DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50791/S-005

SUPPLEMENT APPROVAL

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

Dear Ms. Bryan:

Please refer to your Supplemental New Drug Application (sNDA), submitted and received December 23, 2008, 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 amendments dated:

March 26, 2009	August 5, 2009	August 9, 2012
April 10, 2009	May 17, 2010	September 19, 2012
May 11, 2009	February 1, 2012	
July 13, 2009	July 13, 2012	

This supplemental new drug application provides for a proposed risk evaluation and mitigation strategy (REMS) for Myfortic® (mycophenolic acid).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS, if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated September 4, 2008.

Pursuant to 505-1(f)(1), we have determined that elements necessary to assure safe use are required as part of a REMS to mitigate the increased risk of first trimester pregnancy loss and congenital malformation associated with exposure to mycophenolate during pregnancy listed in the labeling. The elements to assure safe use will help to prevent unplanned pregnancy and minimize fetal exposure to mycophenolate by informing prescribers and females of reproductive potential about the increased risk of first trimester pregnancy loss and congenital malformation associated with exposure to mycophenolate during pregnancy and the importance of pregnancy prevention and planning, and collecting information on pregnancy outcomes through the Mycophenolate Pregnancy Registry.

Your proposed REMS, submitted on August 9, 2012, along with revisions outlined in the September 19, 2012 correspondence and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of section 505-1(f)(8) could result in enforcement action.

This REMS will use a single shared system for the elements to assure safe use. The individual sponsors who are part of the single shared system are collectively referred to as "mycophenolate sponsors." This single shared system, known as the Mycophenolate REMS program, includes the products listed in Appendix 1. Other products may be added in the future if additional NDAs or ANDAs are approved.

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

The REMS assessment plan should include, but is not limited to, the following:

1. With regard to the assessment of the Medication Guide:

   i. An evaluation of patients' understanding of the serious risks of mycophenolate.
   ii. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
   iii. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

2. With regard to the assessment of the REMS material distribution, education, and support services:

   Include in the first assessment only:
   i. The date of REMS launch.
   ii. The date the call center became operational.
   iii. The date the website became operational.
   iv. The date(s) of mailing(s), method(s) of distribution, and number of recipients of the Dear Healthcare Provider (DHCP) Introductory Letter and DHCP Letter for Centers.
   v. The number of mailings returned.
   vi. The sources of the recipient lists.
   vii. A list of all documents included in each mailing
   viii. Any issues encountered in making the mycophenolate REMS operational

Include in all assessments:

ix. The dates and journal citation where the journal information piece appeared (during the reporting period).
x. The numbers of the Mycophenolate REMS Overview for Patients and Your Birth Control Options downloaded from the Mycophenolate REMS website or ordered from the call center.

3. With regard to Prescriber Training:

Include in the first assessment only:

i. The date training became available to individual prescribers.
ii. The number of healthcare providers who prescribed mycophenolate in the 24 months *preceding* the REMS approval, stratified by specialty. Include a description of the database used and methodology for identifying the number of healthcare providers.

Include in all assessments:

iii. The number of healthcare providers who completed the *Prescriber Training Confirmation* form in the Mycophenolate REMS (during the reporting period and cumulative), stratified by prescriber specialty. Provide an analysis comparing the number of healthcare providers who completed the *Prescriber Training Confirmation* form to the estimated total number of healthcare providers prescribing a mycophenolate containing product (see "ii" above).
iv. A summary of the method prescribers used to complete the *Prescriber Training Confirmation* form (i.e., online, phone, fax).
v. The number of healthcare providers who have confirmed training and were actively prescribing mycophenolate during the reporting period (i.e., have written at least one prescription in the time period), stratified by prescriber specialty.
vi. The number of healthcare providers who have prescribed mycophenolate who have not confirmed training (during the reporting period and cumulative).
vii. The number of newly identified prescribers and the number of new prescribers who were sent materials (monthly; during the reporting period).

4. With regard to Center Training:

i. The date training became available to centers (first assessment only).
ii. The total number of centers, stratified by type of center, that confirmed training (during the reporting period and cumulative).
iii. A descriptive summary of how newly confirmed centers incorporated the mycophenolate REMS into their center's practice (as described on the *Center Training Confirmation* form).
iv. Total prescribers confirmed by centers.

5. With regard to Risk of Teratogenicity:

i. The date of the pregnancy registry launch (first assessment only).
ii. The number of patients receiving mycophenolate stratified by age, gender, and other demographics (during the reporting period and cumulatively over time).

iii. An *analysis* of the post-marketing cases of pregnancy reported in association with mycophenolate (during the reporting period and cumulative) with attention to but not limited to:
   a. the number of pregnancy exposures* reported (during the reporting period and cumulative) and stratified by source (spontaneous report, reported via the REMS call center, enrolled in the pregnancy registry), age, and other demographics, and if the prescriber completed the REMS training.
   b. the pregnancy outcome for each exposed pregnancy reported (during the reporting period and cumulative).
   c. the root cause analysis of each pregnancy reported to determine the cause of the pregnancy exposure (during the reporting period and cumulative).

iv. An evaluation of healthcare providers' understanding of teratogenicity associated with mycophenolate.

*All pregnancy exposures reported to the sponsors <u>from any source</u> should be reported and analyzed as part of the REMS assessment. The cases should be linked to allow matching of the cases reported in the Pregnancy Registry to cases in the global safety database.

6. Based on the information submitted, an assessment of and conclusion regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed, including measures that would be taken to increase awareness if surveys of patients or healthcare providers indicate that awareness is not adequate.

7. An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of the REMS are required every 6 months for the first year from the date of initial approval of the REMS and annually thereafter, with the exception of the assessments of the prescriber and patient survey, which will be submitted at 2 years, 4 years, and 7 years.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g) of FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 50791 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g., UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 50791 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 50791
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 50791
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 Hyun J. Son, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1939.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Appendix 1: List of Applications
REMS

Appendix 1: List of Applications

NDA 50722	CellCept® (mycophenolate mofetil) Capsules, 250mg
NDA 50723	CellCept® (mycophenolate mofetil) Tablets, 500 mg
NDA 50758	CellCept® (mycophenolate mofetil hydrochloride for injection) Intravenous, 500 mg/ 20 mL
NDA 50759	CellCept® (mycophenolate mofetil for oral suspension) Oral Suspension, 200 mg/mL
NDA 50791	Myfortic® (mycophenolic acid) Tablet
ANDA 65379	mycophenolate mofetil capsules
ANDA 65410	mycophenolate mofetil capsules
ANDA 65413	mycophenolate mofetil tablets
ANDA 65416	mycophenolate mofetil tablets
ANDA 65451	mycophenolate mofetil tablets
ANDA 65457	mycophenolate mofetil tablets
ANDA 65491	mycophenolate mofetil capsules
ANDA 65520	mycophenolate mofetil capsules
ANDA 65521	mycophenolate mofetil tablets
ANDA 90055	mycophenolate mofetil capsules
ANDA 90111	mycophenolate mofetil capsules
ANDA 90253	mycophenolate mofetil capsules
ANDA 90419	mycophenolate mofetil capsules
ANDA 90456	mycophenolate mofetil tablets
ANDA 90499	mycophenolate mofetil tablets
ANDA 90606	mycophenolate mofetil tablets
ANDA 91249	mycophenolate mofetil tablets
ANDA 91558	mycophenolic acid tablets

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/s/

OZLEM A BELEN
09/25/2012