

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-527

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
Division of Neurology Products**

NDA/BLA #s: NDA 22-527
Products: Gilenya (fingolimod) 0.5 mg capsules in cartons of 28 capsules for oral use
APPLICANT: Novartis
FROM: Robert Temple, M.D.
DATE: September 21, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Gilenya (fingolimod) to ensure that the benefits of the drug outweigh the risks of bradyarrhythmia and atrio-ventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk. In reaching this determination, we considered the following:

- A. Gilenya (fingolimod) will be approved for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. A review of published studies determined that the median prevalence of MS in North America was 2.0/1,000 persons (range 1.7-2.3)¹. Although other products are available for relapsing remitting multiple sclerosis, Gilenya (fingolimod) is the first product for MS that will be available for oral use. We do not have an estimate of the percentage of such patients who might be treated with Gilenya (fingolimod).

¹ Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohammed M, Chaudhuri AR, Zalutsky R. How common are the “common” neurological disorders? *Neurology* 2007;68:326-337

B. MS is an immune-mediated neurodegenerative disorder that leads to physical disability. Onset is most commonly in early to middle adulthood, but pediatric onset is possible. MS patients may experience weakness of the limbs, impaired ability to walk, visual symptoms including decreased acuity and visual blurring, sensory symptoms including tingling, ataxia, bladder dysfunction, memory loss and impaired attention, depression, and fatigue. MS can rapidly evolve to an incapacitating disease requiring profound lifestyle adjustments.²

C. A 2-year randomized, double-blind, placebo-controlled study was performed in patients with relapsing-remitting MS (RRMS) who had not received any interferon-beta or glatiramer acetate for at least the previous 3 months and had not received any natalizumab for at least the previous 6 months. The annualized relapse rate (primary endpoint) was significantly lower in patients treated with Gilenya (fingolimod) than in patients who received placebo. The key secondary endpoint was the time to 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for patients with baseline EDSS of 5.5) sustained for 3 months. Time to onset of 3-month confirmed disability progression was significantly delayed with Gilenya (fingolimod) treatment compared to placebo.

A 1-year randomized, double-blind, double-dummy, active-controlled (interferon beta-1a, 30 micrograms, intramuscular, once weekly) study was performed in patients with RRMS who had not received any natalizumab in the previous 6 months. Prior therapy with interferon-beta or glatiramer acetate up to the time of randomization was permitted. The annualized relapse rate (primary endpoint) was significantly lower in patients treated with Gilenya (fingolimod) than in patients who received interferon beta-1a IM. The number of new and newly enlarging T2 lesions, a key secondary endpoint, was lower in patients treated with Gilenya (fingolimod) than in patients who received interferon beta-1a IM.

D. The duration of therapy is expected to be chronic, potentially life-long.

E. Initiation of treatment with Gilenya (fingolimod) results in a transient decrease in heart rate and atrioventricular (AV) conduction delays upon first dose. Heart rate decrease starts within an hour and the Day 1 decline is maximal at approximately 6 hours. The mean decrease in heart rate in patients on Gilenya (fingolimod) 0.5 mg at 6 hours after the first dose was approximately 13 beats per minute (bpm). Bradycardia upon first dose was reported in 0.8% of patients receiving Gilenya (fingolimod) 0.5mg and no patients receiving placebo. First-degree AV block after the first dose was reported in 0.1% of patients receiving Gilenya (fingolimod) 0.5 mg and no patients receiving placebo. Second-degree AV block after the first dose was reported in 0.1% of patients receiving Gilenya (fingolimod) 0.5 mg and no patients receiving placebo. Twenty-four-hour Holter monitoring identified AV block, usually Mobitz type I

² Harrison's Principles of Internal Medicine-17th Ed. (2008)

(Wenckebach), in 5% of patients receiving Gilenya (fingolimod) 0.5 mg and 2% of patients receiving placebo. The conduction abnormalities occasionally required specific treatment with atropine or isoproterenol.

Gilenya (fingolimod) causes dose-dependent reduction of peripheral lymphocyte count to 20 - 30% of baseline values. This may increase the risk of infections. Two patients died of herpetic infections during Gilenya (fingolimod) controlled studies in the premarketing database (one disseminated herpes zoster and one herpes simplex encephalitis). Both cases were receiving Gilenya (fingolimod) 1.25 mg and had also received high dose corticosteroid therapy for suspected MS relapse. In MS controlled studies, the overall rate of infections (72%) and serious infections (2%) at the 0.5 mg dose was similar to placebo, but lower respiratory tract infections, bronchitis and pneumonia were more common in Gilenya (fingolimod)-treated patients.

Macular edema with or without visual symptoms has been reported in 0.4 % of patients treated with 0.5 mg Gilenya (fingolimod), occurring predominately in the first 3-4 months of therapy.

In the controlled trials for MS, dyspnea was reported in 5% of patients receiving Gilenya (fingolimod) 0.5mg and 4% of patients receiving placebo. Dose-dependent reductions in Forced Expiratory Volume over one second (FEV1) and diffusing lung capacity of carbon monoxide (DLCO) were observed in patients treated with Gilenya (fingolimod). For DLCO, the reductions from baseline in percent of predicted values at Month 24 were 3.8% for fingolimod 0.5 mg and 2.7% for placebo. The changes in FEV1 appeared to be reversible on treatment discontinuation. There is insufficient information to determine reversibility of the decreased DLCO upon drug discontinuation.

During clinical trials, elevation of liver transaminases to ≥ 3 times the upper limit of normal (ULN) occurred in 9% of patients treated with Gilenya (fingolimod) 0.5 mg as compared to 2% of patients on placebo. Elevations to ≥ 5 times the ULN occurred in 2% of patients on Gilenya (fingolimod) and 1% of patients on placebo.

Fingolimod was teratogenic in the rat at doses of 0.1 mg/kg or higher. The most common fetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. The receptor affected by fingolimod (sphingosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. At the present time it is not known whether cardiovascular malformations will be found in humans. There has been one report of Tetralogy of Fallot.

F. Gilenya (fingolimod) is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Gilenya (fingolimod). 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 serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use, Gilenya (fingolimod).

The elements of the REMS for Gilenya (fingolimod) will be a Medication Guide, a communication plan, and a timetable for the submission of assessments of the REMS.

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/s/

ROBERT TEMPLE
09/21/2010

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 21, 2010

To: Russell Katz, M.D., Director
Division of Neurology Products (DNP)

Thru: Claudia Karwoski, Pharm. D., Director
Division of Risk Management (DRISK)

From: DRISK Fingolimod REMS Review Team

Scientific Lead:

Yasmin Choudhry, M.D., Medical Officer, DRISK

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Subject: Review of the proposed Risk Evaluation and Mitigation
Strategy (REMS)

Drug Name(s): GILENYA (fingolimod HCL)

Indication For the treatment of relapsing forms of multiple sclerosis
(MS) to reduce the frequency of clinical exacerbations and to
delay the accumulation of physical disability

Application Type/Number: NDA 22-527

Applicant/sponsor: Novartis

OSE RCM #: 2010-155

1. EXECUTIVE SUMMARY

This review follows a request from the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Fingolimod.

Fingolimod HCL (Gilenya) is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

The safety concerns related to fingolimod include bradyarrhythmia, including first and second degree atrioventricular blocks, infections, macular edema, respiratory effects, hepatic effects, and fetal effects.

Novartis Pharmaceuticals voluntarily submitted a proposed REMS for fingolimod on December 21, 2009 that included a Medication Guide (MG), a communication plan that includes a Dear Healthcare Professional letter (DHCPL) and a *Guide to Important Safety Information for Prescribers*, and a timetable for submission of REMS assessments. The REMS review team finds the proposed REMS submitted on September 18, 2010, to be acceptable.

2. BACKGROUND

Fingolimod HCL (Gilenya) is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing remitting multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Novartis Pharmaceuticals voluntarily submitted a proposed REMS for fingolimod on December 21, 2009. The proposed REMS includes a Medication Guide (MG), a communication plan, and a timetable for submission of REMS assessments.

During the fingolimod REMS review, DNP and DRISK agreed to convey the safety concerns of high importance such as bradyarrhythmia / atrioventricular blocks, infections, macular edema, respiratory effects, hepatic effects, and fetal risk via the REMS while all safety concerns associated with fingolimod will be addressed via the fingolimod label.

2.1. REGULATORY HISTORY

- The Sponsor submitted the NDA application as a rolling NDA; the first piece was submitted on June 5, 2009, the clinical data for MS was submitted on December 18, 2009, and the remaining application along with the proposed REMS was submitted on December 21, 2009.
- The Agency granted the application priority review on February 18, 2010. The original PDUFA goal date for the review of this application was June 21, 2010.
- A Peripheral and Central Nervous System Drugs Advisory Committee meeting was convened on June 10, 2010 to discuss the fingolimod application. The

Advisory Committee members strongly agreed on the effectiveness of fingolimod for the proposed indication. The advisory panel also agreed that patients treated with fingolimod should be monitored for cardiovascular, pulmonary, ophthalmological, and hepatic function. We refer you to the Advisory Committee transcript for a fuller discussion regarding the specific monitoring recommendations made by the committee.

- The Sponsor submitted a major amendment on April 2, 2010. The Agency issued a review extension due to the major amendment May 14, 2010, and established the new PDUFA goal date of September 21, 2010.

3. MATERIALS REVIEWED

The fingolimod REMS proposal was reviewed for responsiveness to Agency comments communicated to the applicant during the course of this review and for conformance with the Food and Drug Administration Amendments Act of 2007. The following REMS related submissions were reviewed:

- Fingolimod NDA 22-527 REMS submissions # 0003 submitted December 21, 2009; # 0031 submitted March 18, 2010; # 0053 submitted April 20, 2010; # 0070 submitted May 11, 2010; # 0111 submitted July 9, 2010; # 0131 submitted September 13, 2010; REMS materials submission #0118 submitted August 6, 2010; and #0137 submitted September 19, 2010.
- FDA comments dated April 14, 2010; September 2, 2010; and September 15, 2010 (via email).

4. SPONSOR'S PROPOSED PLAN

4.1. GOALS

The REMS goals for Gilenya are:

- To inform healthcare providers about the serious risks of GILENYA (fingolimod) including bradyarrhythmia and atrioventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk.
- To inform patients about the serious risks associated with GILENYA (fingolimod) treatment

Each REMS component is described below and the final formatted REMS is presented in Appendix A.

4.2 REMS ELEMENTS

4.2.1 Medication Guide

A Medication Guide (MG) will be dispensed with each Gilenya prescription as part of the packaging for each product carton in compliance with 21 CFR 208.24.

4.2.2 Communication Plan

Novartis will implement a communication plan to healthcare providers to support implementation of the REMS. The communication plan will target the following healthcare providers:

- Potential prescribers of GILENYA – The targeted HCPs will be compiled from a list of potential prescribers using the membership lists of professional societies and prescription data from currently available products indicated for the treatment of multiple sclerosis.
- Leadership of medical societies including the Consortium of Multiple Sclerosis Centers, the American Academy of Neurology, and the American Neurology Association, as well as medical leadership of the National Multiple Sclerosis Society.

The communication plan includes:

- A Dear Healthcare Professional Letter (DHCPL) (see Appendix B)
- Guide to Important Safety Information: Using Gilenya in Patients with Relapsing Forms of Multiple Sclerosis (see Appendix C)

The Gilenya DHCPL includes information about the approved indication for GILENYA and describes the serious risks of the product; the information and recommendations included are based on relevant sections of the label.

The Gilenya Guide to Important Safety Information includes further detail on the safety information as well as information about appropriate observation and patient counseling.

The DHCPL and the Guide to Important Safety Information will be distributed to the potential prescribers and the professional societies via direct mail, within 60 days of the REMS approval and annually thereafter from REMS approval for a period of 5 years.

4.3 REMS ASSESSMENT

Novartis will submit REMS Assessment to FDA at 18 months, 3 years, and 7 years from the date of REMS approval. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novartis will submit each assessment so that it will be received by the FDA on or before the due date.

4.4 INFORMATION NEED FOR ASSESSMENT OF THE REMS

Information needed for assessment is not a required element of the REMS proposal. However, this information should be addressed in the REMS approval letter and

discussed in the REMS supporting document. Each REMS assessment report will include the following information:

- 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, 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 Provide (DHCP) letter and the Safety Information Guide
 - iii. The number of mailings returned.
 - iv. The sources of the recipient lists
- e. Periodic summaries of serious adverse event reports of symptomatic and nonsymptomatic bradyarrhythmia and atrioventricular blocks, infections, macular edema, respiratory effects, hepatic effects, and teratogenicity
- f. Periodic summaries of pregnancies in women exposed to fingolimod and maternal and fetal outcomes, including updates from fingolimod pregnancy exposure registry.
- g. 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.
- h. Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate

5. CONCLUSION

Novartis' proposed REMS for Gilenya includes a MG, communication plan, and timetable for submission of assessments of the REMS. DRISK/OSE finds the proposed REMS for Gilenya to be acceptable and recommends approval of the REMS.

Appendix A: Gilenya REMS Document

NDA 22- 527

GILENYA™ (fingolimod) 0.5mg capsules

Sphingosine1-phosphate Receptor Modulator

Novartis Pharmaceutical Corporation

One Health Plaza

East Hanover, NJ 07936

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1 Goals

The goals of the GILENYA™ (fingolimod) REMS are:

- To inform healthcare providers about the serious risks of GILENYA (fingolimod) including bradyarrhythmia and atrioventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk.
- To inform patients about the serious risks associated with GILENYA (fingolimod) treatment

2 REMS Elements

2.1 Medication Guide

A Medication Guide will be dispensed with each GILENYA prescription in accordance with 21 CFR 208.24.

Please see appended Medication Guide.

2.2 Communication Plan

Novartis will implement a communication plan to healthcare providers to support implementation of this REMS. The communication plan will include:

1. An Dear Healthcare Professional Letter

This letter includes information about the approved indication for GILENYA and describes the serious risks of the product, including bradyarrhythmia and atrioventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk. The information and recommendations included are based on relevant sections of the Package Insert.

2. Guide to Important Safety Information: Using GILENYA in Patients with Relapsing Forms of Multiple Sclerosis:

This Guide to Important Safety Information will present more detail on the safety information related to bradyarrhythmia and atrioventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk. The Guide to Important Safety Information will include information about appropriate observation and counseling of patients during GILENYA therapy.

The communication plan will target the following healthcare providers:

- Potential prescribers of GILENYA – The targeted HCPs will be compiled from a list of potential prescribers using the membership lists of professional societies and prescription data from currently available products indicated for the treatment of multiple sclerosis.
- Leadership of medical societies including the Consortium of Multiple Sclerosis Centers, the American Academy of Neurology, and the American Neurology Association, as well as medical leadership of the National Multiple Sclerosis Society.

Distribution of the Dear Healthcare Professional Letter and the Guide to Important Safety Information will be via direct mail with the following timeline:

- a) Initial distribution within 60 days of REMS approval
- b) Annually thereafter from approval of the REMS for a period of 5 years

In addition to the direct mailing approach, email or other technologies may be used to distribute materials.

All of the materials described above, and the Medication Guide, will be available on the product website (www.GILENYA.com), the Novartis company website (www.pharma.us.novartis.com), by request through the Sponsor's toll-free information number (1-888-NOW-NOVA or 1-888-669-6682) and through Novartis sales representatives and field-based medical personnel. The Dear Healthcare Professional Letter and the Guide to Important Safety Information will be available on the product website and the Novartis company website for 5 years from the date of launch.

The following materials are part of the REMS and are attached:

- i. Dear Healthcare Professional Letter Guide to Important Safety Information
- ii. Guide to Important Safety Information

3 Timetable for Submission of Assessments

Novartis will submit the REMS assessments to the FDA 18 months, 3 years and 7 years from the date of approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment time interval.

Novartis will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix B: The Dear Healthcare Professional Letter (DHCPL)

IMPORTANT SAFETY INFORMATION

Dear Healthcare Professional:

Novartis Pharmaceuticals Corporation is pleased to inform you that GILENYA[®] (fingolimod) for oral administration has been approved by the US Food and Drug Administration (FDA) for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. GILENYA is a sphingosine 1-phosphate receptor (S1P) modulator. GILENYA blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood to approximately 30% of baseline values. The mechanism by which fingolimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

Novartis in collaboration with FDA developed a risk evaluation and mitigation strategy (REMS) to ensure the benefits of GILENYA outweigh the risks. Please review the full prescribing information (PI) for detailed safety information (see attachments).

Important Information about the Safety of GILENYA

Novartis is providing the following information concerning potential risks to consider when prescribing GILENYA:

Bradycardia and Atrioventricular Block

GILENYA, in controlled studies, was shown to induce a dose-dependent reduction in heart rate and has been associated with atrioventricular (AV) conduction delays including 1st or 2nd degree AV block following administration of the initial dose.

- When beginning treatment with GILENYA, observe all patients for a period of 6 hours for signs and symptoms of bradycardia. Should post-dose bradycardia-related symptoms occur, initiate appropriate management and continue observation until the symptoms have resolved.
- To identify underlying risk factors for bradycardia and AV block, if a recent electrocardiogram (i.e. within 6 months) is not available, obtain one in patients using antiarrhythmics including beta-blockers and calcium channel blockers, those with cardiac risk factors (2nd-degree or higher AV blocks, sick sinus syndrome, prolonged QT interval, ischemic cardiac disease, or congestive heart failure), and those who on examination have a slow or irregular heart beat prior to starting GILENYA.
- After the first dose of GILENYA, the heart rate decrease starts within an hour and is maximal after approximately 5 hours. In clinical studies, the average decrease in heart rate was approximately 13 beats per minute (bpm). Heart rates below 40 bpm were rarely observed. Patients who experienced bradycardia were generally asymptomatic, but some patients experienced mild to moderate symptoms, including dizziness, fatigue, palpitations and chest pain, which resolved within the first 24 hours on treatment. GILENYA has not been studied in patients with sitting heart rate less than 55 bpm nor in patients with arrhythmias requiring treatment with Class Ia (e.g. quinidine,

procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic drugs. Class Ia and Class III antiarrhythmic drugs have been associated with cases of torsades de pointes in patients with bradycardia.

Infections

GILENYA causes a dose dependent reduction in the peripheral lymphocyte count to about 20-30% of baseline values.

- Before initiating treatment with GILENYA, a recent CBC (i.e. within 6 months) should be available.
- Consider suspending treatment with GILENYA if a patient develops a serious infection, and reassess the benefits and risks prior to re-initiation of therapy.
- Patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with GILENYA, following which initiation of treatment with GILENYA should be postponed for one month to allow for full effect of vaccination to occur.
- The use of live attenuated vaccines should be avoided during and for 2 months after treatment with GILENYA because of the risk of infection.

Macular edema

In clinical trials, macular edema occurred in 0.4% of patients who received GILENYA 0.5mg, predominantly within the first 3-4 months. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmologic examination. Macular edema generally improved or resolved with or without treatment after drug discontinuation, but some patients had residual visual acuity loss even after resolution of macular edema.

- An adequate ophthalmologic evaluation should be performed at baseline and 3-4 months after treatment initiation.
- If patients report visual disturbances at any time while taking GILENYA, additional ophthalmologic evaluation should be undertaken.
- Patients who have a history of uveitis or diabetes are at increased risk of macular edema. It is recommended that MS patients with diabetes mellitus or a history of uveitis undergo an ophthalmologic examination prior to initiating GILENYA therapy and have follow-up ophthalmologic evaluations while receiving GILENYA therapy.

Respiratory Effects

Small dose-dependent reductions in forced expiratory volume over one second (FEV1) and Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) were observed in patients treated with GILENYA, as early as 1 month after treatment initiation. The changes in FEV1 appear to be reversible after treatment discontinuation. There is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation.

- Spirometric evaluation of respiratory function and evaluation of diffusion lung capacity of carbon monoxide (DLCO) should be performed during therapy with GILENYA if clinically indicated.

Hepatic Effects

Elevations of liver function tests may occur in patients receiving GILENYA.

- Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before

- initiation of GILENYA therapy.
- Liver enzymes should be monitored in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. GILENYA should be discontinued if significant liver injury is confirmed. Patients with pre-existing liver disease may be at increased risk of developing elevated liver function tests when taking GILENYA.

Fetal Risk

Based on animal studies, GILENYA may cause fetal harm.

- There are no adequate and well-controlled studies of GILENYA in pregnant women
- Women of childbearing potential should be counseled on the potential risk to the fetus and advised to use effective contraception during and for at least 2 months following discontinuation of GILENYA therapy.
- Women who become pregnant while on therapy must be counseled on potential risk to the fetus.
- GILENYA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Registry

Since there are no adequate and well-controlled studies of GILENYA in pregnant women, a pregnancy registry has been established to collect information about the effects of GILENYA during pregnancy.

Physicians are encouraged to register patients who become pregnant while exposed to GILENYA or within 2 months after stopping therapy.

Pregnant women may enroll themselves in the GILENYA pregnancy registry by calling 1-877-598-7237.

Adverse Events

Healthcare providers should report all suspected adverse events associated with the use of GILENYA.

Please contact Novartis Drug Safety & Epidemiology at 1-888-NOW-NOVA (669-6682) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the accompanying complete Prescribing Information and Medication Guide. For more information regarding GILENYA, please contact Novartis Medical Information and Communication at 1-888-NOW-NOVA (669-6682) or visit the website at www.GILENYA.com.

Sincerely,

Medical Director Novartis Pharmaceuticals Corporation

Novartis Pharmaceuticals Corporation

This letter has been reviewed and approved by the FDA as part of the Gilenya (fingolimod) REMS.

Appendix C: Guide to Important Safety Information

Guide to Important Safety Information

Using GILENYA[®] In Patients with Relapsing Forms of Multiple Sclerosis

Novartis in collaboration with the Food and Drug Administration developed a Risk Evaluation Strategy (REMS) to ensure the benefits of Gilenya outweigh the risks. The purpose of this guide is to highlight safety issues and a summary of recommendations healthcare professionals should consider before prescribing Gilenya. Please review the full prescribing information for detailed safety information for Gilenya.

SUMMARY OF RECOMMENDATIONS*

TIMING	RECOMMENDATION
Considerations prior to initiating treatment	<ul style="list-style-type: none"><input type="checkbox"/> Recent (i.e. within 6 months) CBC should be available<input type="checkbox"/> Recent (i.e. within 6 months) transaminase and bilirubin levels should be available<input type="checkbox"/> Patients using antiarrhythmics (including beta-blockers and calcium channel blockers, Class Ia and Class III antiarrhythmics), or with history of 2nd degree or higher AV block, sick sinus syndrome, prolonged QT interval, ischemic cardiac disease or congestive heart failure, heart rate below 55 bpm, or irregular heart beat: Obtain ECG if no recent EKG available (i.e. within 6 months)<input type="checkbox"/> Baseline ophthalmologic examination<input type="checkbox"/> Women of childbearing potential: Counsel on potential for adverse fetal outcomes and need for contraception<input type="checkbox"/> Patients without a history of chicken pox or without vaccination against varicella zoster virus (VZV): Consider serology. If patient is antibody negative, VZV vaccine should be considered.<input type="checkbox"/> Patients who get VZV vaccination should not begin GILENYA treatment for one month.
Treatment initiation (first dose)	<ul style="list-style-type: none"><input type="checkbox"/> Measure baseline pulse and blood pressure just before first dose<input type="checkbox"/> Observe all patients for 6 hours after the first dose<input type="checkbox"/> If patient becomes symptomatic, repeat pulse and blood pressure measurement, assess need for additional monitoring procedures or clinical intervention, and continue observation until the symptoms have resolved.

During treatment	<ul style="list-style-type: none"> <input type="checkbox"/> Instruct patients to report symptoms of infection <input type="checkbox"/> Avoid live attenuated vaccines <input type="checkbox"/> Perform ophthalmologic examination 3-4 months after starting GILENYA, and at any time if patient reports visual disturbances. Perform regular follow-up ophthalmologic evaluations in patients with diabetes mellitus or a history of uveitis <input type="checkbox"/> Counsel women of childbearing potential about the importance of contraception use <input type="checkbox"/> Obtain spirometric evaluation of respiratory function and diffusion lung capacity of carbon monoxide (DLCO) if clinically indicated <input type="checkbox"/> Monitor liver enzymes in patients who develop symptoms suggestive of hepatic dysfunction
After treatment discontinuation	<ul style="list-style-type: none"> <input type="checkbox"/> Instruct patients to report symptoms of infection for up to two months <input type="checkbox"/> If GILENYA is discontinued for more than 14 days, the effects on heart rate and AV conduct may recur on therapy re-initiation <input type="checkbox"/> Counsel women of childbearing potential on need for continuing contraception for 2 months

*Please see the accompanying complete Prescribing Information for more information.

Adverse Events

Healthcare providers should report all suspected adverse events associated with the use of GILENYA. Please contact Novartis Drug Safety and Epidemiology at 1-888-NOW-NOVA (669-6682) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

GILENYA[®] (fingolimod) is a sphingosine 1-phosphate receptor (S1P) modulator indicated for treatment of patients with relapsing forms of multiple sclerosis. GILENYA has been shown to reduce the frequency of clinical exacerbations and delay the accumulation of physical disability in these patients.

Novartis Pharmaceuticals Corporation is providing the following information concerning potential risks to consider when prescribing GILENYA:

IMPORTANT SAFETY INFORMATION

Bradycardia and Atrioventricular Block

GILENYA, in controlled studies, was shown to induce a dose-dependent reduction in heart rate and has been associated with atrioventricular (AV) conduction delays including 1st or 2nd degree AV block following administration of the initial dose.

- When beginning treatment with GILENYA, observe all patients for a period of 6 hours for signs and symptoms of bradycardia. Should post-dose bradycardia-related symptoms occur, initiate appropriate management and continue observation until the symptoms have resolved.
- To identify underlying risk factors for bradycardia and AV block, if a recent electrocardiogram (i.e. within 6 months) is not available, obtain one in patients using antiarrhythmics including beta-blockers and calcium channel blockers, those with cardiac risk factors (2nd-degree or higher AV blocks, sick sinus syndrome, prolonged QT interval, ischemic cardiac disease, or congestive heart failure), and those who on examination have a slow or irregular heart beat prior to starting GILENYA.
- After the first dose of GILENYA, the heart rate decrease starts within an hour and is maximal after approximately (b) (4). In clinical studies, the average decrease in heart rate was approximately 13 beats per minute (bpm). Heart rates below 40 bpm were rarely observed. Patients who experienced bradycardia were generally asymptomatic, but some patients experienced mild to moderate symptoms, including dizziness, fatigue, palpitations and chest pain, which resolved within the first 24 hours on treatment. GILENYA has not been studied in patients with sitting heart rate less than 55 bpm nor in patients with arrhythmias requiring treatment with Class Ia (e.g. quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic drugs. Class Ia and Class III antiarrhythmic drugs have been associated with cases of torsades de pointes in patients with bradycardia.

Infections

GILENYA causes a dose dependent reduction in the peripheral lymphocyte count to about 20-30% of baseline values.

- Before initiating treatment with GILENYA, a recent CBC (i.e. within 6 months) should be available.
- Consider suspending treatment with GILENYA if a patient develops a serious infection, and reassess the benefits and risks prior to re-initiation of therapy.
- Patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with GILENYA, following which initiation of treatment with GILENYA should be postponed for one month to allow for full effect of vaccination to occur.
- The use of live attenuated vaccines should be avoided during and for 2 months after treatment with GILENYA because of the risk of infection.

Macular edema

In clinical trials, macular edema occurred in 0.4% of patients who received GILENYA 0.5mg, predominantly within the first 3-4 months. Some patients presented with blurred vision or decreased visual acuity, but others

were asymptomatic and diagnosed on routine ophthalmologic examination. Macular edema generally improved or resolved with or without treatment after drug discontinuation, but some patients had residual visual acuity loss even after resolution of macular edema.

- An adequate ophthalmologic evaluation should be performed at baseline and 3-4 months after treatment initiation.
- If patients report visual disturbances at any time while taking GILENYA, additional ophthalmologic evaluation should be undertaken.
- Patients who have a history of uveitis or diabetes are at increased risk of macular edema. It is recommended that MS patients with diabetes mellitus or a history of uveitis undergo an ophthalmologic examination prior to initiating GILENYA therapy and have regular follow-up ophthalmologic evaluations while receiving GILENYA therapy.

Respiratory Effects

Small dose-dependent reductions in forced expiratory volume over one second (FEV1) and Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) were observed in patients treated with GILENYA, as early as 1 month after treatment initiation. The changes in FEV1 appear to be reversible after treatment discontinuation. There is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation.

- Spirometric evaluation of respiratory function and evaluation of diffusion lung capacity for carbon monoxide (DLCO) should be performed during therapy with GILENYA if clinically indicated.

Hepatic Effects

Elevations of liver function tests may occur in patients receiving GILENYA.

- Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of GILENYA therapy.
- Liver enzymes should be monitored in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. GILENYA should be discontinued if significant liver injury is confirmed. Patients with pre-existing liver disease may be at increased risk of developing elevated liver function tests when taking GILENYA.

Fetal Risk

Based on animal studies, GILENYA may cause fetal harm.

- There are no adequate and well-controlled studies of GILENYA in pregnant women
- Women of childbearing potential should be counseled on the potential risk to the fetus and advised to use effective contraception during and for at least 2 months following discontinuation of GILENYA therapy.
- Women who become pregnant while on therapy must be counseled on potential risk to the fetus.
- GILENYA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Registry

Since there are no adequate and well-controlled studies of GILENYA in pregnant women, a pregnancy registry has been established to collect information about the effects of GILENYA during pregnancy. Physicians are encouraged to register patients who become pregnant while exposed to GILENYA or within 2 months after stopping therapy.

Pregnant women may enroll themselves in the GILENYA pregnancy registry by calling 1-877-598-7237.

Patient Counseling

Prescribers should inform patients about the benefits and risks of GILENYA before a decision is made to prescribe. Patients should be instructed to read the Medication Guide. Patients should be given an opportunity to discuss the contents of the Medication Guide with their physician or healthcare professional and to obtain answers to any questions they may have.

Patients should especially be counseled on the safety information in the Medication Guide Section "What is the most important information I should know about GILENYA?"

Please see the accompanying complete Prescribing Information for more information.

This Guide to Important Safety Information has been reviewed and approved by the FDA as part of the Gilenya (fingolimod) REMS.

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/s/

KENDRA C WORTHY
09/21/2010

CLAUDIA B KARWOSKI
09/21/2010
concur

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: September 20, 2010

TO: NDA 22-527

THROUGH: Suzanne Barone, Ph. D., Team Leader
Compliance Risk Management and Strategic Problem
Solving Team
Division of Compliance Risk Management and
Surveillance
Office of Compliance

FROM: Kendra Biddick, CSO
Compliance Risk Management and Strategic Problem
Solving Team
Division of Compliance Risk Management and
Surveillance
Office of Compliance

SUBJECT: Office of Compliance review and comment on the risk
evaluation and mitigation strategy (REMS) for Gilenya
(Fingolimod) dated September 9, 2010.

This memo is the Office of Compliance response to the REMS for Gilenya (Fingolimod) submitted by Novartis, Inc. on September 9, 2010.

Background

In 2007, the Food and Drug Administration Amendments Act (FDAAA) granted the FDA authority to require risk evaluation and mitigation strategies (REMS) to help ensure that the benefits of a drug outweigh the risks. FDAAA also gave the FDA additional enforcement tools including misbranding charges and civil penalties for sponsors that do not follow requirements of an approved REMS.

The goals of the REMS are:

- To inform healthcare providers about the serious risks of GILENYA (fingolimod) including bradyarrhythmia and atrio-ventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk.

- To inform patients about the serious risks associated with GILENYA (fingolimod) treatment

The REMS consists of a Medication Guide, a communication plan and a timetable for assessments. The Medication Guide is to be dispensed with each GILENYA (fingolimod) prescription.

The Communication Plan consists of two documents identified in the REMS as: Introductory Letter and Important Safety Information Guide or Safety Information Guide. The actual documents included in the REMS package are identified as follows: Dear Healthcare Professional Letter (entitled Important Safety Information), and the Guide to Important Safety Information; Using Gilenya in Patients with Relapsing Forms of Multiple Sclerosis. These documents will be distributed via direct mail, email or other technologies 60 days from REMS approval and annually thereafter. The Introductory Letter and Safety Information Guide for Gilenya Prescribers will be distributed to potential prescribers of GILENYA (fingolimod) and the leadership of medical societies, including the Consortium of Multiple Sclerosis Centers, the American Academy of Neurology, and the American Neurology Association, as well as medical leadership of the National Multiple Sclerosis Society. These materials will also be available on the product website and the Novartis company website.

The Timetable for submission of assessments is 18 months, 3 years, and 7 years from the date of approval of the REMS.

Comments and Recommendations

The Office of Compliance recommends the following:

The launch of the communication plan is to be within 60 days of the approval of the REMS and is not tied to the launch of the drug. If the drug launch is delayed there is a possibility that the materials will be sent to prescribers but the drug will not be available. We recommend that the mailing of the Introductory letter correspond with the date of the launch of the drug instead of the approval of the REMS.

There is no end date for the annual mailings or for the presentation of the Dear Healthcare Professional Letter (entitled Important Safety Information) and the Guide to Important Safety Information; Using Gilenya in Patients with Relapsing Forms of Multiple Sclerosis on the website. These components of the REMS should have an end date.

OC requests that the titles Introductory Letter, Important Safety Information Guide for Gilenya Prescribers, and the Safety Information Guide be replaced in the REMS text with the titles used on the pieces themselves: Dear Healthcare Professional Letter (entitled Important Safety Information), and Guide to Important Safety Information; Using Gilenya in Patients with Relapsing Forms of Multiple Sclerosis, respectively. This will facilitate inspection of the Communication Plan.

The information required for assessments section of the approval letter includes the following, as requested by OC:

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 Letter (entitled Important Safety Information) 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

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/s/

KENDRA A BIDDICK
09/20/2010

SUZANNE BARONE
09/20/2010

*****Pre-decisional Agency Information*****

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 2, 2010

To: Russell Katz, M.D., Director
Division of Neurology Products (DNP)

Through: Claudia Karwoski, Pharm. D., Director
Division of Risk Management (DRISK)

From: DRISK Scientific Lead:
Yasmin Choudhry, M.D., Medical Officer and Risk
Management Analysis

Reviewers:
Marcia Britt, Ph.D., Health Education Reviewer

Subject: Interim REMS Review Comment Set #1

Drug Name (Established Name): GILENYA (fingolimod HCl) for the treatment of relapsing
remitting multiple sclerosis

Therapeutic Class: Sphingosine-1-phosphate receptor modulator

Dosage and Route: 0.5 mg per day oral tablets

Application Type/Number: NDA: 22-527

Applicant: Novartis

OSE RCM #: 2010-155

1 Materials Reviewed

- Fingolimod NDA 22-527 REMS materials submitted # 0111, dated July 9, 2010 (with the new proposed name Gilenya)
 1. Proposed REMS Document
 2. REMS Supporting Document
 3. Dear Healthcare Professional Letter
 4. Using Gilenya in Patients with Relapsing Forms of Multiple Sclerosis

2 Introduction and Background

This interim review provides comments on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Gilenya (fingolimod HCl) submitted by Novartis on May 11 and July 9, 2010.

Novartis voluntarily submitted a REMS proposal for fingolimod on December 21, 2009 that included a Medication Guide (MG), a communication plan with a Dear Healthcare Provider letter (DHCPL), a brochure for prescribers, and a timetable for submission of assessments at 18 months, 3 years and 7 years after approval of the REMS. The REMS was submitted as sequence 003 which along with sequence 004 completed the initial submission of the rolling New Drug Application (NDA).

The first round of FDA comments dated April 14, 2010 (via email) asked the Sponsor to submit the proposed REMS and all REMS materials in WORD format; the subsequent REMS submissions on April 20 and May 11, 2010 from the Sponsor included the revised REMS materials and the prescriber and patient surveys. The July 9, 2010 submission included the new proposed name other revisions to the REMS materials based on revised labeling and post-advisory committee discussions between the sponsor and DNP.

An official REMS notification letter was not sent to the sponsor because the sponsor voluntarily submitted a REMS that included all of the elements the Agency considered necessary to ensure the benefits outweigh the risks.

3 Summary of the REMS Proposal

The REMS proposal for fingolimod includes the following:

1. Goals: The sponsor proposes the following REMS goal:

The goal of the Gilenya (fingolimod) REMS is to educate prescribers and patients about the potential serious risks of Gilenya. These risks include bradycardia/bradyarrhythmia, infections, macular edema, and teratogenicity.

2. A Medication Guide: The sponsor proposes to package the Medication Guide in the carton and will include the following statement on the carton:
“Dispense with Enclosed Medication Guide”
3. A Communication Plan: The sponsor proposes the following communication materials for targeted prescribers:
 - a. Introductory letter
 - b. Important Safety Information Brochure for Gilenya Prescribers

Novartis plans to distribute the REMS educational materials to the HCPs via direct mail at the REMS approval and then annually; the sponsor plans to post these materials on the company’s website which is not proposed as part of the REMS.

Novartis plans to disseminate the fingolimod letter and the brochure primarily to the neurologists and the leadership of the following medical societies: Consortium of Multiple Sclerosis Centers, the American Academy of Neurology, the American Neurology Association and the National Multiple Sclerosis Society.

4. Timetable for submission of assessment of the REMS submitted no later than 18 months, 3 years, and 7 years following the REMS approval.



The July 9, 2010 submission also included a Draft Protocol Synopsis & Logistical Sheet of the Fingolimod Exposure Registry.

4 Comments and Recommendations for DNP

DRISK concurs with DNP about requiring a REMS with a MG and a communication plan REMS for fingolimod to ensure the benefits of the drug outweigh the risks.

Our understanding is that most safety concerns associated with fingolimod will be addressed via the fingolimod label, while the safety concerns of high importance such as those in the warnings and precautions sections of the draft label (bradycardia, bradyarrhythmia and atrio-ventricular blocks, infections, macular edema, respiratory

effects, hepatic effects, blood pressure effects, and teratogenicity) will additionally be conveyed to the prescribers via the REMS communication materials.

Below are our recommendations on the proposed REMS and REMS materials based upon the 8-17-10 draft label. Any additional revisions to the label may warrant modifications to the letter and brochure. We defer to DNP regarding the targeted audience for the REMS communication plan. Further revisions to the proposed REMS will be necessary if you believe additional specialties or professional societies should be targeted. We also recommend DNP review the DHCPL and the brochure for accuracy of information.

Please let us know if you would like a meeting to discuss any of our comments prior to sending to the Applicant. Please request that the Sponsor respond to these comments and questions by September 4, 2010.

We agree with the required post marketing study to study the population that was excluded from the completed clinical trials. The Division of Epidemiology has conducted a separate review of this protocol synopsis.

Comments and Questions for the Sponsor:

1. See Appendix C for the tracked changes version of the Proposed REMS that correspond to the comments below. Some of the details that have been removed from the proposed REMS are more appropriate for the REMS Supporting Document.
2. **REMS Goals:** Revise your REMS goals as follows:
 - To inform healthcare providers about:
 - The serious risks of Gilenya (fingolimod) including bradycardia, bradyarrhythmia and atrio-ventricular block, infections, macular edema, respiratory effects, hepatic effects, blood pressure effects, and teratogenicity.
 - To inform patients about the serious risks associated with Gilenya (fingolimod) treatment.
3. **Medication Guide:**
 - a. Your Medication Guide distribution plan is acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document.
 - b. See our editorial comments on this section of the proposed REMS (see Appendix C).
 - c. Comments on the Medication Guide will follow separately.

4. Communication Plan:

- a. Your communication plan materials must include information about the blood pressure effects, the respiratory effects, and the hepatic effects as described in the current draft label.
- b. See Appendix A for our revisions to the Introductory Letter
 - Your letter and brochure should be disseminated to the targeted audience within 60 days of the approval of the REMS and then annually from the date of approval. We have made these revisions in proposed REMS document (see Appendix C).
- c. See Appendix B for our revisions to the brochure.
- d. The letter and brochure may need to undergo additional revisions to reflect the most recent labeling changes.

5. Timetable for Assessment of the REMS:

Your proposed timetable for submission of REMS assessment at 18 months, 3 years, and 7 years is acceptable. See our editorial comments on this section of the proposed REMS (see Appendix C).



7. General Comments:

- a. Resubmission instructions: Submit your revised proposed REMS with attached materials and the REMS Supporting Document. Provide a WORD version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

*****Pre-decisional Agency Information*****

- b. Format Request: Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single WORD document. 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 be in a single WORD document.
- c. Consider these comments interim comments. You will receive additional comments on your proposed REMS, REMS materials, and REMS supporting document as we continue our review of the application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22527	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	FINGOLIMOD HCL ORAL CAPSULES

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/s/

YASMIN A CHOUDHRY
09/02/2010
Fingolimod REMS interim comments #1

CLAUDIA B KARWOSKI
09/02/2010
concur