DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-573/S-031
NDA 50-574/S-040
NDA 50-625/S-044

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, USP) 50 mg/mL	S-031	September 7, 2005	September 8, 2005
50-574	SANDIMMUNE® Oral Solution (cyclosporine oral solution, USP) 100 mg/mL	S-040	September 7, 2005	September 8, 2005
50-625	SANDIMMUNE® Soft Gelatin Capsules (cyclosporine capsules, USP) 25 mg, 50mg, 100 mg	S-044	September 7, 2005	September 8, 2005

These supplemental new drug applications provide for the following revisions to the **PRECAUTIONS** section of the package insert (additions are double underlined and ~~Strikeout~~ are deleted text):

1. The following information was added to the end of the second paragraph of the **Carcinogenisis, Mutagenesis, and Impairment of Fertility** subsection:

   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. In two published research studies,

   rabbits exposed to cyclosporine *in utero* (10 mg/kg/day subcutaneously) demonstrated reduced numbers of nephrons, renal hypertrophy, systemic hypertension and progressive renal

insufficiency up to 35 weeks of age. Pregnant rats which received 12 mg/kg/day of cyclosporine intravenously (twice the recommended human intravenous dose) had fetuses with an increase incidence of ventricular septal defect. These findings have not been demonstrated in other species and their relevance for humans is unknown.

2. The following changes were made to the **Pregnancy:** ***Pregnancy Category C*** subsection:

Animal studies have shown reproductive toxicity in rats and rabbits. Cyclosporine gave no evidene of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally). Sandimmune® Oral Solution (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), Sandimmune® Oral Solution (cyclosporine oral solution, USP) was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. In the well-tolerated dose range (rats at up to 17 mg/kg/day and rabbits at up to 30 mg/kg/day), Sandimmune® Oral Solution (cyclosporine oral solution, USP) proved to be without any embryolethal or teratogenic effects.

There are no adequate and well-controlled studies in pregnant women and, therefore,~~.~~ Sandimmune® (cyclosporine) should not be used during pregnancy unless ~~only if~~ the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant transplant recipients who are being treated with immunosuppressants the risk of premature births is increased. The following data represent the reported outcomes of 116 pregnancies in women receiving Sandimmune® (cyclosporine) during pregnancy, 90% of whom were transplant patients, and most of whom received Sandimmune® (cyclosporine) throughout the entire gestational period. Since most of the patients were not prospectively identified, the results are likely to be biased 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 age. It is not possible to separate the effects of Sandimmune® (cyclosporine) on these pregnancies from the effects of the other immunosuppressants, the underlying maternal disorders, or other aspects of the transplantation milieu. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, preeclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility and fetoplacental dysfunction. Preterm delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-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 normal. More information on cyclosporine use in pregnancy is available from Novartis Pharmaceuticals Corporation.

A limited number of observations in children exposed to cyclosporine *in utero* is available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal.

3. The following changes were made to the **Nursing Mothers** subsection:

   Cyclosporine passes into breast milk. Mothers receiving treatment with Sandimmune® (cyclosporine) should not breast feed. ~~Since Sandimmune® (cyclosporine) is excreted in human milk, nursing should be avoided.~~

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 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 September 7, 2005).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in ElectronicFormat – Content of Labeling* (February 2004). The guidances specify that labeling is to be submitted in PDF format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated "**FPL for approved supplement NDA 50-573/S-031, NDA 50-574/S-040 and NDA 50-625/S-044**." Approval of these submissions 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
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 Christine Lincoln, RN, MS, MBA, Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Drug Products
Office of Antimicrobial Products
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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