



NDA 50-573/S-035
NDA 50-574/S-043
NDA 50-625/S-049

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) for the following:

NDA number	Supplemental number	Drug Name	Date of Submission	Date Received
50-573	035	Sandimmune [®] Injection (cyclosporine, USP) 50 mg/mL	February 17, 2010	February 17, 2010
50-574	043	Sandimmune [®] Oral Solution (cyclosporine oral solution, USP)	February 17, 2010	February 17, 2010
50-625	049	Sandimmune [®] Soft Gelatin Capsules (cyclosporine, USP) 25mg, 50 mg, 100 mg	February 17, 2010	February 17, 2010

We acknowledge receipt of your amendments dated March 8, 2012 and August 23, 2012.

Your submissions dated March 8, 2012 constituted a complete response to our April 29, 2011 action letter.

These “Prior Approval” supplemental new drug applications propose revisions to the **WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS** sections of the package insert. The following changes were observed in the package insert (added text is double underlined, and deleted text is ~~strikethrough~~.)

1. **WARNINGS** section has been revised as follows:

WARNINGS

Kidney, Liver and Heart Transplant

(See boxed WARNINGS): Sandimmune® (cyclosporine), when used in high doses, can cause hepatotoxicity and nephrotoxicity.

Nephrotoxicity

It is not unusual for serum creatinine and BUN levels to be elevated during Sandimmune® (cyclosporine) therapy.....

Thrombotic Microangiopathy

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure.....

Hyperkalemia

Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients.

Hepatotoxicity

Cases of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis, and liver failure have been reported in patients treated with cyclosporine. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and comedications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see ADVERSE REACTIONS, Postmarketing Experience).

Hepatotoxicity, usually manifested by elevations in hepatic enzymes and bilirubin, was reported in patients treated with cyclosporine in clinical trials: has been noted in 4% of cases of in renal transplantation, 7% of cases of in cardiac transplantation, and 4% of cases of in liver transplantation. This was usually noted during the first month of therapy when high doses of Sandimmune® (cyclosporine) were used and consisted of elevations of hepatic enzymes and bilirubin. The chemistry elevations usually decreased with a reduction in dosage.

Malignancies

As in patients receiving other immunosuppressants, those patients receiving Sandimmune® (cyclosporine) are at increased risk for development of lymphomas and other malignancies,.....

Latent Viral Infections

~~Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus-associated nephropathy which has been observed in patients receiving immunosuppressants, including Sandimmune. This infection is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated~~

~~nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy~~

Serious Infections

Patients receiving immunosuppressants, including Sandimmune, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. [See BOXED WARNING, and ADVERSE REACTIONS]

Polyoma Virus Infections

Patients receiving immunosuppressants, including Sandimmune are at increased risk for opportunistic infections, including polyoma virus infections. Polyoma virus infections in transplant patients may have serious, and sometimes, fatal outcomes. These include cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), and polyoma virus-associated nephropathy (PVAN), especially due to BK virus infections, which have been observed in patients receiving cyclosporine.

PVAN is associated with serious outcomes, including deteriorating renal function and renal graft loss, (see ADVERSE REACTIONS/Postmarketing Experience). Patient monitoring may help detect patients at risk for PVAN.

Cases of PML have been reported in patients treated with Sandimmune. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Consideration should be given to reducing the total immunosuppression in transplant patients who develop PML or PVAN. However, reduced immunosuppression may place the graft at risk.

Neurotoxicity

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high-dose methylprednisolone.....

Anaphylactic reactions

Rarely (approximately 1 in 1000), patients receiving Sandimmune[®] Injection (cyclosporine injection, USP) have experienced anaphylactic reactions....

Conversion from Neoral to Sandimmune

Because Sandimmune[®] (cyclosporine) is not bioequivalent to Neoral[®], conversion from Neoral[®] to Sandimmune[®] (cyclosporine) using a 1:1 ratio (mg/kg/day) may result in a lower cyclosporine blood....

2. **PRECAUTIONS** section has been revised as follows:

General

Patients with malabsorption may have difficulty in achieving therapeutic levels with Sandimmune® Soft Gelatin Capsules or Oral Solution.

Hypertension

Hypertension is a common side effect of Sandimmune® (cyclosporine) therapy. (See ADVERSE REACTIONS.)....

Vaccination

During treatment with Sandimmune® (cyclosporine), vaccination may be less effective and the use of live attenuated vaccines should be avoided.

3. **PRECAUTIONS/Drug Interactions** section has been revised as follows:

Drug Interactions

A. Effect of Drugs and Other Agents on Cyclosporine Pharmacokinetics and/or Safety

Drugs That May Potentiate Renal Dysfunction

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

Drugs That Alter Cyclosporine Concentrations

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. ~~Cyclosporine is extensively metabolized by cytochrome P-450 3A.~~ Monitoring of circulating cyclosporine concentrations and appropriate Sandimmune® (cyclosporine) dosage adjustment are essential when these drugs are used concomitantly. (See Blood Concentration Level Monitoring.)

1. Drugs That Increase Cyclosporine Concentrations

HIV protease inhibitors

The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 3A....

Grapefruit Juice

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

2. Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations

St. John's Wort

There have been reports of a serious drug interaction between cyclosporine and the herbal dietary supplement, St. John's Wort....

Rifabutin

Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system.

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 levels of cyclosporine, it has been associated with approximate doubling of diclofenac blood levels 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 coadministered 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).~~

B. Effect of Cyclosporine on the Pharmacokinetics and/or Safety of Other Drugs or Agents

Other Drug Interactions

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 are is used concurrently with cyclosporine, serum digoxin concentrations should be monitored.

Colchicine

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. Concomitant administration of cyclosporine and colchicine results in significant increases in colchicine plasma concentrations. If digoxin or colchicine is are used concurrently with cyclosporine, a reduction in the dosage of colchicine is recommended. 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.

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. ~~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.~~

Repaglinide

Cyclosporine may increase the plasma concentrations of repaglinide and thereby increase the risk of hypoglycemia.....

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 Cmax 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.

Potassium-Sparing Diuretics

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.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

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 coadministered 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. ...

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

Nifedipine

Frequent gingival hyperplasia when with nifedipine is given concurrently with cyclosporine have been reported.

Methylprednisolone

Convulsions when high dose methylprednisolone is given concomitantly 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.

C. Effect of Cyclosporine on the Efficacy of Live Vaccines

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

~~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).

4. **ADVERSE REACTIONS** section has been revised as follows:

The principal adverse reactions of Sandimmune® (cyclosporine) therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.

Hypertension

Hypertension, which is usually mild to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

Glomerular Capillary Thrombosis

Glomerular capillary thrombosis has been found in patients treated with cyclosporine and may progress to graft failure.

Hypomagnesemia

Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine therapy.

Clinical Studies

The following reactions occurred in 3% or greater of 892 patients involved in clinical trials of kidney, heart, and liver transplants:...

5. **ADVERSE REACTIONS/Postmarketing Experience** section has been revised as follows:

Postmarketing Experience

Hepatotoxicity

Cases of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure; serious and/or fatal outcomes have been reported [See WARNINGS/Hepatotoxicity]

~~BK virus associated nephropathy has been observed in patients receiving immunosuppressants, including Sandimmune. This infection is associated with serious outcomes, including deteriorating renal function and renal graft loss (see WARNINGS)~~

Increased Risk of Infections

Cases of JC virus associated progressive multifocal leukoencephalopathy (PML), sometimes fatal, and Polyoma virus associated nephropathy (PVAN), especially due to BK virus resulting in graft loss have been reported. [See WARNINGS/ Polyoma Virus Infection]

Headache, including Migraine

Cases of migraine have been reported. In some cases, patients have been unable to continue Cyclosporine, however the final decision on treatment discontinuation should be made by the treating physician following the careful assessment of benefits versus risks.

6. The following phrases have been revised throughout the package insert:
 - a. “blood level(s)” to “blood concentration(s)”
 - b. “blood level monitoring” to “blood concentration monitoring”

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.

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 Effectuated” (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 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).

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, M.S., Regulatory Health Project Manager, at (301) 796-1600.

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:
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
08/30/2012