



NDA 50-573/S-033
NDA 50-574/S-041
NDA 50-625/S-047

SUPPLEMENT APPROVAL

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

Dear Mr. Van Valen:

Please refer to your supplemental new drug applications (NDA) dated and received on August 6, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 50-573 SANDIMMUNE[®] Injection (cyclosporine injection, USP) 50 mg/mL, NDA 50-574 SANDIMMUNE[®] Oral Solution (cyclosporine oral solution, USP) 100 mg/mL, and NDA 50-625 SANDIMMUNE[®] Soft Gelatin Capsules (cyclosporine capsules, USP) 25 mg, 50 mg, 100 mg.

We acknowledge receipt of your submission dated September 15, 2009.

Reference is made to our letter dated July 7, 2009, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling of CellCept[®] to address the risk of BK virus-associated nephropathy connected with the use of certain immunosuppressants.

We also refer to the letter we sent on September 1, 2009, informing you that we determined that a 30-day extension of the discussion period was warranted to allow us to complete our review and reach agreement on the content of the labeling. We also refer to modified labeling language that we sent to you on September 4, 2009.

These labeling supplements provide for the following changes to the package insert.
(Underlined text = addition, ~~strikethrough~~ text = deletion)

1. A new subsection titled "Latent Viral Infections" in the **WARNINGS** section has been added as shown below :

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.

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.

2. A new subsection titled “**Postmarketing Experience**” at the end of the **ADVERSE REACTIONS** section has been added as shown below:

Postmarketing Experience

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**).

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the 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 to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved supplements NDA 50-573/S-033, NDA 50-574/S-041 and NDA 50-625/S-047**”.

In addition, within 21 days of the date of this letter, amend any pending applications for the NDA with content of labeling in structured product labeling (SPL) format to include the changes approved in this application. Failure to make these changes within the specified period of time could make your product misbranded under 21 USC 321(n) and 352(a).

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to 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 following address or by facsimile at 301-847-8444:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (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).

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If you have any questions, please contact Hyun J. Son Pharm.D., Safety 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-50573	SUPPL-33	NOVARTIS PHARMACEUTICA LS CORP	SANDIMMUNE
NDA-50574	SUPPL-41	NOVARTIS PHARMACEUTICA LS CORP	SANDIMMUNE
NDA-50625	SUPPL-47	NOVARTIS PHARMACEUTICA LS CORP	SANDIMMUNE

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
10/08/2009