DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-573/S-030
NDA 50-574/S-039
NDA 50-625/S-043

Novartis Pharmaceuticals Corporation
Attention: Inna Kissen, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Kissen:

Please refer to your supplemental new drug applications, which were submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA #	Drug Product	Supplement Number	Letter Date	Receipt Date
50-573	Sandimmune® Injection, (cyclosporine injection), 50 mg/mL	S-030	January 18, 2005	January 19, 2005
50-574	Sandimmune® Oral Solution (cyclosporine oral solution), 100 mg/mL	S-039	January 18, 2005	January 19, 2005
50-625	Sandimmune® Soft Gelatin Capsules (cyclosporine capsules), 25 mg,100 mg	S-043	January 18, 2005	January 19, 2005

We acknowledge the receipt of your submissions dated: June 9, June 27, and July 15, 2005.

These supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined and deletions are ~~strikethrough~~):

1. "Prescribing Information" was added to the beginning of the label immediately following "**Rx only**".

2. WARNINGS

The following revisions were made to this section:

> Another rare manifestation of cyclosporine-induced neurotoxicity is optic disc edema including papilloedema, with possible visual impairment, secondary to benign intracranial hypertension.

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

"Cyclosporine" was added to the following paragraph to read:

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

3. PRECAUTIONS

The following drugs were added to the list of ***Drugs That May Potentiate Renal Dysfunction:***

Antibiotics	*Antineoplastic*	*Anti-Inflammatory Drugs*	*Gastrointestinal Agents*
ciprofloxacin	melphalan	azapropazon	cimetidine
gentamicin		colchicine	ranitidine
tobramycin	*Antifungals*	diclofenac	
vancomycin	amphotericin B	naproxen	*Immunosuppressives*
trimethoprim with sulfamethoxazole	ketoconazole	sulindac	tacrolimus
			Other Drugs
			fibric acid derivatives (e.g. bezafibrate, fenofibrate)

The following drugs were added to the list of ***Drugs That Increase Cyclosporine Concentrations****:*

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

The following drugs were added to the list of ***Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations:***

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

The following information was added to ***Other Drug Interactions:***

Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur. Caution is also required when cyclosporine is co-administered with potassium sparing drugs (e.g. angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists), potassium containing drugs as well as in patients on a potassium rich diet. Control of potassium levels in these situations is advisable.

Elevations in serum creatinine were observed in studies using sirolimus in combination with full-dose cyclosporine. This effect is often reversible with cyclosporine dose reduction. Simultaneous co-administration of cyclosporine significantly increases blood levels of sirolimus. To minimize increases in sirolimus blood concentrations, it is recommended that sirolimus be given 4 hours after cyclosporine administration.

We have completed the review of these supplemental applications as amended, and have concluded that adequate information has been presented to demonstrate that these drug products are safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted July 15, 2005).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "**FPL for approved supplement NDA 50-573/S-030, 50-574/S-039, and 50-625/S-043.**" Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Dr. Brenda Marques, Project Manager at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

7/19/05 04:44:49 PM