DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-791/S-001

Novartis Pharmaceuticals Corporation
Attention: Sabine Vukelich, PhD
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 October 5, 2007, 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.

We also refer to the Agency's Supplement Request letters issued on August 7 and September 26, 2007.

This "Changes Being Effected" supplemental new drug application provides for the following revisions to the package insert (~~strikethrough~~ indicates deletion, underline indicates addition).

1. The **BOXED WARNING** was modified as follows**:**

WARNING

Immunosuppression may lead to i~~I~~ncreased susceptibility to infection and ~~the~~ possible development of lymphoma and other neoplasms ~~may result from immunosuppression~~. 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.

2. In the **WARNINGS** section, a new subsection titled "**Pregnancy: *Teratogenic Effects*:** Pregnancy Category D" is added as follows:

Pregnancy: *Teratogenic Effects*: Pregnancy Category D

Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant woman. Following oral or IV administration, MMF is metabolized to mycophenolic acid (MPA), the active ingredient in Myfortic and the active form of the drug. Use of Myfortic 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 the National Transplantation Pregnancy Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant patients; 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 postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. These malformations are similar to findings in animal reproductive toxicology studies. For comparison, the background rate for congenital anomalies in the United States is about 3%, and NTPR data show a rate of 4-5% among babies born to organ transplant patients using other immunosuppressive drugs.

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.

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. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. Women using Myfortic at any time during pregnancy should be encouraged to enroll in the National Transplantation Pregnancy Registry.

3. In the **WARNINGS** section, a new subsection titled "**Pregnancy Exposure Prevention"** is added 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 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. (See PRECAUTIONS/Information for Patients and PRECAUTIONS/Drug Interactions/Oral Contraceptives)

~~There are no adequate and well-controlled studies in pregnant women conducted with MPA, Myfortic, or mycophenolate mofetil. Since MPA may cause fetal harm when administered to a pregnant woman, Myfortic should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus.~~

~~Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 1 week prior to beginning therapy. It is recommended that Myfortic therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.~~

~~Effective contraception must be used before beginning Myfortic therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the potential risk to the fetus (see PRECAUTIONS, Pregnancy and Information for Patients).~~

4. The **PRECAUTIONS/Information for Patients** subsection was modified as follows:

- It is recommended that Myfortic be administered on an empty stomach, one hour before or two hours after food intake (see DOSAGE AND ADMINISTRATION).
- In order to maintain the integrity of the enteric coating of the tablet, patients should be instructed not to crush, chew, or cut Myfortic tablets and to swallow the tablets whole.
- Give patients complete dosage instructions and inform them about the increased risk of lymphoproliferative disease and certain other malignancies.
- Inform patients that they need repeated appropriate laboratory tests while they are taking Myfortic.

~~Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving Myfortic. Patients should be given complete dosage instructions and informed of the increased risk of lymphoproliferative disease and certain other malignancies.~~

- Inform women of childbearing potential that use of Myfortic in pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of birth defects, and that they must use effective contraception.
- Discuss pregnancy plans with female patients of childbearing potential.
    - Any female of childbearing potential must use highly effective (two methods) contraception 4 weeks prior to starting Myfortic therapy and continue contraception until 6 weeks after stopping Myfortic treatment, unless abstinence is the chosen method (see WARNINGS/Pregnancy).
    - A patient who is planning a pregnancy should not use Myfortic unless she can not be successfully treated with other immunosuppressant drugs. Risks and benefits of Myfortic and alternative immunosuppressants should be discussed with the patient.

~~Women of childbearing potential should be instructed of the potential risks during pregnancy, and that they should use effective contraception before beginning Myfortic therapy, during therapy, and for 6 weeks after Myfortic has been stopped (see WARNINGS and PRECAUTIONS, Pregnancy).~~

5. The **PRECAUTIONS/Pregnancy** subsection was modified as follows:

Pregnancy ~~Category C~~

Teratogenic Effects: Pregnancy Category D. See **WARNINGS** section.

~~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. There are no adequate and well-controlled studies in pregnant women, Myfortic should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus.~~

~~It is recommended that Myfortic therapy should not be initiated until a negative pregnancy test has been obtained. Patients should be instructed to consult their physician immediately should pregnancy occur.~~

~~Effective contraception must be used before beginning Myfortic therapy, during therapy, and for six weeks following discontinuation of therapy (see WARNINGS).~~

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

In addition, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the revised product labeling and has determined that it contains significant new risk information relating to your drug product. We are hereby requesting that all promotional materials for your drug product that include representations about your drug product be revised to include the new risk information immediately. These revisions should include prominent disclosure of the important new information described in the **BOXED WARNINGS**, **WARNINGS** and **PRECAUTIONS** sections of the revised package labeling. Please submit a written response to this request on or before November 9, 2007, stating whether you intend to comply with this request, by facsimile at (301)796-9878 or by mail to:

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

When 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
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
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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