DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022527

NDA APPROVAL

Novartis Pharmaceutical Corporation
Attention: Mara Stiles
Regional Branch Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to your new drug application (NDA) dated December 18, 2009, received December 21, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for GILENYA® (fingolimod) 0.5 mg Capsules.

We acknowledge receipt of your submissions dated June 15, 2009, July 24, 2009, October 5, 2009, January 20, 2010, January 28, 2010, February 3, 2010, February 8, 2010, February 9, 2010, February 11, 2010, February 15, 2010, February 16, 2010 (2), February 18, 2010, February 22, 2010, March 1, 2010, March 4, 2010 (2), March 9, 2010, March 10, 2010, March 11, 2010, March 12, 2010 (3), March 13, 2010, March 15, 2010, March 16, 2010, March 18, 2010 (4), March 19, 2010, March 23, 2010, March 29, 2010 (2), March 30, 2010 (2), March 31, 2010, April 1, 2010, April 2, 2010 (2), April 7, 2010, April 8, 2010 (3), April 20, 2010 (2), April 21, 2010 (3), April 22, 2010, April 23, 2010, April 27, 2010, April 28, 2010 (4), April 29, 2010 (2), May 3, 2010 (3), May 4, 2010, May 11, 2010, May 12, 2010 (4), May 13, 2010 (2), May 17, 2010, May 18, 2010 (2), May 19, 2010, May 20, 2010, May 21, 2010, May 24, 2010 (2), May 25, 2010, May 26, 2010, May 28, 2010 (3), June 1, 2010 (2), June 3, 2010, June 4, 2010, June 8, 2010 (2), June 14, 2010, June 16, 2010 (2), June 17, 2010, June 18, 2010, June 21, 2010, June 22, 2010, June 28, 2010, June 29, 2010 (2), June 30, 2010, July 1, 2010 (2), July 6, 2010, July 7, 2010 (2), July 8, 2010, July 9, 2010, July 20, 2010, July 27, 2010, July 30, 2010 (3), August 6, 2010, August 10, 2010, August 11, 2010, August 13, 2010, August 16, 2010, August 18, 2010, August 25, 2010 (2), August 31, 2010, September 1, 2010, September 3, 2010, September 8, 2010 (2), September 10, 2010, September 13, 2010, September 14, 2010 (2), September 16, 2010, September 17, 2010 (2), September 18, 2010, September 20, 2010 (2), and September 21, 2010.

This new drug application provides for the use of GILENYA® (fingolimod) 0.5 mg Capsules for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of relapses and to delay the accumulation of physical disability.

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

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on September 17, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022527**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth through nine years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients less than 10 years of age with multiple sclerosis is too small.

Additionally, we are deferring submission of your pediatric study for ages 10 through 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1679-1: Deferred pediatric study under PREA: a 24-month, randomized, active-controlled, parallel group study to evaluate the single and multiple dose pharmacokinetics of fingolimod, and the safety and efficacy of multiple doses of fingolimod compared to interferon beta 1-a-intramuscular (Avonex) for the treatment of relapsing-remitting multiple sclerosis. The efficacy portion of this trial should be designed to show superiority of fingolimod over active control.

Final Protocol Submission Date:	December 1, 2011
Study Completion Date:	August 6, 2015
Final Report Submission:	January 1, 2016

Submit the protocol for the study to your IND as a special protocol assessment (SPA), with a cross-reference letter to this NDA. Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute [section 505(o)(3)(A)].

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of adverse effects including eye toxicity, cardiac and vascular toxicity, pulmonary toxicity, seizures, serious and opportunistic infection, malignancies, liver toxicity, adverse maternal, fetal, and infant outcomes in women exposed to fingolimod during pregnancy, and effects on postnatal growth and development in exposed fetuses. In addition, analysis of spontaneous postmarketing adverse events will not be sufficient to identify unexpected serious risks related to the potential for fingolimod to inhibit CYP2C8, and for fingolimod-P to inhibit CYP2B6, or induce CYP450 isoenzymes, and the potential for statins to induce the metabolism of fingolimod by CYP4F2.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1679-2: A postmarketing observational prospective, parallel cohort study in relapsing multiple sclerosis patients to assess the potentially serious risk of: eye toxicity, cardiac and vascular toxicity, pulmonary toxicity, seizures, serious and opportunistic infections, malignancies, liver toxicity and atypical multiple sclerosis relapse. Specific outcomes examined should include, but not be limited to, macular edema, symptomatic bradycardia, second and third degree atrioventricular block, and lymphoma. The two observed cohorts should consist of 1) patients newly prescribed fingolimod and 2) patients receiving another disease modifying therapy. The study population should be representative of patients with relapsing multiple sclerosis who take disease modifying therapies and should include patients with a history of diabetes or other cardiovascular risk factors. The study design should minimize differences between the cohorts by defining the populations in both cohorts so that they will be similar, by ensuring that both cohorts have similar clinical assessments, and by ensuring that patients who discontinue treatment have continued follow-up. In addition, the study protocol should account for duration of exposure, treatment changes, and loss to follow-up. Sample size should be supported by estimates of the rates of the events of interest.

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	January 31, 2011
Study Completion:	May 15, 2020
Final Report Submission:	December 15, 2020

1679-3: Develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the maternal, fetal, and infant outcomes of women exposed to fingolimod during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes will be assessed through at least the first year of life.

In addition, for guidance on how to establish a pregnancy exposure registry, please review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf.

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: December 21, 2010
Study Completion: March 31, 2017
Final Report Submission: October 31, 2017

1679-4: An *in vitro* study to evaluate the potential for fingolimod-P to induce CYP450 isoenzymes.

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: February 1, 2011
Study Completion: September 1, 2011
Final Report Submission: December 1, 2011

1679-5: An *in vitro* study to evaluate the potential for fingolimod to inhibit CYP2C8 and for fingolimod-P to inhibit CYP2B6.

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Study Completion: July 15, 2010
Final Report Submission: October 15, 2010

1679-6: An *in vitro* study to evaluate the potential for statins (e.g. simvastatin, lovastatin) to induce CYP4F2, an enzyme that metabolizes fingolimod.

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: February 1, 2011
Study Completion: September 1, 2011
Final Report Submission: December 1, 2011

1679-7: An integrated summary of safety for Studies FTY720D2301, FTY720D2302, and FTY720D2309 (upon completion of Study FTY720D2309). The summary should include updated exposure and analyses of safety following the format of a 4-month NDA safety update report, for the double-blind portion of the studies (Pool D + FTY7202309) and all studies (Pool E + 2309 double blind and extension).

The timetable you submitted on September 17, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: December 21, 2010
Study Completion: June 30, 2011
Final Report Submission: January 30, 2012

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