



NDA 50-791/S-002

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 dated and received May 1, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Myfortic[®] (mycophenolic acid) delayed-release tablets, 180 mg and 360 mg.

This application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

This supplemental application provide for revisions to the package insert as follows (~~striketrough text~~ = deletions, underlined text = additions):

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

WARNINGS
(SEE BOXED WARNING)

Lymphoma and Other Malignancies

Patients receiving immunosuppressive regimens involving combinations of drugs, including Myfortic[®] (mycophenolic acid), as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see **ADVERSE REACTIONS**). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

The rates for lymphoproliferative disease or lymphoma in Myfortic-treated patients were comparable to the mycophenolate mofetil group in the *de novo* and maintenance studies (see **ADVERSE REACTIONS**). As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis. Fatal infections can occur in patients receiving immunosuppressive therapy (see **ADVERSE REACTIONS**).

~~As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.~~

Progressive Multifocal Leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with mycophenolate mofetil (MMF). Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. Mycophenolate mofetil (MMF) is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune functions. 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.

Concomitant Use

Myfortic has been administered in combination with the following agents in clinical trials: antithymocyte/lymphocyte immunoglobulin, muromonab-CD3, basiliximab, daclizumab, cyclosporine, and corticosteroids. The efficacy and safety of Myfortic in combination with other immunosuppression agents have not been determined.

~~The rates for lymphoproliferative disease or lymphoma in Myfortic-treated patients were comparable to the mycophenolate mofetil group in the *de novo* and maintenance studies (see **ADVERSE REACTIONS**).~~

2. In the **ADVERSE REACTIONS** section, a new subsection was added after the **Respiratory** subsection as follows:

Postmarketing Experience

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**).

Congenital malformations have been reported in offspring of patients exposed to mycophenolate mofetil (MMF) during pregnancy (see **WARNINGS, Pregnancy**).

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Submit 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 in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions “**SPL for approved supplement NDA 50-791/S-002.**”

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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 Hyun Son, Pharm.D., Senior Regulatory Management Officer, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert

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

/s/

Renata Albrecht
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