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IMPORTANT
DRUG
WARNING

November, 2007

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

Subject: **Important Change in the Myfortic® (mycophenolic acid) Complete Prescribing Information – Use of Myfortic® during pregnancy is associated with increased risks of pregnancy loss and congenital malformations / Change from Pregnancy Category C to Pregnancy Category D**

Dear Healthcare Professional:

Novartis Pharmaceuticals Corporation would like to inform you that use of Myfortic® (mycophenolic acid, MPA) during pregnancy is associated with increased risks of pregnancy loss and congenital malformations. This new important safety information in the Myfortic Prescribing Information includes:

Boxed WARNING and WARNINGS:

- Increased risk of first trimester pregnancy loss and increased risk of congenital malformations, especially external ear and facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney.

PRECAUTIONS/Pregnancy:

- Changed to Pregnancy Category D based on positive evidence of fetal risk associated with MPA observed in postmarketing data and from the United States National Transplantation Pregnancy Registry (NTPR), similar to malformations seen in animal reproductive toxicology studies.

PRECAUTIONS/Information for Patients subsection:

- Informing females of childbearing potential about risks (pregnancy loss / malformations) associated with Myfortic use during pregnancy.
- Requiring that female patients of childbearing potential must receive contraceptive counseling and must use effective contraception.

- Advising that a patient who is planning a pregnancy should not use Myfortic unless she cannot be successfully treated with other immunosuppressant drugs.

The pregnancy category for Myfortic has been changed from Category C (Risk of Fetal Harm Cannot Be Ruled Out) to Category D (Positive Evidence of Fetal Risk). This change is a result of postmarketing data from the United States National Transplantation Pregnancy Registry (NTPR) and additional postmarketing data collected in women exposed to systemic mycophenolate mofetil (MMF) during pregnancy. MMF is converted to 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.

Based on the publication by Sifontis et al (*Transplantation 2006;82:1698-1702, Pregnancy Outcomes in Solid Organ Transplant Recipients with Exposure to Mycophenolate or Sirolimus),* postmarketing data from the NTPR, and MMF worldwide adverse event reporting, use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In December 2006, the NTPR published data from prospective cases where 24 female transplant patients reported 33 pregnancies exposed to MMF-containing regimens. There were 15 spontaneous abortions (45%) and 18 live-born infants. Four of these 18 infants had structural malformations (22%). In postmarketing data (collected from 1995 to 2007) on 77 women exposed to systemic MMF during pregnancy, 25 had spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed offspring had ear abnormalities. Because these post-marketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. Similar structural malformations have been observed in preclinical animal reproductive toxicology studies. Because MMF is converted to MPA, both drugs carry the same teratogenic risk in humans.

During the development of Myfortic, animal reproductive toxicology studies were performed to assess the potential for birth defects. In a teratology study performed with mycophenolate sodium in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly and umbilical hernia. The systemic exposure at this dose represents 0.05 times the clinical exposure at the dose of 1.44 g/day Myfortic. In teratology studies in rabbits fetal resorptions and malformations occurred from 80 mg/kg/day, in the absence of maternal toxicity (dose levels are equivalent to about 0.8 times the recommended clinical dose, corrected for BSA). There are no relevant qualitative or quantitative differences in the teratogenic potential of mycophenolate sodium and mycophenolate mofetil.

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 is obtained. Women of child-bearing 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 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. 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.

National Transplantation Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to immunosuppressant drugs, including Myfortic, a National Transplantation Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-877-955-6877.

At Novartis, patient safety is our highest priority and we are committed to ensuring that healthcare 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.
- Mycophenolic acid 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 patients 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 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.
- Patients receiving Myfortic should be monitored for neutropenia. If neutropenia develops (ANC < 1.3 x $10^3/\mu L$), dosing with Myfortic should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see **DOSAGE AND ADMINISTRATION**).
- 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 12 months).
- Common adverse events reported in ≥20% of patients receiving Myfortic or mycophenolate mofetil in the 12-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, Precautions, and Dosage and Administration.

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

Dr. Stephen Cunningham

Chief Scientific Officer

US Clinical Development