DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-573/S-027, S-028
NDA 50-574/S-035, S-037
NDA 50-625/S-039, S-040

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

Dear Mr. Van Valen:

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® (cyclosporine injection) Injection, 50 mg/mL	S-027	July 31, 2003	August 6, 2003
		S-028	January 23, 2004	February 2, 2004
50-574	Sandimmune® (cyclosporine oral solution) Oral Solution, 100 mg/mL	S-035	July 31, 2003	August 6, 2003
		S-037	January 23, 2004	February 2, 2004
50-625	Sandimmune® (cyclosporine soft gelatin capsules) Soft Gelatin Capsules, 25 mg, 50 mg, 100 mg	S-039	July 31, 2003	August 6, 2003
		S-040	January 23, 2004	February 2, 2004

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

1. In the **PRECAUTIONS** section, ***Other Drug Interactions*** subsection, the following changes were made:

   Other Drug Interactions: ~~Reduced clearance of prednisolone, digoxin, and lovastatin has been observed when these drugs are administered with cyclosporine. In addition, a decrease in the apparent volume of distribution of digoxin has been reported after cyclosporine administration. Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin.~~

Cyclosporine may reduce the clearance of digoxin, colchicine**,** prednisolone and HMG-CoA reductase inhibitors (statins). Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin. There are also reports on the potential of cyclosporine to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. If digoxin or colchicine are used concurrently with cyclosporine, close clinical observation is required in order to enable early detection of toxic manifestations of digoxin or colchicine, followed by reduction of dosage or its withdrawal.
Literature and postmarketing cases of myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely, fluvastatin. When concurrently administered with cyclosporine, the dosage of these statins should be reduced according to label recommendations. Statin therapy need to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis.

Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur.

During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided. ~~Myositis has occurred with concomitant lovastatin,~~ ~~frequent~~ Frequent gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone have been reported.

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).

2. In the **PRECAUTIONS** section, the **Geriatric Use** subsection, was added in accordance with the August 27, 1997 final rule and 21 CFR 201.57(f)(10):

Geriatric Use
Clinical studies of Sandimmune did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

We have completed the review of these supplemental applications, 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 January 23, 2004).

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-027 and S-028, 50-574/S-035 and S-037, and 50-625/S-039 and S-040.**" 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 Christine Lincoln, RN, MS, MBA, Labeling Reviewer, 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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