



NDA 50-715/S-028  
NDA 50-716/S-029

**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 application (NDA) dated and received on August 6, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 50-715 Neoral<sup>®</sup> Soft Gelatin Capsules (cyclosporine capsules, USP) MODIFIED, 25 mg and 100 mg and NDA 50-716 Neoral<sup>®</sup> Oral Solution (cyclosporine oral solution, USP) MODIFIED, 100 mg/mL.

We acknowledge receipt of your submissions dated September 14, 2009 and October 1, 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 Rapamune<sup>®</sup> 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. In the **WARNINGS/Kidney, Liver and Heart Transplant** subsection, a new paragraph has been added as shown below :

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. Transplant patients receiving cyclosporine are at increased risk for serious infection with fatal outcome.

#### 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 Neoral. 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 paragraph titled “**Postmarketing Experience, Kidney, Liver and Heart Transplantation**” at the end of the **ADVERSE REACTIONS/Kidney, Liver and Heart Transplantation** subsection has been added as follows:

#### **Postmarketing Experience, Kidney, Liver and Heart Transplantation**

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

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 50-715/S-028 and NDA 50-716/S-029**”.

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).

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-50715	SUPPL-28	NOVARTIS PHARMACEUTICA LS CORP	NEORAL
NDA-50716	SUPPL-29	NOVARTIS PHARMACEUTICA LS CORP	NEORAL ORAL SOLUTION

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

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/s/

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OZLEM A BELEN  
10/08/2009