DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-715/S-024
NDA 50-716/S-025

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 capsules, USP) MODIFIED, 25 and 100 mg	S-024	September 7, 2005	September 8, 2005
50-716	Neoral® Oral Solution (cyclosporine oral Solution, USP) MODIFIED, 100 mg/mL	S-025	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 <u>double underlined</u> 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:

   Cyclosporine was not mutagenic in appropriate test systems. Cyclosporine has not been found to be 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.<u> 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</u>

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 evidence 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). ~~Cyclosporine was not teratogenic in appropriate test systems.~~ Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. Cyclosporine has been shown to be embryo- and fetotoxic in rats and rabbits following oral administration at maternally toxic doses. Fetal toxicity was noted in rats at 0.8 and rabbits at 5.4 times the transplant doses in humans of 6.0 mg/kg, where dose corrections are based on body surface area. Cyclosporine was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardation.

There are no adequate and well-controlled studies in pregnant women~~.~~ and, therefore, Neoral® 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 cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, pre-eclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility, and fetoplacental dysfunction. Pre-term 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%. Therefore, the risks and benefits of using Neoral® during pregnancy should be carefully weighed.

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.

Because of the possible disruption of maternal-fetal interaction, the risk/benefit ratio of using Neoral® in psoriasis patients during pregnancy should carefully be weighed with serious consideration for discontinuation of Neoral®.

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

Cyclosporine passes into breast milk. Mothers receiving treatment with Neoral should not breast feed. ~~Since cyclosporine is excreted in human milk, breast-feeding 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 50-715/S-024 and NDA 50-716/S-025**." 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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