DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50-625/S-048
NDA 50-573/S-034
NDA 50-574/S-042

SUPPLEMENTS APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Mr. Ronald G. Van Valen
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Mr. Van Valen:

Please refer to your supplemental new drug applications (NDA) dated and received on October 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 50-625 SANDIMMUNE® Soft Gelatin Capsules (cyclosporine capsules, USP) 25 mg, 50 mg, 100 mg, NDA 50-573 SANDIMMUNE® Injection (cyclosporine injection, USP) 50 mg/mL, and NDA 50-574 SANDIMMUNE® Oral Solution (cyclosporine oral solution, USP) 100 mg/mL.

These "Changes Being Effected" supplemental new drug applications propose revision of the content of labeling for the package insert to strengthen safety information in the **WARNINGS** section, **PRECAUTIONS/Drug Interactions/Drugs That Alter Cyclosporine Concentrations, PRECAUTIONS/Other Drug Interactions** subsection, **ADVERSE REACTIONS s**ection, and **OVERDOSAGE** section.

We have completed our review of these applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text, which is identical to the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format submitted on October 30, 2009.

The following changes were made in the package insert (additions are noted with double underline and deletions are noted with ~~strikethrough~~):

1. The last paragraph of the **WARNINGS** section was revised as follows:

   As in patients receiving other immunosuppressants, those patients receiving Sandimmune® (cyclosporine) are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. 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, which can also increase

susceptibility to infection, Sandimmune® (cyclosporine) should not be administered with other immunosuppressive agents except adrenal corticosteroids. The efficacy and safety of cyclosporine in combination with other immunosuppressive agents have not been determined. 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 of the package insert was 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 or whole blood of cyclosporine levels usually by inhibition or induction of CYP3A4 or P-glycoprotein transporter or both. Compounds that decrease cyclosporine absorption such as orlistat should be avoided. ~~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 Sandimmune® (cyclosporine) dosage adjustment are essential when these drugs are used concomitantly. (See Blood Level Monitoring.)

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
		quinupristin/		
	voriconazole	dalfopristin		colchicine
				danazol
				imatinib
				metoclopramide
				nefazodone
				oral contraceptives

The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 3A and thus could potentially increase the concentrations of cyclosporine, however no formal studies of the interaction are available. Care should be exercised when these drugs are administered concomitantly.

Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine, thus should be avoided.

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	

3. The first paragraph in the **PRECAUTIONS/Other Drug Interactions** subsection was revised 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 or both.

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 and 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. Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur. Caution is also required when cyclosporine is coadministered with potassium-sparing drugs (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists), potassium-containing drugs as well as in patients on a potassium-rich diet. Control of potassium levels in these situations is advisable.

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 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.

Elevations in serum creatinine were observed in studies using sirolimus in combination with full-dose cyclosporine. This effect is often reversible with cyclosporine dose reduction. Simultaneous coadministration of cyclosporine significantly increases blood levels of sirolimus. To minimize increases in sirolimus blood concentrations, it is recommended that sirolimus be given 4 hours after cyclosporine administration.

During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided. 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).

1. The following paragraph was added to the **ADVERSE REACTIONS** section of the package insert, below the table titled "Renal Transplant Patients in Whom Therapy Was Discontinued":

   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**)

2. The **OVERDOSAGE** section of the package insert was revised as follows:

   There is a minimal experience with overdosage. Because of the slow absorption of Sandimmune® Soft Gelatin Capsules or Oral Solution, forced emesis and gastric lavage would be of value up to 2 hours after administration. 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. Sandimmune® (cyclosporine) is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion. The

oral LD50 is 2329 mg/kg in mice, 1480 mg/kg in rats, and > 1000 mg/kg in rabbits. The I.V. LD50 is 148 mg/kg in mice, 104 mg/kg in rats, and 46 mg/kg in rabbits.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for these NDAs, 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 MS Word format that includes the changes approved in these supplemental applications.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
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, please contact Rebecca McKinnon, Pharm.D., Regulatory Project Manager, at (301)796-1600.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Package Insert

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50625	SUPPL-48	NOVARTIS PHARMACEUTICALS CORP	SANDIMMUNE
NDA-50574	SUPPL-42	NOVARTIS PHARMACEUTICALS CORP	SANDIMMUNE
NDA-50573	SUPPL-34	NOVARTIS PHARMACEUTICALS CORP	SANDIMMUNE

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/s/

OZLEM A BELEN
04/30/2010