DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50715/S-033
NDA 50716/S-034

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Ronald Van Valen
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07856-1080

Dear Mr. Van Valen:

Please refer to your Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Supplement Number	Drug Product	Submission Date	Receipt Date
50-715	033	Neoral® Soft Gelatin Capsules (cyclosporine capsules, USP)	November 2, 2012	November 2, 2012
50-716	034	Neoral® Oral Solution (cyclosporine oral solution, USP)	November 2, 2012	November 2, 2012

We acknowledge receipt of your amendments dated January 31, March 27, April 25 and 30, 2013.

These "Prior Approval" supplemental new drug applications provide for revisions to the **CLINICAL PHARMACOLOGY**, **WARNINGS**, **PRECAUTIONS**, **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION** sections of the package insert.

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

LABELING REVISIONS

The revisions to the package insert are as follow (added text is double underlined, and deleted text is ~~strikethrough~~.)

1. In the **CLINICAL PHARMACOLOGY** section, the title **Special Population** is modified

and two new subsections are added under it as follows:

Specific ~~**Special**~~ **Populations**

Renal impairment

In a study performed in 4 subjects with end-stage renal disease (creatinine clearance < 5 mL/min), an intravenous infusion of 3.5 mg/kg of cyclosporine over 4 hours administered at the end of a hemodialysis session resulted in a mean volume of distribution (Vdss) of 3.49 L/kg and systemic clearance (CL) of 0.369 L/hr/kg. This systemic CL (0.369 L/hr/kg) was approximately two thirds of the mean systemic CL (0.56 L/hr/kg) of cyclosporine in historical control subjects with normal renal function. In 5 liver transplant patients, the mean clearance of cyclosporine on and off hemodialysis was 463 mL/min and 398 mL/min, respectively. Less than 1% of the dose of cyclosporine was recovered in the dialysate

Hepatic Impairment

Cyclosporine is extensively metabolized by the liver. Since severe hepatic impairment may result in significantly increased cyclosporine exposures, the dosage of cyclosporine may need to be reduced in these patients.

2. In the **WARNINGS/ Kidney, Liver, and Heart Transplant/Nephrotoxicity** subsection, the sixth and eighth paragraphs are modified as follows:

When considering the development of cyclosporine-associated nephropathy, it is noteworthy that several authors have reported an association between the appearance of interstitial fibrosis and higher cumulative doses or persistently high circulating trough concentrations ~~levels~~ of cyclosporine. This is particularly true during the first 6 post-transplant months when the dosage tends to be highest and when, in kidney recipients, the organ appears to be most vulnerable to the toxic effects of cyclosporine. Among other contributing factors to the development of interstitial fibrosis in these patients are prolonged perfusion time, warm ischemia time, as well as episodes of acute toxicity, and acute and chronic rejection. The reversibility of interstitial fibrosis and its correlation to renal function have not yet been determined. Reversibility of arteriolopathy has been reported after stopping cyclosporine or lowering the dosage.

In the event of severe and unremitting rejection, when rescue therapy with pulse steroids and monoclonal antibodies fail to reverse the rejection episode, it may be preferable to switch to alternative immunosuppressive therapy rather than increase the Neoral® dose to excessive blood concentrations ~~levels~~.

3. In the **WARNINGS/ Kidney, Liver, and Heart Transplant/Nephrotoxicity** subsection, a new last paragraph is added as follows:

Due to the potential for additive or synergistic impairment of renal function, caution should be exercised when co-administering Neoral with other drugs that may impair renal function. (See PRECAUTIONS, Drug Interactions)

4. In the **WARNINGS/Kidney, Liver, and Heart Transplant/Neurotoxicity** subsection, the second paragraph is modified as follows:

   Encephalopathy, including Posterior Reversible Encephalopathy Syndrome (PRES), has been described both in post-marketing reports and in the literature. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances. In many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. Predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high cyclosporine blood concentrations, and graft-versus-host disease have been noted in many but not all of the reported cases. The changes in most cases have been reversible upon discontinuation of cyclosporine, and in some cases improvement was noted after reduction of dose. It appears that patients receiving liver transplant are more susceptible to encephalopathy than those receiving kidney transplant. Another rare manifestation of cyclosporine-induced neurotoxicity, occurring in transplant patients more frequently than in other indications, is optic disc edema including papilloedema, with possible visual impairment, secondary to benign intracranial hypertension.

5. In the **WARNINGS** section, a new subsection is added titled **Special Excipients** covering the new subsection titled **Alcohol (ethanol)** at the end of the section as follows:

   Specific Excipients

   Alcohol (ethanol)
   The alcohol content *(See DESCRIPTION)* of Neoral should be taken into account when given to patients in whom alcohol intake should be avoided or minimized, e.g. pregnant or breast feeding women, in patients presenting with liver disease or epilepsy, in alcoholic patients, or pediatric patients. For an adult weighing 70 kg, the maximum daily oral dose would deliver about 1 gram of alcohol which is approximately 6% of the amount of alcohol contained in a standard drink.

6. The **PRECAUTIONS/Drug Interactions** subsection has been revised as follows:

   Drug Interactions

   A. Effect of Drugs and Other Agents on Cyclosporine Pharmacokinetics and/or Safety
   All of the individual drugs cited below are well substantiated to interact with cyclosporine. In addition, concomitant use of nonsteroidal anti-inflammatory drugs with cyclosporine, particularly in the setting of dehydration, may potentiate renal dysfunction. Caution should be exercised when using other drugs which are known to impair renal function. (See WARNINGS, Nephrotoxicity)

Drugs That May Potentiate Renal Dysfunction

Antibiotics	*Antineoplastics*	*Antifungals*	*Anti-inflammatory Drugs*	*Gastrointestinal Agents*	*Immunosuppressives*	*Other Drugs*
ciprofloxacin	melphalan	amphotericin B	azapropazon	cimetidine	tacrolimus	fibric acid derivatives (e.g., bezafibrate, fenofibrate)
gentamicin		ketoconazole	colchicine	ranitidine		methotrexate
tobramycin			diclofenac			
vancomycin			naproxen			
trimethoprim with sulfamethoxazole			sulindac			

During the concomitant use of a drug that may exhibit additive or synergistic renal impairment with cyclosporine, close monitoring of renal function (in particular serum creatinine) should be performed. If a significant impairment of renal function occurs, the dosage of the co-administered drug should be reduced or an alternative treatment considered.

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 concentrations ~~levels~~ of cyclosporine usually by inhibition or induction of CYP3A4 or P-glycoprotein transporter or both. Compounds that decrease cyclosporine absorption such as orlistat should be avoided. ~~Montoring of circulating cyclosporine concentrations and~~ ~~a~~.Appropriate Neoral® dosage adjustment to achieve the desired cyclosporine concentrations is ~~are~~ essential when ~~these~~ drugs that significantly alter cyclosporine concentrations are used concomitantly. *(*See Blood Concentration Monitoring*)*

7. In the **PRECAUTIONS/Drug Interactions/ 2 Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations** subsection, three new subsections has been added after the table as follows:

Bosentan
Co-administration of bosentan (250 - 1000 mg every 12 hours based on tolerability) and cyclosporine (300 mg every 12 hours for 2 days then dosing to achieve a C_{min} of 200-250 ng/mL) for 7 days in healthy subjects resulted in decreases in the cyclosporine mean dose-normalized AUC, C_{max}, and trough concentration of approximately 50%, 30% and 60%, respectively, compared to when cyclosporine was given alone (See also Effect of Cyclosporine on the Pharmacokinetics and/or Safety of Other Drugs or Agents).
Boceprevir
Co-administration of boceprevir (800 mg three times daily for 7 days) and cyclosporine (100 mg single dose) in healthy subjects resulted in increases in the mean AUC and C_{max} of

cyclosporine approximately 2.7-fold and 2-fold, respectively, compared to when cyclosporine was given alone.

Telaprevir

Co-administration of telaprevir (750 mg every 8 hours for 11 days) with cyclosporine (10 mg on day 8) in healthy subjects resulted in increases in the mean dose-normalized AUC and C_{max} of cyclosporine approximately 4.5-fold and 1.3-fold, respectively, compared to when cyclosporine (100 mg single dose) was given alone.

8. The **PRECAUTIONS/Drug Interactions/B. Effect of Cyclosporine on the Pharmacokinetics and/or Safety of Other Drugs or Agents** subsection is revised and three new subsections has been 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 or both.

Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins), and, aliskiren, repaglinide, NSAIDs, sirolimus, etoposide, and other drugs. See the full prescribing information of the other drug for further information and specific recommendations. The decision on co-administration of cyclosporine with other drugs or agents should be made by the physician following the careful assessment of benefits and risks.

Digoxin

Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin. If digoxin is used concurrently with cyclosporine, serum digoxin concentrations should be monitored.

Colchicine

There are reports on the potential of cyclosporine to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. Concomitant administration of cyclosporine and colchicine results in significant increases in colchicine plasma concentrations. If colchicine is used concurrently with cyclosporine, a reduction in the dosage of colchicine is recommended.

HMG-CoA reductase inhibitors (statins)

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.

Repaglinide

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 C_{max} 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.

Ambrisentan

Co-administration of ambrisentan (5 mg daily) and cyclosporine (100-150 mg twice daily initially, then dosing to achieve C_{min} 150-200 ng/mL) for 8 days in healthy subjects resulted in mean increases in ambrisentan AUC and C_{max} of approximately 2-fold and 1.5-fold, respectively, compared to ambrisentan alone.

Anthracycline antibiotics

High doses of cyclosporine (e.g., at starting intravenous dose of 16 mg/kg/day) may increase the exposure to anthracycline antibiotics (e.g., doxorubicin, mitoxantrone, daunorubicin) in cancer patients.

Aliskiren

Cyclosporine alters the pharmacokinetics of aliskiren, a substrate of P-glycoprotein and CYP3A4. In 14 healthy subjects who received concomitantly single doses of cyclosporine (200 mg) and reduced dose aliskiren (75 mg), the mean C_{max} of aliskiren was increased by approximately 2.5 fold (90% CI: 1.96 - 3.17) and the mean AUC by approximately 4.3 fold (90% CI: 3.52 - 5.21), compared to when these subjects received aliskiren alone. The concomitant administration of aliskiren with cyclosporine prolonged the median aliskiren elimination half-life (26 hours versus 43 to 45 hours) and the T_{max} (0.5 hours versus 1.5 to 2.0 hours). The mean AUC and C_{max} of cyclosporine were comparable to reported literature values. Co-administration of cyclosporine and aliskiren in these subjects also resulted in an increase in the number and/or intensity of adverse events, mainly headache, hot flush, nausea, vomiting, and somnolence. The co-administration of cyclosporine with aliskiren is not recommended.

Bosentan

In healthy subjects, co-administration of bosentan and cyclosporine resulted in mean increases in dose-normalized bosentan trough concentrations on day 1 and day 8 of approximately 21-fold and 2-fold , respectively, compared to when bosentan was given alone as a single dose on day 1 (See also Effect of Drugs and Other Agents on Cyclosporine Pharmacokinetics and/or Safety).

Potassium-Sparing Diuretics

Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur. Caution is also required when cyclosporine is co-administered 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.

Nonsteroidal Anti-inflammatory Drug (NSAID) Interactions

Clinical status and serum creatinine should be closely monitored when cyclosporine is used with nonsteroidal anti-inflammatory agents in rheumatoid arthritis patients. *(See WARNINGS)*

Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal

function, as determined by ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) and (*p*-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood concentrations of cyclosporine, it has been associated with approximate doubling of diclofenac blood concentrations and occasional reports of reversible decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

Methotrexate Interaction

Preliminary data indicate that when methotrexate and cyclosporine were co-administered to rheumatoid arthritis patients (N=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine concentrations do not appear to have been altered (N=6).

Sirolimus

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 co-administration of cyclosporine significantly increases blood levels of sirolimus. To minimize increases in sirolimus concentrations, it is recommended that sirolimus be given 4 hours after cyclosporine administration.

Nifedipine

Frequent gingival hyperplasia when nifedipine is given concurrently with cyclosporine has been reported. The concomitant use of nifedipine should be avoided in patients in whom gingival hyperplasia develops as a side effect of cyclosporine.

Methylprednisolone

Convulsions when high dose methylprednisolone is given concurrently with cyclosporine have been reported.

Other Immunosuppressive Drugs and Agents

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

9. In the **PRECAUTIONS/Pregnancy Pregnancy Category C** subsection, a new last paragraph is added to the subsection as follows:

   The alcohol content of the Neoral formulations should also be taken into account in pregnant women. (See WARNINGS, Special Excipients)

10. The **PRECAUTIONS/Nursing Mothers** subsection is revised as follows:

    Cyclosporine is present in ~~passes into~~ breast milk. ~~Mothers receiving treatment with Neoral® should not breast feed.~~ Because of the potential for serious adverse drug reactions in nursing infants from Neoral, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Neoral contains ethanol. Ethanol will be present in human milk at levels similar to that found in

maternal serum and if present in breast milk will be orally absorbed by a nursing infant. (See WARNINGS)

11. In the **ADVERSE REACTIONS** section, a new subsection titled **Postmarketing Experience, Psoriasis** is added after the **Psoriasis** subsection as follows:

Postmarketing Experience, Psoriasis
Cases of transformation to erythrodermic psoriasis or generalized pustular psoriasis upon either withdrawal or reduction of cyclosporine in patients with chronic plaque psoriasis have been reported.

12. In the **DOSAGE AND ADMINISTRATION** section, a new subsection titled **Specific Populations** is added at the end of the section as follows:

Specific Populations
Renal Impairment in Kidney, Liver and Heart Transplantation
Cyclosporine undergoes minimal renal elimination and its pharmacokinetics do not appear to be significantly altered in patients with end-stage renal disease who receive routine hemodialysis treatments (See CLINICAL PHARMACOLOGY). However, due to its nephrotoxic potential (See WARNINGS), careful monitoring of renal function is recommended; cyclosporine dosage should be reduced if indicated. (See WARNINGS and PRECAUTIONS)

Renal Impairment in Rheumatoid Arthritis and Psoriasis
Patients with impaired renal function should not receive cyclosporine (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Hepatic Impairment
The clearance of cyclosporine may be significantly reduced in severe liver disease patients (See CLINICAL PHARMACOLOGY). Dose reduction may be necessary in patients with severe liver impairment to maintain blood concentrations within the recommended target range. (See WARNINGS and PRECAUTIONS)

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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 that includes labeling changes for this NDA, including 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 this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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 Ms. June Germain, MS, Acting Safety Regulatory Project Manager, at (301) 796-4024.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S): Content of Labeling

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
05/02/2013