DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-573/S-021 and S-023
NDA 50-574/S-027 and S-029
NDA 50-625/S-030 and S-032

Novartis Pharmaceuticals Corporation
Attention: Ronald G. Van Valen
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

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

NDA #	Drug Product	Supplement number	Letter Date	Receipt Date
50-573	Sandimmune® Intravenous (cyclosporine injection) 50 mg/mL	S-021	December 5, 2000	December 13, 2000
		S-023	July 18, 2001	July 19, 2001
50-574	Sandimmune® Oral Solution (cyclosporine oral solution) 100 mg/mL	S-027	December 5, 2000	December 13, 2000
		S-029	July 18, 2001	July 19, 2001
50-625	Sandimmune® Soft Gelatin Capsules (cyclosporine) 25, 50, and 100 mg	S-030	December 5, 2000	December 6, 2000
		S-032	July 18, 2001	July 19, 2001

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to the package insert (additions are underlined and deletions are struck out):

- The **PRECAUTIONS** subsection on drugs that exhibit nephrotoxic synergy was renamed, "*Drugs That May Potentiate Renal Dysfunction*." The following drugs were added to the list of nonsteroidal anti-inflammatory drugs: naproxen, sulindac, and colchicine. The following sentence was taken out of this section:

  ~~Careful monitoring of renal function should be practiced when Sandimmune® (cyclosporine) is used with nephrotoxic drugs.~~

- The **PRECAUTIONS:** ***Drugs That Alter Cyclosporine Concentrations*** subsection was revised:

Compounds that decrease cyclosporine absorption such as orlistat should be avoided. 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~~ 3A. Substances that inhibit this enzyme could decrease metabolism and increase cyclosporine ~~levels~~ concentrations. Substances that are inducers of cytochrome P-450 activity ~~will~~ could increase ~~hepatic~~ metabolism and decrease cyclosporine ~~levels~~ concentrations. Monitoring of circulating cyclosporine ~~levels~~ concentrations and appropriate Sandimmune® ~~(cyclosporine)~~ dosage adjustment are essential when these drugs are used concomitantly.

- In **PRECAUTIONS**, quinupristin and dalfopristin were added to the list of antibiotics under *Drugs That Increase Cyclosporine Concentrations*, while colchicine and amiodarone were added to the list of other drugs. Below this table, the following three sentences were added:

  The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 3A and thus could potentially increase the concentrations of cyclosporine, however no formal studies of the interaction are available. Care should be exercised when these drugs are administered concomitantly.

  Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine, thus should be avoided.

- In **PRECAUTIONS**, the dietary supplement St. John's Wort and orlistat were added to the table for *Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations*. Below this table, the following five sentences were added:

  There have been reports of a serious drug interaction between cyclosporine and the herbal dietary supplement, St. John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss.

  Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these two drugs are administered concomitantly.

- A new subsection was added to **PRECAUTIONS**, "***Nonsteroidal Anti-inflammatory Drug (NSAID) Interactions***" containing the following language:

  Clinical status and serum creatinine should be closely monitored when cyclosporine is used with nonsteroidal anti-inflammatory agents in rheumatoid arthritis patients. *(See WARNINGS)*

  Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function, as determined by ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) and (*p*-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood levels of cyclosporine, it has been associated with approximate doubling of diclofenac blood levels and occasional reports of reversible

decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

- A new subsection was added to **PRECAUTIONS**, "***Methotrexate Interaction***" containing the following language:

  Preliminary data indicate that when methotrexate and cyclosporine were co-administered to rheumatoid arthritis patients (N=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine concentrations do not appear to have been altered (N=6).

- The following changes were made to the **PRECAUTIONS:** ***Other Drug Interactions*** subsection:

  ~~Further information on drugs that have been reported to interact with Sandimmune® (cyclosporine) is available from Novartis Pharmaceuticals Corporation.~~

  Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive concurrent cyclosporine because of the possibility of excessive immunosuppression.

  For additional information on Cyclosporine Drug Interactions please contact Novartis Medical Affairs Department at 888-NOW NOVA (888-669-6682).

- The following changes were made to the **HOW SUPPLIED** section to indicate that the 50-mg capsule will no longer be manufactured and the storage information was revised:

  ~~***50 mg:*** Oblong, corn-yellow, branded "Δ S 78/242". Unit dose packages of 30 capsules, 3 blister cards of 10 capsules (NDC 0078-0242-15).~~

  ***Store and Dispense*:** ~~In the original unit dose container at temperatures below 86°F (30°C).~~ Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature] An odor may be detected upon opening the unit dose container, which will dissipate shortly thereafter. This odor does not affect the quality of the product.

We have completed the review of these applications 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 final printed labeling submitted on July 18, 2001. Accordingly, these supplemental new drug applications are approved effective on the date of this letter.

If a letter communicating important information about these drugs products (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to each 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, please call Matthew A. Bacho, Regulatory 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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