HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GILENYA™ safely and effectively. See full prescribing information for GILENYA.

GILENYA (fingolimod) capsules
Initial U.S. Approval: 2010

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2)	04/2012
Contraindications (4)	04/2012
Warnings and Precautions (5.1, 5.7)	04/2012

----------INDICATIONS AND USAGE----------

GILENYA is a sphingosine 1-phosphate receptor modulator indicated 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. (1)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose: 0.5 mg orally once daily, with or without food (2)
- First Dose Monitoring:
  - Observe all patients for signs and symptoms of bradycardia for at least 6 hours after first dose with hourly pulse and blood pressure measurement. Obtain ECG prior to dosing and at the end of the observation period.
  - Patients who develop a heart rate <45 bpm, or a new onset 2nd degree or higher atrioventricular block should be monitored until resolution of the finding. Patients at lowest post-dose heart rate at the end of the observation period should be monitored until heart rate increases.
  - In patients experiencing symptomatic bradycardia, begin continuous ECG monitoring until the symptoms have resolved; if pharmacological intervention is required to treat bradycardia, continuous ECG monitoring should continue overnight in a medical facility, and first-dose monitoring procedures should be repeated for the second dose.
  - Patients at higher risk of symptomatic bradycardia or heart block because of a coexisting medical condition or certain concomitant medications should be observed overnight with continuous ECG monitoring (2).
  - Patients with prolonged QTc interval at baseline or during the observation period, or taking drugs with known risk of torsades de pointes should be observed overnight with continuous ECG monitoring (2).

----------DOSAGE FORMS AND STRENGTHS----------

0.5 mg hard capsules. (3)

----------CONTRAINDICATIONS----------

- Recent (within the last 6 months) occurrence of: myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure (4)
- History or presence of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker (4)
- Baseline QTc interval ≥500 ms (4)
- Treatment with Class Ia or Class III anti-arrhythmic drugs (4)

----------WARNINGS AND PRECAUTIONS----------

- Decrease in heart rate and/or atrioventricular conduction after first dose of GILENYA: Monitor patients (2, 5.1)
- Infections: GILENYA may increase the risk of infections. A recent CBC should be available before initiating treatment with GILENYA. Monitor for signs and symptoms of infection during treatment and for two months after discontinuation. Do not start GILENYA treatment in patients with active acute or chronic infections. (5.2)
- Macular edema: Can occur with or without visual symptoms. An ophthalmologic evaluation should be performed before starting GILENYA and at 3-4 months after treatment initiation. Monitor visual acuity at baseline and during routine evaluations of patients. Patients with diabetes mellitus or a history of uveitis are at increased risk and should have regular ophthalmologic evaluations. (5.3)
- Decrease in pulmonary function tests with GILENYA: Obtain spirometry and diffusion lung capacity for carbon monoxide (DLCO) when clinically indicated. (5.4)
- Hepatic effects: GILENYA may increase liver transaminases. Recent liver enzyme results should be available before starting GILENYA. Assess liver enzymes if hepatic injury is suspected. Discontinue GILENYA if significant liver injury occurs (5.5)
- Fetal risk: Women of childbearing potential should use effective contraception during and for 2 months after stopping GILENYA (5.6)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥10% and > placebo): Headache, influenza, diarrhea, back pain, liver transaminase elevations and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Ketoconazole: Monitor patients closely, as GILENYA exposure is increased by 70% during concomitant use with systemic ketoconazole, and risk of adverse reactions is greater. (7, 12.3)
- Vaccines: Avoid live attenuated vaccines during, and for 2 months after stopping GILENYA treatment, due to risk of infection. (5.2, 7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm. Pregnancy registry available. (8.1)
- Pediatric patients: Safety and effectiveness not established. (8.4)
- Hepatic impairment: Monitor patients with severe hepatic impairment closely, as GILENYA exposure is doubled, and risk of adverse reactions is greater. (5.5, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

Recommended Dose

The recommended dose of GILENYA is 0.5 mg orally once daily. Fingolimod doses higher than 0.5 mg are associated with a greater incidence of adverse reactions without additional benefit. GILENYA can be taken with or without food.

First Dose Monitoring

Initiation of GILENYA treatment results in a decrease in heart rate [see *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.2)]. 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.

The first dose of GILENYA should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. In order to assess patient response to the first dose of fingolimod, observe all patients for 6 hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Obtain in all patients an electrocardiogram prior to dosing, and at the end of the observation period.

Additional observation should be instituted until the finding has resolved in the following situations:

- The heart rate 6 hours post-dose is <45 bpm
- The heart rate 6 hours post-dose is at the lowest value post-dose (suggesting that the maximum pharmacodynamic effect on the heart may not have occurred)
- The ECG 6-hours post-dose shows new onset second degree or higher AV block

Should post-dose symptomatic bradycardia occur, initiate appropriate management, begin continuous ECG monitoring, and continue observation until the symptoms have resolved.

Should a patient require pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated after the second dose of GILENYA.

Patients with some pre-existing conditions (e.g., ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, history of symptomatic bradycardia, history of recurrent syncope, severe untreated sleep apnea, AV block, sino-atrial heart block) may poorly tolerate the GILENYA-induced bradycardia, or experience serious rhythm disturbances after the first dose of GILENYA. Prior to treatment with GILENYA, these patients should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation, and, if treated with GILENYA, should be monitored overnight with continuous ECG in a medical facility after the first dose. GILENYA is contraindicated in patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure) *[see Contraindications (4)]*.

Since initiation of GILENYA treatment results in decreased heart rate and may prolong the QT interval, patients with a prolonged QTc interval (>450 msec males, >470 msec females) before dosing or during 6 hour observation, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome), or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility *[see Drug Interactions (7)]*.

Experience with GILENYA is limited in patients receiving concurrent therapy with drugs that slow heart rate or atrioventricular conduction (e.g., beta blockers, heart-rate lowering calcium channel blockers such as diltiazem or verapamil, or digoxin). Because the initiation of GILENYA treatment is also associated with slowing of the heart rate, concomitant use of these drugs during GILENYA initiation may be associated with severe bradycardia or heart block.

The possibility to switch to drugs that do not slow the heart rate or atrioventricular conduction should be evaluated by the physician prescribing these drugs before initiating GILENYA. In patients who cannot switch, overnight continuous ECG monitoring after the first dose is recommended [see Drug Interactions (7)].

Clinical data indicate effects of GILENYA on heart rate are maximal after the first dose although milder effects on heart rate may persist for, on average, 2-4 weeks after initiation of therapy at which time heart rate generally returns to baseline. Physicians should continue to be alert to patient reports of cardiac symptoms.

Re-initiation 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. Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of one day or more, during week 3 and 4 of treatment first dose procedures are recommended after treatment interruption of more than 7 days.

3 DOSAGE FORMS AND STRENGTHS

GILENYA is available as 0.5 mg hard capsules with a white opaque body and bright yellow cap imprinted with "FTY 0.5 mg" on the cap and two radial bands imprinted on the capsule body with yellow ink.

4 CONTRAINDICATIONS

Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization or Class III/IV heart failure

History or presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless patient has a functioning pacemaker

Baseline QTc interval ≥500 ms

Treatment with Class Ia or Class III anti-arrhythmic drugs

5 WARNINGS AND PRECAUTIONS

5.1 Bradyarrhythmia and Atrioventricular Blocks

Because of a risk for bradyarrhythmia and atrioventricular (AV) blocks, patients should be monitored during GILENYA treatment initiation [*see Dosage and Administration (2)*].

Reduction in heart rate

After the first dose of GILENYA, the heart rate decrease starts within an hour. On Day 1, the maximal decline in heart rate generally occurs within 6 hours and recovers, although not to baseline levels, by 8-10 hours post dose. Because of physiological diurnal variation, there is a second period of heart rate decrease within 24 hours after the first dose. In some patients, heart rate decrease during the second period is more pronounced than the decrease observed in the first 6 hours. Heart rates below 40 beats per minute were rarely observed. Adverse reactions of symptomatic bradycardia following the first dose were reported in 0.5% of patients receiving GILENYA 0.5 mg, but in no patient on placebo. Patients who experienced bradycardia were generally asymptomatic, but some patients experienced hypotension, dizziness, fatigue, palpitations, and chest pain that usually resolved within the first 24 hours on treatment.

Following the second dose, a further decrease in heart rate may occur when compared to the heart rate prior to the second dose, but this change is of a smaller magnitude than that observed following the first dose. With continued dosing, the heart rate returns to baseline within one month of chronic treatment.

Atrioventricular blocks

Initiation of GILENYA treatment has resulted in transient AV conduction delays. In controlled clinical trials, adverse reactions of first-degree AV block (prolonged PR interval on ECG) following the first dose were reported in 0.1% of patients receiving GILENYA 0.5 mg, but in no patient on placebo. Second-degree AV blocks following the first dose were also identified in 0.1% of patients receiving GILENYA 0.5 mg, but in no patient on placebo. In a study of 698 patients with available 24-hour Holter monitoring data after their first dose (N=351 on GILENYA 0.5 mg and N=347 on placebo), second-degree AV blocks, Mobitz types I (Wenckebach) and/or II, were reported in 3.7% (N=13) of patients

receiving GILENYA 0.5 mg and 2% (N=7) 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.

Post-marketing experience

In the post-marketing setting, third degree AV block and AV block with junctional escape have been observed during the first-dose six-hour observation period with GILENYA. Isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These events were confounded by concomitant medications and/or pre-existing disease, and the relationship to GILENYA is uncertain. Cases of syncope were also reported after the first dose of GILENYA.

5.2 Infections

Risk of infections

GILENYA causes a dose-dependent reduction in peripheral lymphocyte count to 20 - 30% of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues. GILENYA may therefore increase the risk of infections, some serious in nature [see *Clinical Pharmacology* (12.2)].

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. Because the elimination of fingolimod after discontinuation may take up to two months, continue monitoring for infections throughout this period. Instruct patients receiving GILENYA to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment until the infection(s) is resolved.

Two patients died of herpetic infections during GILENYA controlled studies in the premarketing database (one disseminated primary herpes zoster and one herpes simplex encephalitis). In both cases, the patients were receiving a fingolimod dose (1.25 mg) higher than recommended for the treatment of MS (0.5 mg), and had received high dose corticosteroid therapy for suspected MS relapse. No deaths due to viral infections occurred in patients treated with GILENYA 0.5 mg in the premarketing database.

In MS controlled studies, the overall rate of infections (72%) and serious infections (2%) with GILENYA 0.5 mg was similar to placebo. However, bronchitis and, to a lesser extent, pneumonia were more common in GILENYA-treated patients.

Concomitant use with antineoplastic, immunosuppressive or immune modulating therapies

GILENYA has not been administered concomitantly with antineoplastic, immunosuppressive or immune modulating therapies used for treatment of MS. Concomitant use of GILENYA with any of these therapies would be expected to increase the risk of immunosuppression [see Drug Interactions (7)].

Varicella zoster virus antibody testing/vaccination

As for any immune modulating drug, before initiating GILENYA 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 1 month to allow the full effect of vaccination to occur.

5.3 Macular Edema

In patients receiving GILENYA 0.5 mg, macular edema occurred in 0.4% of patients. 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 on GILENYA therapy, additional ophthalmologic evaluation should be undertaken.

In MS controlled studies involving 1204 patients treated with GILENYA 0.5 mg and 861 patients treated with placebo, macular edema with or without visual symptoms was reported in 0.4% of patients treated with GILENYA 0.5 mg and 0.1% of patients treated with placebo; it occurred predominantly in the first 3-4 months of therapy. 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.

Continuation of GILENYA in patients who develop macular edema has not been evaluated. A decision on whether or not to discontinue GILENYA therapy should include an assessment of the potential benefits and risks for the individual patient. The risk of recurrence after rechallenge has not been evaluated.

Macular edema in patients with history of uveitis or diabetes mellitus

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during GILENYA therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. The rate was approximately 20% in patients with a history of uveitis vs. 0.6% in those without a history of uveitis, in the combined experience with all doses of fingolimod. MS patients with diabetes mellitus or a history of uveitis should undergo an ophthalmologic evaluation prior to initiating GILENYA therapy and have regular follow-up ophthalmologic evaluations while receiving GILENYA therapy. GILENYA has not been tested in MS patients with diabetes mellitus.

5.4 Respiratory Effects

Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in patients treated with GILENYA as early as 1 month after treatment initiation. At Month 24, the reduction from baseline in the percent of predicted values for FEV1 was 3.1% for GILENYA 0.5 mg and 2% for placebo. For DLCO, the reductions from baseline in percent of predicted values at Month 24 were 3.8% for GILENYA 0.5 mg and 2.7% for placebo. 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. In MS controlled trials, dyspnea was reported in 5% of patients receiving GILENYA 0.5 mg and 4% of patients receiving placebo. Several patients discontinued GILENYA because of unexplained dyspnea during the extension (uncontrolled) studies. GILENYA has not been tested in MS patients with compromised respiratory function.

Spirometric evaluation of respiratory function and evaluation of DLCO should be performed during therapy with GILENYA if clinically indicated.

5.5 Hepatic Effects

Elevations of liver enzymes 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.

During clinical trials, 3-fold the upper limit of normal (ULN) or greater elevation in liver transaminases occurred in 8% of patients treated with GILENYA 0.5 mg, as compared to 2% of patients on placebo. Elevations 5-fold the ULN occurred in 2% of patients on GILENYA and 1% of patients on placebo. In clinical trials, GILENYA was discontinued if the elevation exceeded 5 times the ULN. Recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to drug. The majority of elevations occurred within 6-9 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of GILENYA.

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 enzymes when taking GILENYA.

Because GILENYA exposure is doubled in patients with severe hepatic impairment, these patients should be closely monitored, as the risk of adverse reactions is greater [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

5.6 Fetal Risk

Based on animal studies, GILENYA may cause fetal harm. Because it takes approximately 2 months to eliminate GILENYA from the body, women of childbearing potential should use effective contraception to avoid pregnancy during and for 2 months after stopping GILENYA treatment.

5.7 Blood Pressure Effects

In MS clinical trials, patients treated with GILENYA 0.5 mg had an average increase of approximately 2 mmHg in systolic pressure, and approximately 1 mmHg in diastolic pressure, first detected after approximately 1 month of treatment initiation, and persisting with continued treatment. In controlled studies involving 854 MS patients on GILENYA 0.5 mg and 511 MS patients on placebo, hypertension was reported as an adverse reaction in 5% of patients on

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