NOVARTIS

IMPORTANT PRESCRIBING INFORMATION ABOUT MYFORTIC® (mycophenolic acid) delayed-release tablet

Subject: **Important Change in the Myfortic®(mycophenolic acid) Complete Prescribing Information – Postmarketing Reports of Progressive Multifocal Leukoencephalopathy (PML)**

June 2008

Dear Healthcare Professional:
Novartis Pharmaceuticals Corporation would like to inform you that new postmarketing safety information has been added to the WARNINGS and ADVERSE REACTIONS sections of the Myfortic Prescribing Information. Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients treated with mycophenolate mofetil (MMF). MMF is converted to mycophenolic acid (MPA), the active ingredient in Myfortic, following oral or IV administration. The prescribing information revisions are in response to a Food and Drug Administration (FDA) request sent to all marketed MMF and MPA products.

This new important safety information in the Myfortic Prescribing Information includes:

WARNINGS
Infections

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.

ADVERSE REACTIONS

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**).

BACKGROUND INFORMATION ON PML AND CASES REPORTED WITH MMF

PML is a rare, progressive, demyelinating disease of the central nervous system (CNS) that usually leads to death or severe disability. PML is caused by the reactivation of the JC virus, a polyomavirus that resides in latent form in 70-90% of the adult population worldwide. JC virus usually remains latent, typically only causing PML in immunocompromised patients. The factors leading to activation of the latent infection are not fully understood although abnormalities in T-cells have been described as important for reactivation of JC virus and PML. Patients usually present with focal CNS abnormalities and radiographic evidence of white matter disease without mass effect.

PML has been described in transplant patients involving different immunosuppressant medicines. Seventy-five percent of all the PML cases reported in transplant recipients presented subacutely: hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia were the most frequently presented features. PML should be considered in any transplant recipient who develops neurological symptoms prompting consultation with a neurologist as clinically indicated. Other than reducing the amount of immunosuppression in patients who develop PML, there are no interventions that may prevent, treat or stop the progression of PML if disease develops. In transplant patients, reduced immunosuppression may place the graft at risk.

Roche has confirmed that in the Roche worldwide adverse event reporting system, there are currently seventeen cases of PML that are potentially associated with MMF. To date, the Novartis global safety database for MPA has no cases of PML. Because MMF is converted to MPA, both drugs carry the same risk in humans.

Roche has confirmed that ten confirmed and seven possible cases of PML were reported with MMF. Diagnoses were confirmed by detection of JC virus in the cerebrospinal fluid and/or brain biopsy. The indication for MMF use for the ten confirmed cases was as follows: six

solid organ transplant patients (three renal, two lung, and one heart transplant patient) and four systemic lupus erythematosus (SLE) patients. The indication for MMF use for the possible cases was as follows: four solid organ transplant patients (three renal, one heart) and two SLE patients. The seventh possible case was an HIV positive patient who received MMF after being diagnosed with PML and who subsequently died of PML infection. Transplant patients were taking concomitant immunosuppressants including steroids, cyclosporine, tacrolimus and azathioprine; SLE patients were taking concomitant medications including steroids, cyclophosphamide, and cyclosporine.

Of the seventeen cases, seven had a fatal outcome, five improved, and five had an unknown outcome or the event was ongoing at the time of reporting. One of the fatal cases initially improved with no signs of PML at two years after diagnosis and later died of unrelated causes.

At Novartis, patient safety is our highest priority and we are committed to ensuring that health-care professionals continue to have the information necessary to prescribe Myfortic appropriately. Please carefully review this information and the revised labeling including the information for patients section.

The complete revised prescribing information can be found on the Internet at http://www.myfortic.com. Contact Novartis if you have any questions about this information or the safe and effective use of Myfortic.

Healthcare professionals should report all serious adverse events suspected to be associated with the use of Myfortic to Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936 or by phone 1-888-NOW-NOVA(1-888-669-6682), Monday – Friday 8:30am -5:00pm EST.

Alternatively, this information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, or by mail using the form 3500 at http://www.fda.gov/medwatch/index.html.

Important Information About Myfortic® (mycophenolic acid)

Indications:

Myfortic® (mycophenolic acid) delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

Contraindications:

Myfortic is contraindicated in patients with a hypersensitivity to mycophenolate sodium, mycophenolic acid, mycophenolate mofetil, or to any of its excipients.

Important Safety Information:

WARNING

Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma and other neoplasms. Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should use Myfortic® (mycophenolic acid). Patients receiving Myfortic should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Female users of childbearing potential must use contraception. Use of Myfortic during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.

- Patients receiving immunosuppressive regimens involving combinations of drugs, including Myfortic, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.
- Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.
- 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. MMF is metabolized to 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 (See **WARNINGS**, **Infections**).
- Myfortic can cause fetal harm when administered to a pregnant woman. A patient who is planning a pregnancy should not use Myfortic unless she cannot be successfully treated with other immunosuppressant drugs. Risks and benefits of Myfortic and alternative immunosuppressants should be discussed with the patient. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Women of childbearing potential (including pubertal girls and peri-menopausal women) taking Myfortic must receive contraceptive counseling and use effective contraception. The patient should begin using her two chosen contraceptive methods four weeks prior to starting Myfortic therapy, unless abstinence is the chosen method. She should continue contraceptive use during therapy and for six 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.

- Patients receiving Myfortic should be monitored for neutropenia. If neutropenia develops (ANC < 1.3 x 10^3/μL), dosing with Myfortic should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see **DOSAGE AND ADMINISTRATION**).
- Gastrointestinal bleeding (requiring hospitalization) has been reported in *de novo* renal transplant patients (1.0%) and maintenance patients (1.3%) treated with Myfortic (up to twelve months).
- Common adverse events reported in ≥20% of patients receiving Myfortic or mycophenolate mofetil in the twelve-months *de novo* renal study and maintenance renal study, when used in combination with cyclosporine, USP (MODIFIED) and corticosteroids, are listed in Table 4 of the **ADVERSE REACTIONS** section of the Myfortic Prescribing Information

Please see the enclosed Myfortic complete Prescribing Information, which includes additional information for Warnings and Adverse Reactions.

If you have any questions about this information or the safe and effective use of Myfortic, please contact Novartis Pharmaceuticals at 1-888-NOW-NOVA (1-888-669-6682), Monday – Friday 8:30am -5:00pm EST.

Sincerely,

✍ Stephen Cunningham
Chief Scientific Officer, US Clinical Development