



Initial REMS Approval: 9/2010

Most Recent Modification: 05/2015

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 professionals (HCPs) about the serious risks of GILENYA (fingolimod) including bradyarrhythmia and atrioventricular (AV) block at treatment initiation, infections, macular edema, posterior reversible encephalopathy syndrome (PRES), respiratory effects, liver injury, and fetal risk.

2 REMS Elements

2.1 Communication Plan

Novartis will implement a communication plan to HCPs to support implementation of the REMS. The communication plan includes the:

1. Dear Healthcare Professional Letter (DHCPL)

This letter for prescribers includes information about the approved indication for GILENYA and describes the contraindications for use, the potential serious risks of the product, including bradyarrhythmia and AV block following initiation of treatment, infections, macular edema, posterior reversible encephalopathy syndrome, respiratory effects, liver injury, and fetal risk. It also summarizes the specific recommendations and monitoring related to these risks, based on relevant sections of the revised Package Insert (PI) dated May 2015. The letter also includes information about the GILENYA Pregnancy Registry and encourages prescribers to register patients.

The communication plan will target the following HCPs:

Potential prescribers of GILENYA: The main prescribers of GILENYA are neurologists with experience in treating patients with MS. A list of potential prescribers will be compiled from IMS data providing prescribers of MS drugs and the membership list from the Consortium of Multiple Sclerosis Centers.

2. Dear Professional Society Letter

A letter will be provided to the leadership of the following professional societies: Consortium of Multiple Sclerosis Centers, the American Academy of Neurology, the American Neurology Association, and the National Multiple Sclerosis Society. The content of the letter will be the same as described above for the DHCPL, with the exception of the introduction and a statement describing that the leadership of the society should distribute the letter to their members.

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

This guide will present more detail on the safety information related to bradyarrhythmia and AV block following initiation of treatment, infections, macular edema, posterior reversible encephalopathy syndrome, respiratory effects, liver injury, and fetal risk. It also highlights contraindications for GILENYA, information about each risk and guidance for prescribers related to monitoring and counseling of patients at treatment initiation and during GILENYA therapy. The guide also includes information about the GILENYA Pregnancy Registry and encourages prescribers to register patients.

4. GILENYA REMS website

The GILENYA REMS website (www.gilenyarems.com) will contain the current full Prescribing Information (PI), the DHCPL, the Dear Professional Society Letter, the Guide to Important Safety Information: Using GILENYA in Patients with Relapsing Forms of Multiple Sclerosis, and information about the GILENYA Pregnancy Registry. The GILENYA REMS website will be available until September 21, 2015.

Distribution of the DHCPL, Dear Professional Society Letter and the Guide to Important Safety Information will be sent by direct mail via the US Postal Service regular mail according to the following timeline.

- a) Letters were sent within 60 days of approval of the REMS, on September 21, 2011, and June 26, 2013.
- b) Letters must be sent within 30 days of this REMS modification approval.
- c) Novartis will ensure that all materials listed in or appended to the GILENYA REMS will be available through the GILENYA REMS website. This information will be available on the website until September 21, 2015. All of these materials will also be available by request through Novartis's toll-free information number (1-888-NOW-NOVA or 1-888-669-6682), through Novartis sales representatives and field-based medical personnel.

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

- (i) DHCPL
- (ii) Dear Professional Society Letter
- (iii) Guide to Important Safety Information: Using GILENYA in Patients with Relapsing Forms of Multiple Sclerosis
- (iv) GILENYA REMS website

3 Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA at 18 months, 3 years, 4 years, and 7 years from the initial date of approval of the REMS (September 21, 2010). An additional assessment is also required to be submitted 11 months from the date of approval of the May 2015 REMS Modification Supplement. 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 each assessment time interval. Novartis will submit each assessment so that it will be received by the FDA on or before the due date.

Attachment A: Dear Healthcare Professional Letter (DHCPL)

XX (Month) 2015

IMPORTANT DRUG WARNING

FDA-Required Risk Evaluation and Mitigation Strategy (REMS)

Dear Healthcare Professional:

The purpose of this letter is to inform you of new important safety information for GILENYA® (fingolimod), based on the May 2015 prescribing information.

GILENYA is indicated 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. 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 GILENYA exerts therapeutic effects in MS is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

The overall exposure in the controlled trials was equivalent to 1716 person-years. Approximately 1000 patients have received at least 2 years of treatment with GILENYA 0.5 mg. In all clinical studies, including uncontrolled extension studies, the exposure to GILENYA 0.5 mg is approximately 4119 person-years.

Bradycardia and Atrioventricular (AV) Block

Initiation of GILENYA treatment results in a decrease in heart rate. In controlled studies, GILENYA has also been associated with AV conduction delays, including first or second degree AV block, following initiation of treatment. After the first dose of GILENYA, the heart rate decrease starts within an hour and the Day 1 nadir generally occurs within approximately 6 hours, although the nadir can be observed up to 24 hours after the first dose in some patients. In controlled clinical trials, adverse reactions of symptomatic bradycardia following the first dose were reported in 0.6% of patients receiving GILENYA 0.5 mg, and in 0.1% of patients on placebo. The conduction abnormalities were usually transient and asymptomatic, and resolved within the first 24 hours on treatment, but they occasionally required treatment with atropine or isoproterenol.

Recommendations for first dose monitoring

When beginning treatment with GILENYA:

- All patients should be observed for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of GILENYA.

- Hourly blood pressure and pulse measurements should be obtained during this timeframe.
- All patients should have an electrocardiogram (ECG) prior to the first dose of GILENYA and after the 6 hour observation period.
- Patients with a heart rate < 45 bpm or new onset 2nd degree or higher AV block at 6 hours postdose or patients registering the lowest postdose heart rate at the end of the observation period should be monitored until resolution of the finding.
- In patients experiencing post dose symptomatic bradycardia, continuous ECG monitoring should be instituted along with initiation of appropriate treatment and observation until the symptoms have resolved; if pharmacological intervention is required to treat symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and first dose monitoring procedures should be repeated after the second dose of GILENYA.
- Patients at higher risk of symptomatic bradycardia or bradyarrhythmia due to coexisting medical conditions or certain concomitant medications should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation prior to treatment with GILENYA, and, if treated with GILENYA, should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients with prolonged QTc interval at baseline or during the observation period, or at additional risk for QT prolongation or taking drugs with known risk of torsades de pointes should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients receiving concomitant therapies that slow heart rate or AV conduction should be evaluated with possibility of switching off these drugs prior to initiation of GILENYA. Patients who cannot switch should have overnight observation in a medical facility with continuous ECG monitoring.

Reinitiation of therapy following discontinuation

If GILENYA therapy is discontinued for more than 14 days after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of GILENYA treatment and the same precautions (first dose monitoring) as for initial dosing should apply.

The need for first dose monitoring following treatment interruption varies depending on time on GILENYA prior to treatment interruption, as described below:

Length of treatment with GILENYA prior to interruption in therapy	Length of interruption necessitating first dose monitoring (consecutive days of missed doses)
Up to 2 weeks	1 day or more
3 to 4 weeks	7 days or more
More than 1 month	14 days or more

Contraindications

GILENYA is contraindicated in patients

- with recent (within the last 6 months) myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure
- with a history or presence of Mobitz Type II 2nd or 3rd degree AV block or sick sinus syndrome, unless the patient has a functional pacemaker

- with a baseline QTc interval \geq 500 msec
- receiving treatment with Class Ia or Class III anti-arrhythmic drugs

Infections

GILENYA causes a dose-dependent, reversible sequestration of lymphocytes in lymphoid tissues resulting in a reduction of peripheral blood lymphocyte count to 20% - 30% of baseline values.

- Before initiating treatment with GILENYA, a recent CBC (i.e. within the last 6 months or after discontinuation of prior therapy) should be available.
- Consider suspending treatment with GILENYA if a patient develops a serious infection, and reassess the benefits and risks prior to reinitiation of therapy.
- Serious, life-threatening events of disseminated varicella zoster and herpes simplex infections, including cases of encephalitis and multiorgan failure, have occurred with GILENYA 0.5 mg in the postmarketing setting. One of these events was fatal. Include disseminated herpetic infections in the differential diagnosis of patients who are receiving GILENYA and present with an atypical MS relapse or multiorgan failure.
- Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV before initiating GILENYA. VZV vaccination of antibody negative patients is recommended 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.
- Avoid the use of live attenuated vaccines during and for 2 months after treatment with GILENYA because of the risk of infection.
- When switching to GILENYA from other immune-modulating or immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

Macular Edema

In 2-year, double-blind, placebo-controlled studies in patients with multiple sclerosis, macular edema with or without visual symptoms occurred in 0.5% of patients treated with GILENYA 0.5 mg and 0.4% of patients treated with placebo. Macular edema occurred predominantly during the first 3 to 4 months of therapy. Routine ophthalmological examination detected macular edema in some patients with no visual symptoms. Macular edema generally partially or completely resolved with or without treatment after drug discontinuation. Some patients had residual visual acuity loss even after resolution of macular edema.

- Perform an examination of the fundus including the macula in all patients before starting treatment, again 3-4 months after treatment initiation, and again any time after a patient reports visual disturbances while on GILENYA therapy.

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during GILENYA therapy. In addition to the examination of the fundus including the macula prior to treatment and at 3-4 months after starting treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

Posterior Reversible Encephalopathy Syndrome

There have been rare cases of posterior reversible encephalopathy syndrome (PRES) reported in patients receiving GILENYA. Symptoms reported included sudden onset of severe headache, altered mental status, visual disturbances and seizure. Symptoms of PRES are usually reversible, but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, GILENYA should be discontinued.

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 DLCO should be performed during therapy with GILENYA if clinically indicated.

Liver Injury

- Elevations of liver function tests may occur in patients receiving GILENYA. The majority of elevations occurred within 6-9 months. Recent (i.e. within the 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.

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. Prescribers with an eligible patient, or patients themselves, can contact the Pregnancy Exposure Registry by calling Outcome at 1-877-598-7237, sending an email to gpr@outcome.com or visiting www.gilenyapregnancyregistry.com.

Reporting adverse events

To report all suspected adverse events associated with the use of GILENYA contact:

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

Please see the accompanying complete updated 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,

Cathryn M. Clary, MD
Head, US Clinical Development and Medical Affairs
Novartis Pharmaceuticals Corporation

Attachment B: Dear Professional Society Letter

XX (Month) 2015

IMPORTANT DRUG WARNING

Please disseminate this information to your members

FDA-Required Risk Evaluation and Mitigation Strategy (REMS)

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- ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure
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 - with a baseline QTc interval \geq 500 msec
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- Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV before initiating GILENYA. VZV vaccination of antibody negative patients is recommended 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.
- Avoid the use of live attenuated vaccines during and for 2 months after treatment with GILENYA because of the risk of infection.
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- Perform an examination of the fundus including the macula in all patients before starting treatment, again 3-4 months after treatment initiation, and again any time a patient reports visual disturbances while on GILENYA therapy.
- Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during GILENYA therapy. In addition to the examination of the fundus including the macula prior to treatment and at 3-4 months after starting treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

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Sincerely,

Cathryn M. Clary, MD
Head, US Clinical Development and Medical Affairs
Novartis Pharmaceuticals Corporation

Attachment C: Guide to Important Safety Information

(Note to reviewer: This is a tri-fold brochure that has been submitted in Word format for review.)

(Month) 2015

Guide to Important Safety Information

Using GILENYA® In Patients with Relapsing Forms of Multiple Sclerosis

Novartis Pharmaceuticals Corporation (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. This Guide to Important Safety Information is provided to you as part of the REMS and is revised based on the full prescribing information updated May 2015. 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 (updated May 2015)** for detailed safety information for GILENYA.

SUMMARY OF RECOMMENDATIONS*

TIMING	RECOMMENDATION
<p>Considerations prior to initiating treatment</p>	<ul style="list-style-type: none"> <input type="checkbox"/> GILENYA treatment is contraindicated in patients: <ul style="list-style-type: none"> ▪ with recent (within last 6 months) myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure ▪ with a history or presence of Mobitz Type II 2nd or 3rd degree AV block or sick sinus syndrome, unless patient has a functioning pacemaker ▪ with a baseline QTc interval \geq500 msec ▪ receiving treatment with Class Ia or III anti-arrhythmic drugs <input type="checkbox"/> The first dose of GILENYA should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available <input type="checkbox"/> All patients should have an electrocardiogram (ECG) prior to the first dose of GILENYA and at the end of the observation period <input type="checkbox"/> Recent (i.e. within 6 months or after discontinuation of prior therapy) CBC should be available <input type="checkbox"/> Recent (i.e. within 6 months) liver transaminase and bilirubin levels should be available <input type="checkbox"/> Examination of the fundus including the macula before starting treatment <input type="checkbox"/> Women of childbearing potential: Counsel on potential for adverse fetal outcomes and need for contraception <input type="checkbox"/> Patients without a healthcare professional confirmed history of chicken pox or without documentation of a full course of vaccination against

	<p>varicella zoster virus (VZV) should be tested for antibodies to VZV before initiating GILENYA. If patient is antibody negative, VZV vaccine is recommended.</p> <ul style="list-style-type: none"> <input type="checkbox"/> Patients who get VZV vaccination should not begin GILENYA treatment for one month <input type="checkbox"/> When switching to GILENYA from other immune-modulating or immunosuppressive medications, the duration and mode of action of such substances must be considered when initiating GILENYA to avoid additive immunosuppressive effects.
<p>Treatment initiation (first dose)</p>	<ul style="list-style-type: none"> <input type="checkbox"/> Monitor blood pressure and pulse hourly <input type="checkbox"/> Observe all patients for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of GILENYA <input type="checkbox"/> All patients should have an ECG prior to and after the 6 hour observation period <input type="checkbox"/> Continue observation beyond 6 hours (until resolution) if: <ul style="list-style-type: none"> ▪ the lowest post-dose heart rate is observed at end of the observation period ▪ heart rate is < 45 bpm ▪ new onset of second degree or higher AV block <p>(Refer to full Prescribing Information updated May 2015 for management of patients experiencing symptomatic bradycardia)</p> <ul style="list-style-type: none"> <input type="checkbox"/> Overnight observation in a medical facility with continuous ECG monitoring should be initiated in: <ul style="list-style-type: none"> ▪ Patients at a higher risk for symptomatic bradycardia or bradyarrhythmia due to coexisting medical conditions (refer to full PI) ▪ Patients receiving concurrent therapies that slow heart rate or AV conduction should be evaluated with possibility of switching off these drugs prior to initiation of GILENYA. Patients who cannot switch should have this observation. ▪ Patients with prolonged QTc interval at baseline or during the observation period, or taking drugs with known risk of torsades de pointes or at additional risk for QT prolongation
<p>During treatment</p>	<ul style="list-style-type: none"> <input type="checkbox"/> Monitor blood pressure <input type="checkbox"/> Instruct patients to report symptoms of infection <input type="checkbox"/> Avoid live attenuated vaccines <input type="checkbox"/> Perform an examination of the fundus including the macula in all patients before starting treatment, again 3-4 months after treatment initiation, and again any time after a patient reports visual disturbances while on GILENYA therapy. MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations. <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 for carbon monoxide (DLCO) if clinically indicated <input type="checkbox"/> Monitor liver enzymes in patients who develop symptoms suggestive of hepatic dysfunction <input type="checkbox"/> Continue to be alert to patient reports of cardiac symptoms. Clinical data show effects of GILENYA on heart rate are maximal after first dose. Milder effects on heart rate may persist for, on average, 2-4 weeks after initiation of treatment when heart rate generally returns to baseline.

After treatment discontinuation

- Instruct patients to report symptoms of infection for up to 2 months
- If GILENYA therapy is discontinued for more than 14 days after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of GILENYA treatment and the same precautions (first dose monitoring) as for initial dosing should apply. Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of one day or more. During weeks 3 and 4 of treatment, first dose procedures are recommended after treatment interruption of more than 7 days.
- Counsel women of childbearing potential on need for continuing contraception for 2 months

*Please see the accompanying complete updated full Prescribing Information (updated May 2015) for more information.

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

The overall exposure in the controlled trials was equivalent to 1716 person-years. Approximately 1000 patients have received at least 2 years of treatment with GILENYA 0.5 mg. In all clinical studies, including uncontrolled extension studies, the exposure to GILENYA 0.5 mg is approximately 4119 person-years.

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

IMPORTANT SAFETY INFORMATION

Bradycardia and Atrioventricular (AV) Block

GILENYA, in controlled studies, was shown to induce a reduction in heart rate and has been associated with AV conduction delays including first or second degree AV block following administration of the initial dose. After the first dose of GILENYA, the heart rate decrease starts within an hour and the Day 1 nadir generally occurs within approximately 6 hours, although the nadir can be observed up to 24 hours after the first dose in some patients. In controlled clinical trials adverse reactions of symptomatic bradycardia following the first dose were reported in 0.6% of patients receiving GILENYA 0.5 mg, and in 0.1% of patients on placebo. The conduction abnormalities were usually transient and asymptomatic, and resolved within the first 24 hours on treatment, but occasionally required treatment with atropine or isoproterenol. For these reasons, all patients should be observed for a period of at least 6 hours after the first GILENYA dose for signs and symptoms of bradycardia and AV block.

Recommendations for first dose monitoring

- All patients should be observed for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of GILENYA.
- Hourly blood pressure and pulse measurements should be obtained during this timeframe.
- All patients should have an electrocardiogram (ECG) prior to and at the end of the observation period.

- Patients with a heart rate < 45 bpm or new onset second degree or higher AV block at 6 hours postdose or patients registering the lowest postdose heart rate at the end of the observation period should be monitored until resolution of the finding.
- In patients experiencing postdose symptomatic bradycardia, continuous ECG monitoring should be instituted along with initiation of appropriate treatment and observation until the symptoms have resolved; if pharmacological intervention is required to treat symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and first dose monitoring procedures should be repeated after the second dose of GILENYA.
- Patients at higher risk of symptomatic bradycardia or bradyarrhythmia due to coexisting medical conditions or certain concomitant medications should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation prior to treatment with GILENYA, and, if treated with GILENYA, should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients with prolonged QTc interval at baseline or during the observation period, or at additional risk for QT prolongation or taking drugs with known risk of torsades de pointes should be observed overnight in a medical facility with continuous ECG monitoring.
- Patients receiving concurrent therapies that slow heart rate or AV conduction should be evaluated with possibility of switching off these drugs prior to initiation of GILENYA. Patients who cannot switch should have overnight observation in a medical facility with continuous ECG monitoring.
- Reinitiation of therapy following discontinuation and appropriate monitoring:
If GILENYA therapy is discontinued for more than 14 days after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of GILENYA treatment and the same precautions (first dose monitoring) as for initial dosing should apply. The need for first dose monitoring following treatment interruption varies depending on time on GILENYA prior to treatment interruption, as described below:

Length of treatment with GILENYA prior to interruption in therapy	Length of interruption necessitating first dose monitoring (consecutive days of missed doses)
Up to 2 weeks	1 day or more
3 to 4 weeks	7 days or more
More than 1 month	14 days or more

Contraindications

- recent (within last 6 months) myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure.
- history or presence of Mobitz Type II 2nd or 3rd degree AV block or sick sinus syndrome, unless patient has a functional pacemaker
- baseline QTc interval \geq 500 msec
- treatment with Class Ia or Class III anti-arrhythmic drugs

Infections

GILENYA causes a dose-dependent, reversible sequestration of lymphocytes in lymphoid tissues resulting in a reduction of peripheral blood lymphocyte count to 20%-30% of baseline values.

- Before initiating treatment with GILENYA, a recent CBC (i.e. within 6 months, or after discontinuation of prior therapy) should be available.
- Consider suspending treatment with GILENYA if a patient develops a serious infection, and reassess the benefits and risks prior to reinitiation of therapy.

- Serious, life-threatening events of disseminated varicella zoster and herpes simplex infections, including cases of encephalitis and multiorgan failure, have occurred with GILENYA 0.5 mg in the postmarketing setting. One of these events was fatal. Include disseminated herpetic infections in the differential diagnosis of patients who are receiving GILENYA and present with an atypical MS relapse or multiorgan failure.
- Patients without a healthcare professional confirmed history of chicken pox or without documentation of a full course of vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV before initiating GILENYA. VZV vaccination of antibody negative patients is recommended prior to commencing treatment with GILENYA, following which initiation of treatment with GILENYA should be postponed for 1 month to allow for full effect of vaccination to occur.
- Avoid the use of live attenuated vaccines during and for 2 months after treatment with GILENYA because of the risk of infection.

When switching to GILENYA from other immune-modulating or immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

Macular Edema

In 2-year, double-blind, placebo-controlled studies in patients with multiple sclerosis, macular edema with or without visual symptoms occurred in 0.5% of patients treated with GILENYA 0.5 mg and 0.4% of patients treated with placebo. Macular edema occurred predominantly during the first 3 to 4 months of therapy. Routine ophthalmological examination detected macular edema in some patients with no visual symptoms. Macular edema generally partially or completely resolved with or without treatment after drug discontinuation. Some patients had residual visual acuity loss even after resolution of macular edema.

- Perform an examination of the fundus including the macula in all patients before starting treatment, again 3-4 months after treatment initiation, and again any time after a patient reports visual disturbances while on GILENYA therapy.
- Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during GILENYA therapy. In addition to the examination of the fundus including the macula prior to treatment and at 3-4 months after starting treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

Posterior Reversible Encephalopathy Syndrome

There have been rare cases of posterior reversible encephalopathy syndrome (PRES) reported in patients receiving GILENYA. Symptoms reported included sudden onset of severe headache, altered mental status, visual disturbances, and seizure. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, GILENYA should be discontinued.

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 DLCO should be performed during therapy with GILENYA if clinically indicated.

Liver Injury

- Elevations of liver function tests may occur in patients receiving GILENYA. The majority of elevations occurred within 6-9 months. 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.

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.

Prescribers with an eligible patient, or patients themselves, can contact the Pregnancy Exposure Registry by calling Outcome at 1-877-598-7237, sending an email to gpr@outcome.com or visiting www.gilenyapregnancyregistry.com.

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 full **Prescribing Information (updated May 2015)** for more information.

Reporting 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.

Please read the following materials:

PRESCRIBING
INFORMATION

DEAR HEALTHCARE
PROFESSIONAL
LETTER

DEAR
PROFESSIONAL
SOCIETY LETTER

GUIDE TO
IMPORTANT SAFETY
INFORMATION

GILENYA
PREGNANCY
REGISTRY

Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

In order for Novartis Pharmaceuticals Corporation to communicate certain risks about GILENYA, we have worked with the FDA to develop materials to communicate the risks of:

- Bradyarrhythmia and Atrioventricular (AV) Block
- Infections
- Macular Edema
- Posterior Reversible Encephalopathy Syndrome
- Respiratory Effects
- Liver Injury
- Fetal Risk

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/s/

ALICE HUGHES
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