



NDA 50791/S-024

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 October 15, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Myfortic® (mycophenolic acid) delayed-release tablets.

This Changes Being Effected supplemental new drug application provides for the following revisions to the **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS** and **USE IN SPECIFIC POPULATIONS** sections of the package insert (additions are noted with underline and deletions are noted with ~~strikethrough~~):

REVISIONS

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----**RECENT MAJOR CHANGES**-----

- | | |
|---|----------------|
| 1. Warnings and Precautions, New or Reactivated Viral Infections (5.6) | 9/2013 |
| <u>Embryofetal Toxicity (5.1)</u> | <u>10/2015</u> |

FULL PRESCRIBING INFORMATION

2. In section **5 WARNINGS AND PRECAUTIONS/5.1 Embryofetal Toxicity** the term “nervous system” is added as follows:

Embryofetal Toxicity

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 and nervous system [see *Use in Specific Populations (8.1)*].

3. In section **6 ADVERSE REACTIONS/6.2 Postmarketing Experience**, the first bullet is revised as follows:

- Congenital malformations including ear, facial, cardiac and nervous system malformations and an increased incidence of first trimester pregnancy loss have been reported following exposure to MMF during pregnancy [see *Boxed Warning, Warnings and Precautions (5.1)*].

4. In section **8 USE IN SPECIFIC POPULATIONS/ 8.1 Pregnancy**, the paragraph titled “**Risk Summary**” is revised as follows:

Following oral or intravenous (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 and nervous system. 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.

5. Minor editorial changes

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

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 and 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 that includes labeling changes 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).

PROMOTIONAL MATERIALS

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, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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
Office of Antimicrobial Products
Division of Transplant and Ophthalmology Products
Center for Drug Evaluation and Research

ENCLOSURE: 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
10/27/2015