



NDA 50-715/S-010, S-014
NDA 50-716/S-014, S-018

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

Dear Mr. Van Valen:

Please refer to your supplemental new drug applications dated December 5, 2000 and December 21, 2001, received December 6, 2000 and December 26, 2001, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neoral[®] Soft Gelatin Capsules (cyclosporine capsules, USP) MODIFIED, 25 mg, 100 mg.

Please refer to your supplemental new drug applications dated December 6, 2000 and December 21, 2001, received December 13, 2000 and December 26, 2001, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neoral[®] Oral Solution (cyclosporine oral solution, USP) MODIFIED, 100 mg/mL.

We acknowledge receipt of your submissions dated March 30, 2001 and May 23, 2002.

These supplemental new drug applications provide for the following changes to the Neoral[®] label. Added text is noted by double underline and deleted text is noted by ~~strikethrough~~:

1. CLINICAL PHARMACOLOGY

- In the **Pharmacokinetics** subsection, the second paragraph was revised to read:

The Neoral[®] Soft Gelatin Capsules (cyclosporine capsules, USP) MODIFIED and Neoral[®] Oral Solution (cyclosporine oral solution, USP) MODIFIED are bioequivalent. Neoral[®] Oral Solution diluted with orange juice or with apple juice is bioequivalent to Neoral Oral Solution diluted with water. The effect of milk on the bioavailability of cyclosporine when administered as Neoral Oral Solution has not been evaluated.

2. PRECAUTIONS

- In the **Drug Interactions, Drugs That May Potentiate Renal Dysfunction** subsection colchicine was added to the list of Anti-inflammatory Drugs.

- The **Drug Interactions, Drugs That Alter Cyclosporine Concentrations** subsection was revised to read:

Compounds that decrease cyclosporine absorption such as orlistat should be avoided. Cyclosporine is extensively metabolized ~~Cyclosporine concentrations may be influenced by drugs that affect microsomal enzymes, particularly cytochrome P-450 III-A 3A.~~ Substances that inhibit this enzyme could decrease metabolism and increase cyclosporine concentrations. Substances that are inducers of cytochrome P-450 activity could increase metabolism and decrease cyclosporine concentrations. Monitoring of circulating cyclosporine concentrations and appropriate Neoral[®] dosage adjustment are essential when these drugs are used concomitantly. (*See Blood Concentration Monitoring*)

- In the **Drug Interactions, Drugs That Increase Cyclosporine Concentrations** subsection, ketoconazole was added to the list of Calcium Channel Blockers, quinupristin/daldopristin was added to the list of Antifungals, and colchicine and amiodarone were added to the list of Other Drugs. The first paragraph in this section was revised to read:

The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 ~~III-A 3A~~ and thus could potentially increase the concentrations of drugs metabolized by the cytochrome P-450 system. ~~The interaction between HIV protease inhibitors and cyclosporine has not been studied.~~ cyclosporine, however no formal studies of the interaction are available. Care should be exercised when these drugs are administered concomitantly.

- The **Drugs That Decrease Cyclosporine Concentrations** subsection was re-named "**Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations**". Orlistat and St. John's Wort were added to the list of Other Drugs. The following sentence was added to read:

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.

- The following sentence was added to the end of the **Drug Interactions** subsection to read:

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

3. DOSAGE AND ADMINISTRATION

- In the **Psoriasis** subsection, the third sentence in the third paragraph was revised to read:

Results of a dose-titration clinical trial with Neoral[®] indicate that an improvement of psoriasis by 75% or more (based on PASI) was achieved in 51% of the patients after 8 weeks and in 79% of the patients after ~~12~~16 weeks.

- In the **Neoral[®] Oral Solution (cyclosporine oral solution, USP) MODIFIED–Recommendations for Administration** subsection, the first paragraph was revised to read:

To make Neoral[®] Oral Solution (cyclosporine oral solution, USP) MODIFIED more palatable, it should be diluted preferably with orange or apple juice that is at room temperature. Patients should avoid switching diluents frequently. Grapefruit juice affects metabolism of cyclosporine and should be avoided. The combination of Neoral[®] solution with milk can be unpalatable. ~~Administration of Neoral Oral Solution with milk has not been evaluated and should be used with caution.~~ The effect of milk on the bioavailability of cyclosporine when administered as Neoral Oral Solution has not been evaluated.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (package insert submitted May 23, 2002).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 50-715/S-010, S-014, NDA 50-716/S-014, S-018." Approval of these submissions 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 Practitioner" 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:

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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, contact Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug
Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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**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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