DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-715/S-022
NDA 50-716/S-024

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
50-715	Neoral ® Soft Gelatin Capsules (cyclosporine injection) Modified, 25 and 100 mg	S-022	January 18, 2005	January 19, 2005
50-716	Neoral ® Oral Solution (cyclosporine oral solution) Modified, 100 mg/mL	S-024	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 <u>double underlined</u>):

1. WARNINGS

The following sentence was added to the Kidney, Liver and Heart Transplant subsection:

> <u>Another rare manifestation of cyclosporine-induced neurotoxicity, occurring in transplant patients more frequently than in other indications, is optic disc edema including papilloedema, with possible visual impairment, secondary to benign intracranial hypertension.</u>

2. PRECAUTIONS

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

Antibiotics
ciprofloxacin
gentamicin
tobramycin
vancomycin
trimethoprim with sulfamethoxazole

Antineoplastics
melphalan

Antifungals
amphotericin B
Ketoconazole

Anti-inflammatory Drugs
azapropazon
colchicine
diclofenac
naproxen
sulindac

Gastrointestinal Agents
cimetidine
ranitidine

Immunosuppressives
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
diltiazem
nicardipine
verapamil

Antifungals
fluconazole
itraconazole
ketoconazole

Antibiotics
azithromycin
clarithromycin
erythromycin
quinupristin/ dalfopristin

Glucocorticoids
methylprednisolone

Other Drugs
allopurinol
amiodarone
bromocriptine
colchicine
danazol
imatinib
metoclopramide
oral contraceptives

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

Antibiotics
nafcillin
rifampin

Anticonvulsants
carbamazepine
phenobarbital
phenytoin
ticlopidine

Other Drugs/Dietary Supplements
octreotide
orlistat
sulfinpyrazone
terbinafine
St. John's Wort

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 the 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 50-715/S-022 and NDA 50-716/S-024**." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about these drug products (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 these NDAs 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

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