



NDA 50-791/S-008

**SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation  
Attention: Sabine Vukelich, Ph.D.  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Dr. Vukelich:

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 Myfortic<sup>®</sup> (mycophenolic acid) delayed-release tablets, 180 mg and 360 mg.

We acknowledge receipt of your submission dated September 23, 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 Myfortic<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 and September 9, 2009.

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

1. The **WARNINGS/Progressive Multifocal Leukoencephalopathy** subsection has been revised as follows:

~~**Progressive Multifocal Leukoencephalopathy (PML)**~~**Latent Viral Infections**  
Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include cases of progressive multifocal leukoencephalopathy (PML) and BK virus-associated nephropathy (BKVAN) which have been observed in patients receiving immunosuppressants, including Myfortic.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept. Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. The reported cases generally had risk factors for PML, including 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 amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

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

2. The **ADVERSE REACTIONS/Postmarketing Experience** subsection has been revised as follows:

- Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolate mofetil (MMF). Mycophenolate mofetil (MMF) is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug (see **WARNINGS, Progressive Multifocal Leukoencephalopathy**~~**Latent Viral Infections**~~).
- BK virus-associated nephropathy has been observed in patients receiving immunosuppressants, including Myfortic. This infection is associated with serious outcomes, including deteriorating renal function and renal graft loss (see **WARNINGS, Latent Viral Infections**).

3. The medication guide has been revised as follows:

In the section “**What is the most important information I should know about Myfortic?**”

- ~~**Viral infections.** Viral infections including shingles, other herpes infections, and cytomegalovirus (CMV), can happen with Myfortic. CMV can cause serious tissue and blood infections. Certain viruses can live in your body and cause active infections when your immune system is weak. Viral infections that can happen with Myfortic include:~~
  - shingles, other herpes infections, and cytomegalovirus (CMV). CMV can cause serious tissue and blood infections.
  - BK virus. BK virus can affect how your kidney works and cause your transplanted kidney to fail.

We have completed our review of this supplemental application, as amended. This application is 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 supplement NDA 50-791/S-008”**.

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

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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