DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022257/S-009

SUPPLEMENT APPROVAL
REMS MODIFICATION NOTIFICATION

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 6, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Gilenya (fingolimod).

We acknowledge receipt of your amendments dated September 17, 2012, May 8, 2013, September 9, 2013, September 23, 2013, October 18, 2013, November 14, 2013, January 8, 2014, January 29, 2014, and February 25, 2014.

This "Prior Approval" supplemental new drug application provides for a change in labeling pursuant to a revision to your Core Data Sheet that includes information regarding posterior reversible encephalopathy syndrome and a change in labeling to add the results of PMR 1679-5, an in vitro study to evaluate the potential for fingolimod to inhibit CYP2C8 and for fingolimod-P to inhibit CYP2B6.

APPROVAL & LABELING

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.

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 include 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).

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

The REMS for Gilenya (fingolimod) was originally approved on September 21, 2010, and the most recent REMS modification was approved on May 28, 2013. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

We have become aware of cases of posterior reversible encephalopathy syndrome (PRES) from clinical trials and from spontaneous adverse event reporting that were included in a supplemental NDA (S-009) for Gilenya (fingolimod) and in a periodic safety update report (PSUR #4).

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that your approved REMS for Gilenya (fingolimod) must be modified based on the new information described above to ensure that the benefits of the drug outweigh its risks.

Specifically, PRES should be added to the list of risks identified in the goal of the REMS, and all of your communication plan materials (including your Dear Healthcare Professional Letter, Dear Professional Society letter, Guide to Important Safety Information brochure, and website) that describe the serious risks of Gilenya (fingolimod) should be updated to add the risk of PRES and therefore reflect the labeling changes currently being approved.

The timetable for submission of assessments of the proposed modified REMS may remain the same as that approved on May 28, 2013.

The proposed REMS modification submission should include a new proposed REMS document that shows the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should include an update to the REMS supporting document that includes the rationale for and description of all proposed modifications and any impact the

proposed modifications would have on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

We request that you submit both a Word tracked changes version and a Word clean version of each document, and that you explain in your cover letter the changes proposed in the documents.

Because we have determined that a REMS with the elements described above is necessary to ensure the benefits of Gilenya (fingolimod) outweigh the risks, you must submit a proposed REMS modification within 60 days of the date of this letter, as a supplement to your NDA.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 22527
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22527
PROPOSED REMS MODIFICATION-AMENDMENT

If you do not submit electronically, please send 5 copies of your submission.

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 LCDR Hamet Touré, PharmD MPH, Regulatory Project Manager, at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
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/

WILLIAM H Dunn
04/30/2014