPECTION STA Inspection status: Inspection requested: (date) Inspection completed: (date)	Inspection results: BRANCH: I 10/15/99 BRANCH: I 10/15/99

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,

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

HFD-652/ Y. Huanc | 5/24/00

HFD-617/ J. Fan

HFD-650/ D. Conner | 5/25/00

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BIOEQUIVALENCY - ACCEPTABLE

Submission Date:

April 12, 2000

STUDY AMENDMENT (STA) or

Strengths 25 mg and 100 mg

Outcome: NC

Outcome Decision: Acceptable

NOTE:

AC - Acceptable

NC - No Action

UN - Unacceptable

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

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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 \sim (Q) of the labeled amount of cyclosporine in the dosage form is dissolved in 90 minutes.

137º

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

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Concur: (

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 : Tori	Pharm, Inc.
DRUG AND DOSAGE FORM	: Cyclosporine Hard Gel	latin Capsule
STRENGTH(S): 25 mg and	d 100 mg	
TYPES OF STUDIES : F	asting, non-fasting, and	d dissolution
III. A. STUDY FACI	LITIES	
CLINICAL STUDY SITE(Clinical Facility: Principal Investig		
ANALYTICAL SITE(S) Analytical Facilit	y:	
STUDY SUMMARY : Sing	-	nfasting studies on the 100
DISSOLUTION : Dissol	ution studies are accept	table.
	DSI INSPECTION STA	TUS
Inspection needed:	Inspection status:	Inspection results:
First Generic	Inspection requested: (date)	
New facility	Inspection completed:	
For cause	(date)	
Other		
PRIMARY REVIEWER : INITIAL :	James Chaney, Ph.D. — DATE : /	BRANCH : I
TEAM LEADER : Yih C		BRANCH : I
	/\$ / DATE :	<u> </u>

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 \longrightarrow (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,

~ · 18

Dale P. Conner, Pharm. D.

Director

Division of Bioequivalence Office of Generic Drugs

Center for Drug Evaluation and Research

APPEARS THIS WAY

CC: ANDA 65-040

ANDA DUPLICATE DIVISION FILE

FIELD COPY

DRUG FILE

HFD-652/ J. Chaney

HFD-652/ Y. Huang

HFD-617/ E. Hu

HFD-650/ D. Conner

11/23/59

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

BIOEQUIVALENCY - ACCEPTABLE

Submission Date: September 30, 1999

STUDY AMENDMENT (STA) of

Strengths 25 mg and 100 mg

Outcome: AC

Outcome Decision: Acceptable

NOTE:

AC - Acceptable

NC - No Action

UN - Unacceptable

IC - Incomplete

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

APPEARS THIS WAY
ON ORIGINAL

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 TorPharm has requested confirmation from the shown in Table 1. FDA of its agreement with this approach.

RECOMMENDATIONS

- The in vivo bioequivalence studies conducted under fasting 1. 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.
- The dissolution testing used by the firm on its cyclosporine 2. 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 \longrightarrow (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.

James E. Chaney, Ph.D.

Division of Bioequivalence

Review Branch I

RD INITIALED YCHuang

FT INITIALED YCHuang

Concur:

Date: 10/15/49

Date: 11/4/99

Date 11/4/99

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	Te	st Produc	t	Ref	erence Prod	luct
Times	Lo	t # FD803	9		Lot # 22959)
(Min)	Str	ength(mg)	25	St	rength(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	<u></u>	2
60	94		12	98		2
90	97		3	96	,	2
120	95		3	93		2
-	Tt.	roduc بد	t	Reference Product		
	Lo	t # FD804	0	Lot # 23923		
	Stre	ngth(mg)	100	Strength(mg) 100		
10	17	-	66	73		5
20	37	•	51	101	·	2
30	57		48	104		2
4.5	76	Name of the last o	23	103		2
60	87	-	13	101		2
90	95	-	2	98		1
120	94	*	2	96		1



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

. IN ACT 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,

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 of

100 mg capsules:

1000 mL of 0.1N HCl containing of 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, range) than (Cyclosporine Capsules) 100 mg (mean of 12% in 60 min, range). A similar trend was observed for Sandimmune Capsules 25 mg (mean of 40%, range) compared to Capsules 25 mg (mean of 22% dissolved in 60 min, 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 _______, Capsules 100 mg and three capsules from Sandimmune Capsules 100 mg. For 100 mg Sandimmune Capsules was dissolved in 60 min and for 100 mg ______, was dissolved in 60 min.

In conclusion, both ____ 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.

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.

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

RD INITIALED YCHuang
FT INITIALED YCHuang

Concur:
Date: 7/23/99

Date: 7/23/99

Date: 7/23/99

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 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,

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

15/ 7/21/89 HFD-652/ Y. Huang 7/2/ [99] HFD-617/ E. Hu 8/4/99

HFD-650/ D. Conner

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BIOEQUIVALENCY - INCOMPLETE

Submission Date: June 9, 1999

STUDY AMENDMENT (STA) 010

Strengths 25 mg and 100 mg

Outcome: IC

Outcome Decision: Incomplete

NOTE:

AC - Acceptable

UN - Unacceptable

NC - No Action

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:	
Principal Investigator:	· · · · · · · · · · · · · · · · · · ·
Analytical Facility:	

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: ____ 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 _____

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).

APPEARS THIS WAY

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)

			Lev	els (ng/mL)		
TIME	TEST	•		REFERENC	E	T/R
(HRS)	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	<u> </u>	0		•
72	0			0	'	•
1	Pha	rmacokir	etic	Parameter	s	•
PARAMETER	T	EST	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. Statis	tics or	ı Individual	Test/Re	eference Ra	tios and			
Individual AUCT	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

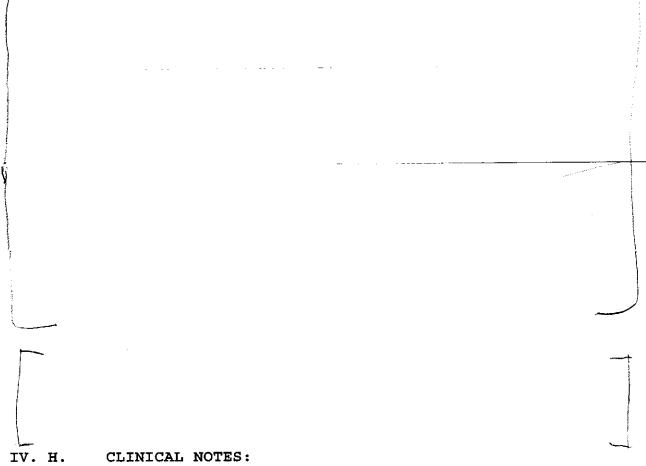
Treatment A: Under fasting conditions, same product (test) and amount as in Part III. D. of review (Fasting Study)

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



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.

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ON ORIGINAL

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)

Cyclosporine Under Fasted/Fed Conditions (N=15) Whole Blood Levels (ng/mL)							
TEST FA						TEST FAST/	TEST FED/
MEAN	%CV	MEAN	%CV	MEAN	%CV	TEST FED	REF FED
0		0		0	-	•	•
0.73	385	0		0			•
56.23	46	0		15.36	258	•	0
223.28	50	0		57.57	230	•	0
379.05	48	7.73	158	87.01	224	49.02	0.09
631.39	33	74.19	126	113.6	233	8.51	0.65
641.53	32	195.95	107	139.59	169	3.27	1.40
599.94	30	290.93	84	182.62	132	2.06	1.59
521.94	27	340.45	57	248.39	103	1.53	1.37
417.01	24	405.73	52	308.89	90	1.03	1.31
329.79	27	454.51	50	345.75	74	0.73	1.31
247.44	35	610.5	36	521.15	50	0.41	1.17
177.89	43	530.26	40	478.06	53	0.34	1.11
114.83	40	271.79	39	359.95	48	0.42	0.76
80.79	41	174.55	36	265.17	44	0.46	0.66
57.77	40	118.25	32	185.38	60	0.49	0.64
34.45	40	65.9	36	87.81	50	0.52	0.75
17.02	56	31.95	42	43.7	50	0.53	0.73
6.86	114	16.66	57	22.41	47	0.41	0.74
2.94	213	10.4	70	13.41	76	0.28	0.78
1.23	386	6.76	115	9.99	83	0.18	0.68
0.87	386	2.62	209	3.82	179	0.33	0.69
0.98	388	0.69	390	0		1.41	•
0.89	385	0		0			
,•]						
		i				TEST FAST/	1
MEAN	%CV	MEAN	%CV	MEAN	%CV		REF FED
3501.93	36	4631.13	28			0.76	0.91
3312.2	33	4454.27	29	4935.27	27	0.74	0.90
714.48	27	675.96	31	717.49	25	1.06	0.94
9.23	107	8.87	28	8.82	29	1.04	1.00
1.87	24	4.43	28	5.2	50	0.42	0.85
	TEST FA MEAN 0 0.73 56.23 223.28 379.05 631.39 641.53 599.94 521.94 417.01 329.79 247.44 177.89 114.83 80.79 57.77 34.45 17.02 6.86 2.94 1.23 0.87 0.98 0.89 TEST FA MEAN 3501.93 3312.2 714.48 9.23	TEST FAST MEAN %CV 0 0.73 385 56.23 46 223.28 50 379.05 48 631.39 33 641.53 32 599.94 30 521.94 27 417.01 24 329.79 27 247.44 35 177.89 43 114.83 40 80.79 41 57.77 40 34.45 40 17.02 56 6.86 114 2.94 213 1.23 386 0.87 386 0.87 386 0.89 385 TEST FAST MEAN %CV 3501.93 36 3312.2 33 714.48 27 9.23 107	Whole B1 TEST FAST TEST F MEAN %CV MEAN 0 0 0.73 385 0 56.23 46 0 223.28 50 0 379.05 48 7.73 631.39 33 74.19 641.53 32 195.95 599.94 30 290.93 521.94 27 340.45 417.01 24 405.73 329.79 27 454.51 247.44 35 610.5 177.89 43 530.26 114.83 40 271.79 80.79 41 174.55 57.77 40 118.25 34.45 40 65.9 17.02 56 31.95 6.86 114 16.66 2.94 213 10.4 1.23 386 6.76 0.87 388	Whole Blood TEST FAST TEST FED MEAN %CV MEAN %CV 0 0 0.73 385 0 56.23 46 0 379.05 48 7.73 158 631.39 33 74.19 126 641.53 32 195.95 107 599.94 30 290.93 84 521.94 27 340.45 57 417.01 24 405.73 52 329.79 27 454.51 50 247.44 35 610.5 36 177.89 43 530.26 40 114.83 40 271.79 39 80.79 41 174.55 36 57.77 40 118.25 32 34.45 40 65.9 36 17.02 56 31.95 42	Whole Blood Levels TEST FAST TEST FED REF MEAN %CV MEAN %CV MEAN 0 0 0 56.23 46 0 57.57 379.05 48 7.73 158 87.01 631.39 33 74.19 126 113.6 641.53 32 195.95 107 139.59 599.94 30 290.93 84 182.62 521.94 27 340.45 57 248.39 417.01 24 405.73 52 308.89 329.79 27 454.51 50 345.75 247.44 35 610.5 36 521.15 177.89 43 530.26 40 478.06 114.83 40 271.79 39 359.95 80.79 41 174.55 36 265.17 57.77 40 118.25	## Whole Blood Levels (ng/mL) TEST FAST	Whole Blood Levels (ng/mL) TEST FAST TEST FED REF FED TEST FAST/TEST FED 0 0 0 0.73 385 0 0 56.23 46 0 57.57 230 223.28 50 0 57.57 230 379.05 48 7.73 158 87.01 224 49.02 631.39 33 74.19 126 113.6 233 8.51 641.53 32 195.95 107 139.59 169 3.27 599.94 30 290.93 84 182.62 132 2.06 521.94 27 340.45 57 248.39 103 1.53 417.01 24 405.73 52 308.89 90 1.03 329.79 27 454.51 50 345.75 74 0.73 247.49

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.

APPEARS THIS WAY ON ORIGINAL

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	Te	est Produc	t	Refe	erence Prod	uct	
Times	Lot # FD8039			1	Lot # 22959		
(Min)	Str	ength(mg)	25	St	rength(mg)	25	
	Mean %	Range	%CV	Mean %	Range	%CV	
10	14	1	98	93		8	
20	39	Name - Company -	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	
	Te	est Produc	t	Reference Product			
	Lo	ot # FD804	0	Lot # 23923			
	Stre	ength(mg)	100	Str	ength(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.

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

100 mg capsules:

1000 mL of 0.1N HCl containing

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.

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.

James E. Chaney, Division of Bioequivalence Review Branch I

RD INITIALED YCHuang FT INITIALED YCHuang $_$ Date: $\frac{3}{12}/99$

Concur:

1

Dale P. Conner, Pharm.D.

Director, Division of Bioequivalence

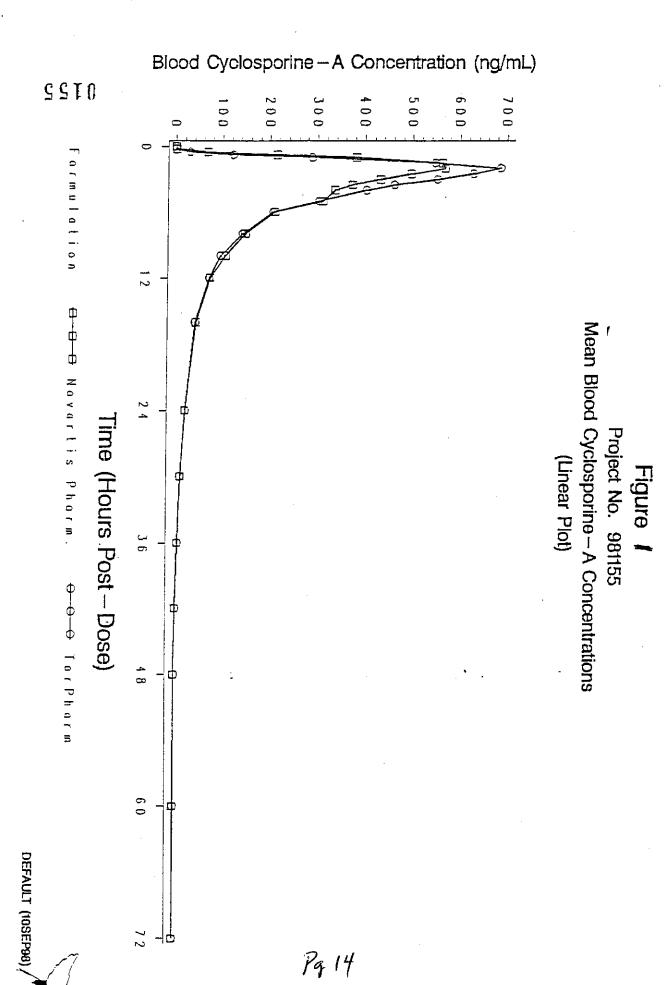
JEC/031199

CC:	ANDA 65-040		·	
	ANDA DUPLICATE			
	DIVISION FILE			
	FIELD COPY DRUG FILE			
	I 0%			
	HFD-652/ J. Chaney / 12/99			
	HFD-652/ Y. Huang HFD-617/ E. Hu \$\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\			
	HFD-650/ D. Conner			
	S S S S S S S S S S S S S S S S S S S			
V:∖F	IRMSNZ\TORPHARM\LTRS&REV\65040)sdw.199		
•				প
BIOE	QUIVALENCY - ACCEPTABLE Su	ubmission Date:	January 1	1, 1998
				1
				100
1.	FASTING STUDY (STF)		trength:	IOO Mg IC
	Clinical:		utcome:	IC
	Analytical:	<u> </u>		
	mary crear.	4		
2.	FOOD STUDY (STP)		Strength:	100 mg
	Clinical:		Outcome:	IC
	Analytical: ————			
_			0+	25
6.	WAIVER (WAI)		Strength: Outcome:	Z5 Mg IC
			Outcome:	10
·Out c	come Decision: Incomplete			
Outco	:	• .	•	
NOTE				
	· Acceptable	UN - Unaccept	able	
	· No Action	IC - Incomple		
-		-		

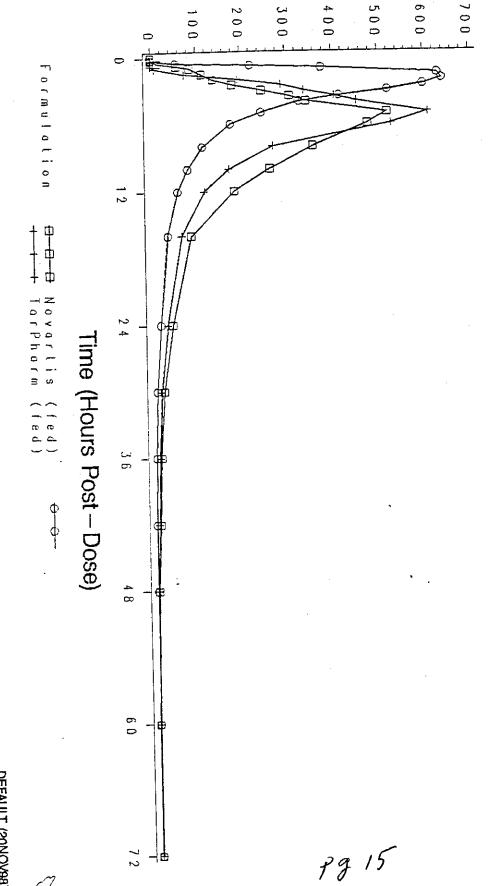
•

WinBio Comments: Incomplete, pending acceptable dissolution data

APPEARS THIS WAY ON ORIGINAL



IEGI Whole Blood Cyclosporine Concentration (ng/mL)



Mean Whole Blood Cyclosporine Concentrations Project No. 981180 (Linear Plot)

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 _____ 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,

/\$/

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,

Tst

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

COVER LETTER

ORIG ASSENDMENT N/A/M

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
Supervisor, Regulatory Affairs

<u>November 8, 2001</u> Date

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



Tor Pharm Inc.

ONG ANENDMENT N/AM

COVER LETTER

TELEPHONE AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W r6Y3, 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.

Leanne Chinn

Supervisor, Regulatory Affairs

. Apr. 10/02

RECEIVED

APR 1 1 2002

OGD / CDER

TORPHARM

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

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secret and /or

confidential

commercial

information

October 6, 2000

Office of Generic Drugs CDER, FDA MPN II, HFD-600 7500 Standish Place Rockville, MD 20855 ONG AMENDMENT N/FA

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

Associate Director Regulatory Affairs Ext. 223





Tor Pharm

NDA ORIG AMENDMENT

MAP

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.

Comer Barrer

Esther Barber Manager, Regulatory Compliance . 9 Janos

Date



TORPHARM

Amendment to ANDA 65-040 Cyclosporine Capsules

25 mg and 100 mg



Tor Pharm

NIAM

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

Manager, Regulatory Compliance

MAY 0 4 2001

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TORPHARM

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



ORIG AMENDMENT

LABELING AMENDMENT

TorPharm, 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 65-040 for Cyclosporine Capsules 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. 2. Draft labeling has been generated for the proposed proprietary name No labeling for 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 " ____ be substituted with " as an alternate naming option for the product. Manager, Regulatory Compliance



TORPHARM

Amendment to ANDA #65-040 Cyclosporine Capsules -

25 mg and 100 mg

NO.157





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 Disso	olution 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

APPEARS THIS WAY ON ORIGINAL

Port 1 of 2 (15 pages)



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, http://www.fda.gov/cder/ogd/rld/labeling review branch, http://www.fda.gov/cder/ogd/rld/labeling review branch, http://www.fda.gov/cder/ogd/rld/labeling review branch, http://www.fda.gov/cder/ogd/rld/labeling review

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.

J\$/ ..

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

February 14, 2000

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

Noted:

Bio already reviewed the identical information includes in bio portion of thes ne spense as part of ravious of a separate bio Submission dated

MAJOR AMENDMENT

7/30/99. Sea

Volume 1.

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, 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,

Mercy macdonald

Marcy Macdonald Associate Director Regulatory Affairs Ext. 223





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

-(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 Associate Director Regulatory Affairs

Marcy Macdonald

Ext. 223

REC'D
JUN 1 4 1999
OGD
THE OWN AND RESERVED

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

(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

Mary Macdonald

Associate Director

Regulatory Affairs

Ext. 223

RECEIVED

FEB 1 8 1999,

GENERIC DRUGS

ANDA 64-040

APPEARS THIS WAY ON ORIGINAL

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

FEB 1 6 1999

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal (Cyclosporine Capsules, USP), does not of the company of the compa Food, Drug and Cosmetic Act.

NAME OF DRUG:

25 mg and 100 mg

January 11, 1999 DATE OF APPLICATION:

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,

APPEARS THIS WAY ON ORIGINAL

RODert L. West, M.S. R.Ph.

Division of Labeling and Program Support

Office of Generic | prugs

Center for Drug Etaluation and Research



labeling review 3/29/99
Suffer 3/29/99

January 11, 1999

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

GEMESTERS (1976)

Mary Macdenald

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.

#FD8040 (100 mg) used for stability and bio-studies and exhibit batch #FD8039 (25 mg) used for stability studies were manufactured with ______ from _____ from _____ 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 - (MANUFACTUR.	ING PROCESS THE SAME AS
BIO/STABILITY?): The size of the propos	sed production batch is
From that . 25 mg capsu	ules (
and 100 mg capsui	les (
will be produced. The many	ufacturing process
described in the master production record	rd is the same as that
described in the exhibit batch record.	
CHEMIST: Ruth Ganunis	DATE: 11/29/01; 3/14/02
SUPERVISOR: Richard Adams	DATE: 11/29/01
/S//~	3/14/02

APPEARS THIS WAY
ON ORIGINAL

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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 Co	omments
a.	Your proposed proprietary names, [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	
2. Container:	25 mg and 100 mg (30s and 1000s)
Delete	following "Cyclosporine Capsules".
3. Insert:	
	following "Cyclosporine Capsules" in the TITLE, DESCRIPTION, ATIONS AND USAGE and HOW SUPPLIED sections.
labels and lab	your container labels and insert labeling, as instructed above, and submit draft eling. We will not request final print, pending the review of OPDRA regarding your prietary name and issues regarding the established name of your drug product.
changes for th website for an	val, it may be necessary to further revise your labeling subsequent to approved be reference listed drug. We suggest that you routinely monitor the following y approved changes-

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.

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 N	Number:	65-040	
Date of	Submiss	sion: February 14, 2000	
Applica	nt's Nam	e: Torpharm	
	shed Nan g Deficie		APPEARS THIS WAY
	.		
1.	GENER	AL COMMENTS	
	a.	Use uppercase print for on you insert labeling.	r container labels and
	b	Following your proposed proprietary name " add the te on your container labels and insert labeling. In addition, to follows:	revise to read as
2.	CONTA	AINER 25 mg and 100 mg (30s and 1000s)	
	a.	Print the "WARNING: supervision" statement in red print and en bordered box.	iclose it in a black
	b.	Relocate the boxed warning statement to appear on the front panel	l.
3.	INSER	Τ '	
	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 Capsules / "" to read "	g revise "Cyclosporine
	C.	Italizize the first "N" in the chemical name.	
	d.	CONTRAINDICATIONS	
		Cyclosporine capsules are contraindicated in patients with a hypercyclosporine or to any of the ingredients of the formulation.	rsensitivity to
	e.	WARNINGS	
		Fifteenth paragraph	

09/30/99

16:01

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

TorPharm

OFFIG AMENDMENT

To:	Mark Ande	rson	From:	Esther Barber	<u> </u>
Fax:	1-301-443-	3839	Pages:	17	
Phone:	1-301-827-	5849	Date:	30/09/99	
Re:	ANDA 65	040	CC:	N/A	
□ Urge	ent ØF	or Review	☐ Please Comment	☐ Please Reply	☐ Please Recycle
• Com	ments:				
Attache may ne	ed are the queed to refer t	uestions we d o. Again, som	Iscussed last week. I hay for the delay and I hope	ve included all of the to hear from you soon	e attachments that you n.
Please	feel free to	call me if you h	nave any further questions	١	

Regards,

Esther Barrer

Esther Barber

APPEARS THIS WAY ON ORIGINAL



