

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-527

APPROVAL LETTER



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

- 1679-8: A juvenile rat toxicology study. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of fingolimod on growth, reproductive development, and neurological and neurobehavioral development.

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 Date: October 29, 2011
Final Report Submission: March 31, 2012

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of the potential for the pharmacokinetic interaction of fingolimod with carbamazepine.

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

- 1679-9 A drug interaction clinical trial to evaluate the effect of carbamazepine on fingolimod pharmacokinetics.

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

Final Protocol Submission: February 1, 2011
Trial Completion: April 1, 2012
Final Report Submission: July 1, 2012

Submit all protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports 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, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to have satisfied the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii)

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment in your submission dated September 8, 2010. This commitment is listed below.

1679-10 A prospective, randomized, controlled study of fingolimod 0.5 mg, fingolimod 0.25 mg, and an appropriate control, of at least one year duration, to evaluate the efficacy and safety of the drug.

Final Protocol Submission: September 30, 2011
Study Completion: March 30, 2015
Final Report Submission: July 30, 2015

Submit the clinical protocol to your IND for this product and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to this postmarketing commitment should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for GILENYA (fingolimod) to ensure that the benefits of the drug outweigh the risk of bradyarrhythmia and atrioventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that GILENYA (fingolimod) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of GILENYA (fingolimod). FDA has determined that GILENYA (fingolimod) is a product for which patient labeling could help

prevent serious adverse effects and that has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use GILENYA (fingolimod). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed GILENYA (fingolimod).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on September 17, 2010 and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

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

- a. An evaluation of healthcare providers' (HCPs) and patients' understanding of the serious risks of GILENYA (fingolimod)
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements of the Medication Guide, and corrective actions taken to address noncompliance with 21 CFR 208.24
- d. With regard to assessment of the communication plan:
 - i. The date of product launch and the launch of the communication plan
 - ii. The date(s) of mailing and number of recipients of the Dear Healthcare Professional (DHCP) letter and the Guide to Important Safety Information; Using Gilenya in Patients with Relapsing Forms of Multiple Sclerosis.
 - iii. The number of mailings returned.
 - iv. The sources of the recipient lists
 - v. Periodic summaries of serious adverse event reports of symptomatic and asymptomatic bradyarrhythmia and atrioventricular blocks, infections, macular edema, respiratory effects, hepatic effects, and fetal risk.
 - vi. Periodic summaries of pregnancies in women exposed to fingolimod and maternal and fetal outcomes, including updates from fingolimod pregnancy exposure registry.
- e. 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.
- f. Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate.

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must

include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that 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)(2)(A) of FDCA.

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

**NDA 022527 REMS ASSESSMENT
NEW SUPPLEMENT FOR NDA 022527
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 022527
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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA

2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call LT Hamet Touré, Pharm.D. MPH, Regulatory Project Manager, at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
09/21/2010