Initial REMS approval: 09/2010

Most Recent Modification: 02/2012

NDA 22- 527

GILENYA™ (fingolimod) 0.5mg capsules

Sphingosine 1-phosphate Receptor Modulator

Novartis Pharmaceuticals Corporation

One Health Plaza

East Hanover, NJ 07936

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

1 Goals

The goal of the GILENYA™ (fingolimod) REMS is:

- 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.

2 REMS Elements

2.1 Communication Plan

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

1. A 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 product launch

b) Annually thereafter from product launch for a period of 5 years.

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

The materials described above 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:

(i) Dear Healthcare Professional [Letter]

(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 initial approval of the REMS (September 21, 2010). 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.

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?"

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.

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

Please see the accompanying complete Prescribing Information for more information.

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

Reference ID: 3087002

SUMMARY OF RECOMMENDATIONS*

TIMING	RECOMMENDATION
Considerations prior to initiating treatment	☐ Recent (i.e. within 6 months) CBC should be available ☐ Recent (i.e. within 6 months) liver transaminase and bilirubin levels should be available ☐ Patients using antiarrhythmics (including beta-blockers, 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, congestive heart failure, heart rate below 55 bpm, or irregular heart beat: Obtain ECG if no recent ECG available (i.e. within 6 months) ☐ Baseline ophthalmologic examination ☐ Women of childbearing potential: Counsel on potential for adverse fetal outcomes and need for contraception ☐ 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 ☐ Patients who get VZV vaccination should not begin GILENYA treatment for one month
Treatment initiation (first dose)	☐ Measure baseline pulse and blood pressure just before first dose ☐ Observe all patients for 6 hours after the first dose ☐ 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	☐ Instruct patients to report symptoms of infection ☐ Avoid live attenuated vaccines ☐ 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 ☐ Counsel women of childbearing potential about the importance of contraception use ☐ Obtain spirometric evaluation of respiratory function and diffusion lung capacity for carbon monoxide (DLCO) if clinically indicated ☐ Monitor liver enzymes in patients who develop symptoms suggestive of hepatic dysfunction
After treatment discontinuation	☐ Instruct patients to report symptoms of infection for up to 2 months ☐ If GILENYA is discontinued for more than 14 days, the effects on heart rate and AV conduction may recur on therapy re-initiation ☐ Counsel women of childbearing potential on need for continuing contraception for 2 months

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

GYA-800006

GILENYA™ (fingolimod) les

Guide to Important Safety Information

Using GILENYA™ in Patients with Relapsing Forms of Multiple Sclerosis

GILENYA™ (fingolimod) les

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

Bradyarrhythmia 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 bradyarrhythmia-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 6 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.

Reference ID: 3087002

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 chicken pox 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 Diffusion 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.

GILENYA™ (fingolimod) les

GILENYA™
(fingolimod) 0.5 mg

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:

Bradyarrhythmia 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 bradyarrhythmia-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 (55 beats per minute or less) 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 6 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, reversible, 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.

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- Patients who have a history of uveitis or diabetes are at increased risk of macular edema. MS patients with diabetes mellitus or a history of uveitis should have regular follow-up ophthalmologic evaluations while receiving GILENYA therapy.

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- 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,

Ralph Kern, MD
VP and Head MS Medical Unit
Novartis Pharmaceuticals Corporation

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

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

/s/

RUSSELL G KATZ
03/01/2012