DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50-715/S-027
NDA 50-716/S-028

SUPPLEMENT APPROVAL

Novartis Corporation
Attention: Ronald Van Valen
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

Please refer to the following supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Neoral® Soft Gelatin Capsule and Neoral® Oral Solution as follows:

NDA number	Supplemental Number	Date of Submission	Date Received
50-715	S-027	March 27, 2009	March 27, 2009
50-716	S-028	March 30, 2009	March 31, 2009

We also acknowledge receipt of your submission dated September 11, 2009.

These "Changes Being Effected" supplemental new drug applications provide for revisions to the **WARNINGS/Kidney, Liver, and Heart Transplant**, **PRECAUTIONS/ Drug Interactions**, **PRECAUTIONS/Other Drug Interactions**, **ADVERSE REACTIONS/Kidney, Liver, and Heart Transplantation**, and **OVERDOSAGE** sections of the package insert.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling submitted on September 11, 2009.

The revisions to the package insert are as follow (additions are noted with underline and deletions with ~~strikethrough~~):

1. In the **WARNINGS/ Kidney, Liver, and Heart Transplant** subsection, the twelfth paragraph is revised as follows:

   As in patients receiving other immunosuppressants, those patients receiving cyclosporine are at increased risk for development of lymphomas and other malignancies, particularly

those of the skin. Patients taking cyclosporine should be warned to avoid excess ultraviolet light exposure. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents. Because of the danger of oversuppression of the immune system resulting in increased risk of infection or malignancy, a treatment regimen containing multiple immunosuppressants should be used with caution. Some malignancies may be fatal. Transplant patients receiving cyclosporine are at increased risk for serious infection with fatal outcome.

2. The **PRECAUTIONS/Drug Interactions/Drugs That Alter Cyclosporine Concentrations** subsection is revised as follows:

Cyclosporine is extensively metabolized by CYP 3A isoenzymes, in particular CYP3A4, and is a substrate of the multidrug efflux transporter P-glycoprotein. Various agents are known to either increase or decrease plasma and whole blood cyclosporine concentrations usually by inhibition or induction of CYP3A4 or P-glycoprotein transporter or both. Compounds that decrease cyclosporine absorption such as orlistat should be avoided. ~~Cyclosporine is extensively metabolized by cytochrome P-450 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)*

3. In the **PRECAUTIONS/Drug Interactions/Drugs That Increase Cyclosporine Concentrations** subsection a new drug "nefazodone" is added to the table under the Other Drugs column as follows:

Drugs That Increase Cyclosporine Concentrations

Calcium Channel Blockers	*Antifungals*	*Antibiotics*	*Glucocorticoids*	*Other Drugs*
diltiazem	fluconazole	azithromycin	methylprednisolone	allopurinol
nicardipine	itraconazole	clarithromycin		amiodarone
verapamil	ketoconazole	erythromycin		bromocriptine
	voriconazole	quinupristin/ dalfopristin		colchicine
				danazol
				imatinib
				metoclopramide
				nefazodone
				oral contraceptives

4. In the **PRECAUTIONS/Drug Interactions/Drugs That Decrease Cyclosporine Concentrations** subsection table the drug "oxcarbazepine" is moved from the column Other Drugs/dietary Supplements to Anticonvulsants as follows:

Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations

Antibiotics	*Anticonvulsants*	*Other Drugs/Dietary Supplements*	
nafcillin	carbamazepine	bosentan	St. John's Wort
rifampin	oxcarbazepine	octreotide	
	phenobarbital	orlistat	
	phenytoin	sulfinpyrazone	
		terbinafine	
		ticlopidine	
		~~oxcarbazepine~~	

5. In the **PRECAUTIONS/Other Drug Interactions** subsection a new first paragraph is added as follows:

Cyclosporine is an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein and may increase plasma concentrations of comedications that are substrates of CYP3A4 or P-glycoprotein transporter or both.

6. In the **PRECAUTIONS/Other Drug Interactions** subsection the second and third paragraphs is revised as follows:

Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone, ~~and~~ HMG-CoA reductase inhibitors (statins), and etoposide. 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 needs 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.

7. In the **PRECAUTIONS/Other Drug Interactions** subsection a fourth paragraph is added as follows:

   Cyclosporine may increase the plasma concentrations of repaglinide and thereby increase the risk of hypoglycemia. In 12 healthy male subjects who received two doses of 100mg cyclosporine capsule orally 12 hours apart with a single dose of 0.25mg repaglinide tablet (one half of a 0.5mg tablet) orally 13 hours after the cyclosporine initial dose, the repaglinide mean Cmax and AUC were increased by 1.8 fold (range: 0.6 - 3.7 fold) and 2.4 fold (range: 1.2 – 5.3 fold), respectively. Close monitoring of blood glucose level is advisable for a patient taking cyclosporine and repaglinide concomitantly.

8. In the **ADVERSE REACTIONS/Kidney, Liver, Heart and Heart Transplantation** subsection, a tenth paragraph is added as follows:

   Patients receiving immunosuppressive therapies, including cyclosporine and cyclosporine- containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic). Both generalized and localized infections can occur. Pre-existing infections may also be aggravated. Fatal outcomes have been reported. (see WARNINGS)

9. The **OVERDOSAGE** section is revised as follows:

   There is a minimal experience with cyclosporine overdosage. Forced emesis and gastric lavage can be of value up to 2 hours after administration of Neoral®. Transient hepatotoxicity and nephrotoxicity may occur which should resolve following drug withdrawal. Oral doses of cyclosporine up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia and, in a few patients, moderately severe, reversible impairment of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with cyclosporine in premature neonates. General supportive measures and symptomatic treatment should be followed in all cases of overdosage. Cyclosporine is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion. The oral dosage at which half of experimental animals are estimated to die is 31 times, 39 times, and >54 times the human maintenance dose for transplant patients (6mg/kg; corrections based on body surface area) in mice, rats, and rabbits.

Within 14 days from the date of this letter, please amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format that includes the changes approved in this supplemental application.

Submit revised content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call June Germain, Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD
Deputy Director for Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50715	SUPPL-27	NOVARTIS PHARMACEUTICALS CORP	NEORAL
NDA-50716	SUPPL-28	NOVARTIS PHARMACEUTICALS CORP	NEORAL ORAL SOLUTION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OZLEM A BELEN
09/24/2009