



NDA 50791/S-022

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Ronald Van Valen
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Van Valen:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 20, 2015, 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 November 6, 2015.

This supplemental new drug application provides for proposed modifications to the approved risk evaluation and mitigation strategy (REMS) for Mycophenolate. This supplement is in response to our April 29, 2015, REMS Modification Notification letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Myfortic (mycophenolic acid) was originally approved on September 25, 2012, and the most recent modification was approved on September 27, 2013. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Myfortic (mycophenolic acid) outweigh its risks we determined that you were required to make the following REMS modifications: include modified and new REMS materials to address the knowledge and behavior gaps identified in the prescriber and patient surveys from the Year 2 REMS assessment, increase exposure of both healthcare providers and patients to the important safe use messages, and reinforce the importance of healthcare provider-patient dialogue. In addition, the following changes to the REMS were also made: modify the goals and remove the Medication Guide as an element of the REMS.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Myfortic (mycophenolic acid) outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance

with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on November 6, 2015, and appended to this letter, is approved. The modified REMS consists of elements to assure safe use and a timetable for submission of assessments of the REMS.

This REMS uses a single, shared system for the elements to assure safe use, and the REMS assessments are jointly completed by the Mycophenolate applicant holders. This shared system, known as the Mycophenolate REMS Program, currently includes the products listed on the FDA REMS website, available at <http://www.fda.gov/remis>. Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS remains the same as that approved on September 25, 2012.

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

1) REMS Program Outreach

- a) For both the *Mycophenolate REMS Dear Healthcare Provider Letters* and the *Mycophenolate REMS Dear Healthcare Provider Letter for Centers*, provide the following:
 - i) Source of recipient lists
 - ii) Date and Number of letters sent electronically
 - iii) Date and Number of hard copy letters sent
 - iv) A list of documents included in the mailings
 - v) Number of letters unopened or returned
- b) Date that the revised materials became available on the website

2) REMS Program Utilization

- a) Prescriber training
 - i) The number of healthcare providers who completed the *Mycophenolate REMS Prescriber Training Confirmation Form* in the Single Shared System (SSS) Mycophenolate REMS (during the reporting period and cumulative), stratified by prescriber specialty. Provide an analysis comparing the number of healthcare providers who completed the *Mycophenolate REMS Prescriber Training Confirmation Form* to the estimated total number of healthcare providers prescribing a mycophenolate containing product
 - ii) A summary of the method prescribers used to complete the *Mycophenolate REMS Prescriber Training Confirmation Form* (i.e., online, phone, fax)
 - iii) 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

- iv) The number of healthcare providers who have prescribed mycophenolate who have not confirmed training (during the reporting period and cumulative).
 - v) The number of newly identified prescribers and the number of new prescribers who were sent materials (monthly; during the reporting period)
 - vi) A description of any activities undertaken during the assessment reporting period to increase training
- b) Center training
- i) The total number of centers, stratified by type of center that confirmed training (during the reporting period and cumulative).
 - ii) A descriptive summary of how newly confirmed centers incorporated the SSS Mycophenolate REMS into their center's practice (as described on the *Mycophenolate REMS Center Training Confirmation Form*).
 - iii) Total prescribers confirmed by centers
- c) Patient demographics
- i) The number of patients receiving mycophenolate stratified by age, gender, and other demographics (during the reporting period and cumulative)
- d) Pregnancy exposures
- i) 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:
 - (1) The number of pregnancy exposures* reported (during the reporting period and cumulative) and stratified by source (spontaneous report, reported via the Mycophenolate REMS Call Center, enrolled in the Mycophenolate Pregnancy Registry), age, and other demographics, and if the prescriber completed the Mycophenolate REMS Training
 - (2) The pregnancy outcome for each exposed pregnancy reported (during the reporting period and cumulative)
 - (3) The root cause analysis of each pregnancy reported to determine the cause of the pregnancy exposure (during the reporting period and cumulative)
 - (4) Results of any follow up from previous years' exposures

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

- 3) Knowledge
- a) An evaluation of healthcare providers' understanding of the increased risks of first trimester pregnancy loss and congenital malformations associated with exposure to mycophenolate during pregnancy, the need to counsel females of reproductive potential on the importance of pregnancy prevention and planning when taking mycophenolate, and the need to report pregnancies to the Mycophenolate Pregnancy Registry.

- b) An evaluation of patients' understanding and awareness of the increased risks of first trimester pregnancy loss and congenital malformations when taking mycophenolate during pregnancy, and the importance of pregnancy prevention and planning when taking mycophenolate.

4) Achievement of REMS goals and objectives

- a) 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

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary; the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

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**

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.

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 this provision in 505-1(f) could result in enforcement action.

Prominently identify any 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/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 50791/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 50791/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 50791/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 50791

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

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 Ms. June Germain, Safety Regulatory Project Manager, at (301) 796-4024.

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

ENCLOSURES:

Content of Labeling
REMS
Appendix 1

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
11/13/2015