



NDA 50-791/S-011

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Anne-Marie van de Merwe
Senior Regulatory Brand Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. van de Merwe:

Please refer to your Supplemental New Drug Application (sNDA) dated April 27, 2010, received April 27, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Myfortic[®] (mycophenolic acid) delayed-release tablet, 180 mg and 360 mg.

We acknowledge receipt of your amendment dated October 20, 2010.

This supplemental new drug application provides for the following revisions to the labeling for Myfortic (additions are noted with underline and deletions are noted with ~~striketrough~~):

1. In the **WARNINGS section**, the title and text of the original **Latent Viral Infections** subsection, is revised as follows:

Latent Viral Infections Polyomavirus Infections

~~Immunosuppressed patients~~ Patients receiving immunosuppressants, including Myfortic are at increased risk for opportunistic infections, including Polyomavirus infections. activation of latent viral infections. Polyomavirus infections in transplant patients may have serious, and sometimes, fatal outcomes. These include cases of JC virus associated progressive multifocal leukoencephalopathy (PML) and Polyomavirus BK virus associated nephropathy (PVAN) (BKVAN) ~~especially due to BK virus infection~~ which have been observed in patients receiving ~~immunosuppressants, including Myfortic.~~

PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss (see ADVERSE REACTIONS). Patient monitoring may help detect patients at risk for PVAN.

Cases of PML progressive multifocal leukoencephalopathy (PML), sometimes fatal have been reported in patients treated with MPA derivatives which include mycophenolate mofetil (MMF) and mycophenolate sodium (see ADVERSE REACTIONS). PML, which is sometimes fatal, commonly presents with

~~Hemiparesis~~ 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~~ Risk factors for PML, ~~including~~ include treatment with immunosuppressant therapies and impairment of immune function ~~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.~~

Reduction in immunosuppression should be considered for patients who develop evidence of PML or PVAN. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft.

~~BKVN 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. In the **WARNINGS** section the title and text of the **Pure Red Cell Aplasia** subsection, is revised as follows:

Blood Dyscrasias Including Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with ~~mycophenolate mofetil (MMF)-mycophenolic acid (MPA) derivatives~~ in combination with other immunosuppressive agents. ~~MMF is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug.~~ The mechanism for ~~MMF~~MPA derivatives induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppressive regimen ~~are~~ is also unknown. In some cases PRCA was found to be reversible with dose reduction or cessation of ~~MMF~~ therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Changes to Myfortic therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimize the risk of graft rejection (see ADVERSE REACTIONS, Postmarketing Experience).

Patients receiving Myfortic should be monitored for blood dyscrasias (e.g., neutropenia or anemia (see PRECAUTIONS, Laboratory Tests). The development of neutropenia may be related to Myfortic itself, concomitant medications, viral infections, or some combination of these events. If blood dyscrasias occur (e.g. neutropenia (ANC <1.3x10³ µL or anemia)), dosing with

Myfortic should be interrupted or the dose reduced, appropriate diagnostic test performed, and the patient managed appropriately (see DOSAGE AND ADMINISTRATION).

Patients receiving Myfortic should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding, or any other manifestation of bone marrow suppression.

3. In the **WARNINGS** section, the last two paragraphs after the **Pregnancy Exposure Prevention** subsection, are deleted as follows:

Pregnancy Exposure Prevention

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 1 week prior to beginning therapy. Myfortic therapy should not be initiated until a negative pregnancy test report is obtained.

Women of childbearing potential (including pubertal girls and perimenopausal women) taking Myfortic must receive contraceptive counseling and use effective contraception. The patient should begin using her two chosen methods of contraception 4 weeks prior to starting Myfortic therapy, unless abstinence is the chosen method. She should continue contraceptive use during therapy and for 6 weeks after stopping Myfortic. Patients should be aware that Myfortic reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness (see PRECAUTIONS, Information for Patients and PRECAUTIONS, Drug Interactions, Oral Contraceptives).

~~Patients receiving Myfortic should be monitored for neutropenia (see PRECAUTIONS, Laboratory Tests). The development of neutropenia may be related to Myfortic itself, concomitant medications, viral infections, or some combination of these events. If neutropenia develops ($ANC < 1.3 \times 10^3/\mu L$), dosing with Myfortic should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see DOSAGE AND ADMINISTRATION).~~

~~Patients receiving Myfortic should be instructed to immediately report any evidence of infection, unexpected bruising, bleeding, or any other manifestation of bone marrow suppression.~~

4. In the **PRECAUTIONS/Drug Interaction** subsection the first paragraph has a new title “*Gastroprotective agents*” and a subtitle as follows:

Gastroprotective agents

Antacids with magnesium and aluminum hydroxides:

Absorption of a single dose of Myfortic was decreased when administered to 12 stable renal transplant patients also taking magnesium-aluminum-containing antacids (30 mL): the mean C_{max} and $AUC_{(0-t)}$ values for MPA were 25% and 37% lower, respectively, than when Myfortic was administered alone under fasting

conditions. It is recommended that Myfortic and antacids not be administered simultaneously.

5. In the **PRECAUTIONS/Drug Interactions/Gastroprotective agents** subsection, a new second subsection titled “**Proton Pump inhibitors**” is added as follows:

Proton Pump inhibitors:

In a study conducted in 12 healthy volunteers, the pharmacokinetics of MPA were observed to be similar when a single dose of 720 mg Myfortic was administered alone and following concomitant administration of Myfortic and pantoprazole, which was administered at a dose of 40 mg BID for 4 days.

6. The **ADVERSE REACTIONS/Postmarketing Experience** section is modified as follows:

Postmarketing Experience:

The following adverse reactions have been identified during post-approval use of Myfortic. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

- Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with MPA derivatives ~~Mycophenolate mofetil (MMF) is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug~~ (see WARNINGS, Latent Viral Infections).
- ~~BK virus~~ Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection, 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).
- Congenital malformations have been reported in offspring of patients exposed to mycophenolate mofetil (MMF) during pregnancy (see WARNINGS, Pregnancy).
- Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives ~~mycophenolate mofetil~~ in combination with other immunosuppressive agents (see WARNINGS).
- Cases of rash have been reported in patients treated with MPA derivatives.

7. In the **DOSAGE AND ADMINISTRATION** section, the second paragraph is revised as follows:

Myfortic delayed-release tablets and mycophenolate mofetil (MMF) tablets and capsules should not be used interchangeably without physician supervision

because the rate of absorption following the administration of these two products is not equivalent.

8. The **HOW SUPPLIED** section, is revised as follows:

Myfortic[®] (mycophenolic acid) delayed-release tablets

360 mg tablet: Pale orange-red film-coated ovaloid tablet with imprint (debossing) “CT” on one side, containing 360 mg mycophenolic acid ~~formulated~~ (MPA) as a mycophenolate sodium salt.

Bottles of 120.....NDC 0078-0386-66

180 mg tablet: Lime green film-coated round tablet with bevelled edges and the imprint (debossing) “C” on one side, containing 180 mg mycophenolic acid ~~formulated~~ (MPA) as a mycophenolate sodium salt.

Bottles of 120.....NDC 0078-0385-66

We have completed our review of this supplemental application, as amended. This supplement is approved, effective on the date of this letter, for use as recommended in the package insert and medication guide submitted on October 20, 2010 and with minor editorial revisions listed below:

In the **ADVERSE REACTIONS/Postmarketing Experience** section, the first and second bullet is modified as follows:

Postmarketing Experience:

- Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with MPA derivatives Mycophenolate mofetil (MMF) is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug (see WARNINGS, ~~Latent Viral Infections~~ Polyomavirus Infections).
- ~~BK virus~~ Polyomavirus associated nephropathy (PVAN), especially due to BK virus infection, 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~~ Polyomavirus Infections).

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. This submission should also include the editorial revisions listed above. 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 pending “Changes Being Effected” (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 which includes the minor editorial changes listed above.

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

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to 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, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, 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 and Medication guide

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
10/27/2010