DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50791/S-014

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals, Inc.
Attention: M. Daniel Gordin, Ph.D.
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gordin:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 1, 2012 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Myfortic® (mycophenolic acid) delayed-release tablets.

We acknowledge receipt of your amendment dated June 8, 2012.

This "Prior Approval" supplemental new drug application proposes changes to the Myfortic labeling to include updated pregnancy information.

The following changes were observed:
(~~strikethrough text~~ = deletions, underlined text = additions)

1. Boxed warning

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS

Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning (see **WARNINGS and PRECAUTIONS**).

Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should ~~use~~ prescribe Myfortic. Patients receiving the 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 (see **WARNINGS and PRECAUTIONS**).

~~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. **WARNINGS**

WARNINGS
(see boxed WARNING)
Embryofetal Toxicity
Myfortic can cause fetal harm when administered to a pregnant female. 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 (see **PRECAUTIONS:Pregnancy).**

Pregnancy Exposure Prevention and Planning

Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning. For recommended pregnancy testing and contraception methods (see **PRECAUTIONS: Pregnancy Exposure Prevention and Planning).**

3. **WARNING/Pregnancy: Teratogenic Effects:** Pregnancy Category D:

~~**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.~~

~~**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).~~

4. **PRECAUTIONS**

PRECAUTIONS

Pregnancy Exposure Prevention and Planning

Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning.

Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause. Menopause is the permanent end of menstruation and fertility. Menopause should be clinically confirmed by a patient's healthcare practitioner. Some commonly used diagnostic criteria include 1) 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or 2) postsurgical from a bilateral oophorectomy.

Pregnancy Testing

To prevent unplanned exposure during pregnancy, females of reproductive potential should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately before starting Myfortic. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient.

In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.

Contraception

Females of reproductive potential taking Myfortic must receive contraceptive counseling and use acceptable contraception (see **Table 4** for acceptable contraception methods). Patients must use acceptable birth control during entire Myfortic therapy, and for 6 weeks after stopping Myfortic, unless the patient chooses abstinence (she chooses to avoid heterosexual intercourse completely).

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**).

Table 4 Acceptable Contraception Methods for Females of Reproductive Potential
Pick from the following birth control options:

Option 1	• Intrauterine devices (IUDs) • Tubal sterilization • Patient's partner had a vasectomy		
OR			
Option 2	**Hormone Methods** choose 1		**Barrier Methods** choose 1
Choose One Hormone Method *AND* **One Barrier Method**	**Estrogen and Progesterone** Oral Contraceptive Pill Transdermal patch Vaginal ring **Progesterone-only** Injection Implant	*AND*	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge Male condom Female condom
OR			
Option 3	**Barrier Methods** choose 1		**Barrier Methods** choose 1
Choose One Barrier Method from each column	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge	*AND*	Male condom Female condom

(must choose two methods)			

Pregnancy Planning

For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of Myfortic should be discussed with the patient.

Gastrointestinal Disorders

Gastrointestinal bleeding (requiring hospitalization) has been reported in de novo renal transplant patients (1.0%) and maintenance patients (1.3%) treated with Myfortic® (mycophenolic acid) (up to 12 months). Intestinal perforations, gastrointestinal hemorrhage, gastric ulcers and duodenal ulcers have rarely been observed. Most patients receiving Myfortic were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with Myfortic. Because MPA derivatives have been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, Myfortic should be administered with caution in patients with active serious digestive system disease (**see ADVERSE REACTIONS**).

Patients with Renal Impairment

Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) may present higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG.

In the de novo study, 18.3% of Myfortic patients versus 16.7% in the mycophenolate mofetil group experienced delayed graft function (DGF). Although patients with DGF experienced a higher incidence of certain adverse events (anemia, leukopenia, and hyperkalemia) than patients without DGF, these events in DGF patients were not more frequent in patients receiving Myfortic compared to mycophenolate mofetil. No dose adjustment is recommended for these patients; however, such patients should be carefully observed (**see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION**).

Concomitant Medications

In view of the significant reduction in the AUC of MPA by cholestyramine when administered with mycophenolate mofetil, caution should be used in the concomitant administration of Myfortic with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy (**see PRECAUTIONS, Drug Interactions**).

Patients with HGPRT Deficiency

On theoretical grounds, because Myfortic is an IMPDH Inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Immunizations

During treatment with Myfortic, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (**see PRECAUTIONS, Drug Interactions, Live Vaccines**).

Information for Patients

See Medication Guide

- Inform females of reproductive potential that use of Myfortic during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, and advise them as to the appropriate steps to manage these risks, including that they must use acceptable contraception (see **WARNINGS: Embryofetal Toxicity, PRECAUTIONS: Pregnancy Exposure Prevention and Planning).**
- Discuss pregnancy testing, pregnancy prevention and planning with females of reproductive potential. In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.
- Females of reproductive potential must use acceptable birth control during entire Myfortic therapy and for 6 weeks after stopping Myfortic, unless the patient chooses to avoid heterosexual intercourse completely (abstinence) (see **PRECAUTIONS: Pregnancy Exposure Prevention and Planning, Table 4)**.
- For patients who are considering pregnancy, discuss appropriate alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of Myfortic should be discussed with the patient.
- 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.
- Advise patients that they should not breastfeed during Myfortic therapy.

- ~~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.~~

5. **PRECAUTIONS/Oral Contraceptives**

Oral Contraceptives*:* ~~Given the different metabolism of Myfortic and oral contraceptives, no drug interaction between these two classes of drug is expected. However, I~~In a drug-drug interaction study, mean levonorgesterol AUC was decreased by 15% when coadministered with mycophenolate mofetil. ~~Therefore, it is recommended that oral contraceptives are coadministered with Myfortic with caution and additional birth control methods be considered (see PRECAUTIONS, Pregnancy).~~ Although Myfortic may not have any influence on the ovulation-suppressing action of oral contraceptives it is recommended to co-administer Myfortic with hormonal contraceptives, (e.g. birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods must be used. (see **PRECAUTIONS: Pregnancy Exposure Prevention and Planning).**

6. **PRECAUTIONS/Pregnancy**

Pregnancy

~~Teratogenic Effects:~~ Pregnancy Category D. (See **WARNINGS)**

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 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 animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. 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.

Risks and benefits of Myfortic should be discussed with the patient. When appropriate, consider alternative immunosuppressants with less potential for embryofetal toxicity. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. For those females using Myfortic at any time during

pregnancy and those becoming pregnant within 6 weeks of discontinuing therapy, the healthcare practitioner should report the pregnancy to the Mycophenolate Pregnancy Registry (1-800-617-8191). The healthcare practitioner should strongly encourage the patient to enroll in the pregnancy registry. The information provided to the registry will help the healthcare community better understand the effects of mycophenolate in pregnancy.

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 1995-2007) on 77 females 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. There are no relevant qualitative or quantitative differences in the teratogenic potential of mycophenolate sodium and mycophenolate mofetil.

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).

7. **PRECAUTIONS/Postmarketing Experience**:

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.

Congenital disorder: Embryofetal toxicity: Congenital malformations and an increased incidence of first trimester pregnancy loss have been reported following exposure to mycophenolate mofetil (MMF) during pregnancy (see **PRECAUTIONS: Pregnancy**).

Infections: 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, Polyomavirus Infections**). Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with MPA derivatives (see **WARNINGS, Polyomavirus Infections**).

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

Hematologic: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA derivatives in combination with other immunosuppressive agents (see **WARNINGS)**.

Dermatologic: Cases of rash have been reported in patients treated with MPA derivatives.

8. **Medication Guide**

Reference of "healthcare provider" replaced with "doctor" throughout the medication guide.

What is the most important information I should know about Myfortic?

Myfortic can cause serious side effects including:

- ~~**Possible**~~ **Increased risk of loss of pregnancy (miscarriage) and higher risk of birth defects.** ~~Women~~ Females who take Myfortic during pregnancy, have a higher risk of ~~losing a pregnancy (~~miscarriage~~)~~ during the first ~~three~~ 3 months (first trimester), and a higher risk that their baby will be born with birth defects.

  If you are a female who can ~~and are able to~~ become pregnant:

  - Your ~~healthcare provider~~ doctor must talk with you about ~~effective~~ acceptable birth control methods (contraceptive counseling) while taking Myfortic.
  - You should have one pregnancy test immediately before starting Myfortic and another pregnancy test 8 to 10 days later. Pregnancy tests should be repeated during routine follow-up visits with your doctor. Talk to your doctor about the results of all of your pregnancy tests.
  - You must use acceptable birth control during your entire Myfortic therapy and for 6 weeks after stopping Myfortic, unless at anytime you choose to avoid sexual intercourse (abstinence) with a man completely. Myfortic decreases blood levels of the hormones in birth control pills that you take by mouth. Birth control pills may not work as well while you take Myfortic and you could become pregnant. If you decide to take birth control pills while using Myfortic you must also use another form of birth control. Talk to your doctor about other birth control methods that can be used while taking Myfortic.

  If you plan to become pregnant, talk with your doctor. Your doctor will decide if other medicines to prevent rejection may be right for you.

- **If you become pregnant while taking Myfortic do not stop taking Myfortic. Call your doctor right away.** In certain situations, you and your doctor may decide that taking Myfortic is more important to your health than the possible risks to your unborn baby.

- You and your doctor should report your pregnancy to

- Mycophenolate Pregnancy Registry (1-800-617-8191)

The purpose of this registry is to gather information about the health of you and your baby.

- You should have a negative pregnancy test within 1 week before starting Myfortic therapy.
- You must use two different types of effective birth control at the same time, for 4 weeks before you start taking Myfortic, during your entire Myfortic therapy, and for 6 weeks after stopping Myfortic, unless you choose to avoid sexual intercourse completely (abstinence). Myfortic decreases blood levels of the hormones in the birth control pills that you take by mouth. Birth control pills may not work as well while you are taking Myfortic, and you could get pregnant.
- If you plan to become pregnant, talk with your healthcare provider. Your healthcare provider will decide if other medicines to prevent rejection may be right for you. In certain situations, you and your doctor may decide that taking Myfortic is more important to your health than the possible risks to your unborn baby.
- **If you get pregnant while taking Myfortic, do not stop taking Myfortic. Call your healthcare provider right away.** You and your healthcare provider should report any cases of pregnancy to:
  - FDA MedWatch at 1-800-FDA-1088
  - Novartis Drug Safety at 1-888-669-6682

Talk to your healthcare provider about joining the National Transplantation Pregnancy Registry at: 1-877-9556877

What is Myfortic?

Myfortic is a prescription medicine given to prevent rejection (antirejection medicine) in people who have received a kidney transplant. Rejection is when the body's immune system senses the new organ as "foreign" and attacks it.

Myfortic is used with other medicines containing cyclosporine (Sandimmune®, Gengraf®, and Neoral®) and corticosteroids. These medicines work together to help prevent rejection to your transplanted kidney. Myfortic can be used to prevent rejection in children who are 5 years or older and are stable after having a kidney transplant. It is not known if Myfortic is safe and works in children younger than 5 years. It is not known how Myfortic works in children who have just received a new kidney transplant.

What should I tell my doctor before I start taking Myfortic?

Tell your healthcare provider about all of your medical conditions, including if you:

- **have any digestive problems, such as ulcers**
- **plan to receive any vaccines.** You should not receive live vaccines while you take Myfortic. Some vaccines may not work as well during treatment with Myfortic.

- **have Lesch-Nyhan or Kelley-Seegmiller syndrome or another rare inherited deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT).** You should not take Myfortic if you have one of these disorders.
- **are pregnant or planning to become pregnant**. **See "What is the most important information I should know about Myfortic"**
- **are breastfeeding or plan to breastfeed.** It is not known if Myfortic passes into breast milk. You and your ~~healthcare provider~~ doctor will decide if you will take Myfortic or breast feed. ~~You should not do both without first talking to your healthcare provider~~.

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

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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 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, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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.

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, please contact Hyun J. Son Pharm.D., Safety Regulatory Project Manager, at (301)796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D., MPH
Deputy Director for Safety
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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
06/22/2012