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, for oral use
Initial U.S. Approval: 2010

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

Indications and Usage (1)	5/2018
Dosage and Administration (2.1, 2.2, 2.3, 2.4, 2.5)	5/2018
Warnings and Precautions (5.1, 5.11)	5/2018
Warnings and Precautions (5.2, 5.3)	12/2017
Warnings and Precautions (5.9)	10/2018

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

GILENYA is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS) in patients 10 years of age and older. (1)

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

- Assessments are required prior to initiating GILENYA (2.1)
- Recommended dosage for adults and pediatric patients (10 years of age and older) weighing more than 40 kg: 0.5 mg orally once-daily, with or without food (2.2, 2.3)
- Recommended dosage for pediatric patients (10 years of age and above) weighing less than or equal to 40 kg: 0.25 mg orally once-daily, with or without food (2.2, 2.3).
- First Dose Monitoring (including re-initiation after discontinuation > 14 days and dose increases):
  - Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of observation period required. (2.4)
  - Monitor until resolution if heart rate < 45 bpm in adults, < 55 bpm in patients aged 12 years and above, or < 60 bpm in pediatric patients aged 10 to below 12 years, atrioventricular (AV) block, or if lowest postdose heart rate is at the end of the observation period. (2.4)
  - Monitor symptomatic bradycardia with ECG until resolved. Continue overnight if intervention is required; repeat first-dose monitoring for second dose. (2.4)
  - Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with known risk of torsades de pointes. (2.4, 7.1)

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

0.25 mg hard capsules (3)
0.5 mg hard capsules (3)

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

- Recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure with hospitalization, or Class III/IV heart failure. (4)
- History 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 msec. (4)
- Treatment with Class Ia or Class III anti-arrhythmic drugs. (4)
- Hypersensitivity to fingolimod or its excipients. (4)

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

- Infections: GILENYA may increase the risk. Obtain a CBC before initiating treatment. Monitor for infection during treatment and for 2 months after discontinuation. Do not start in patients with active infections. (5.2)
- Progressive multifocal leukoencephalopathy (PML): Withhold GILENYA at the first sign or symptom suggestive of PML. (5.3)
- Macular edema: Examine the fundus before and 3–4 months after treatment start. Diabetes mellitus and uveitis increase the risk. (5.4)
- Posterior reversible encephalopathy syndrome (PRES): If suspected, discontinue GILENYA. (5.5)
- Respiratory effects: Evaluate when clinically indicated. (5.6)
- Liver injury: Obtain liver enzyme results before initiation. Closely monitor patients with severe hepatic impairment. Discontinue if significant liver injury occurs. (5.7, 8.6, 12.3)
- Fetal risk: Women of childbearing potential should use effective contraception during and for 2 months after stopping GILENYA. (5.8)
- Severe increase in disability after stopping GILENYA: Monitor for development of severe increase in disability following discontinuation and begin appropriate treatment as needed. (5.9)
- Increased blood pressure (BP): Monitor BP during treatment. (5.10)
- Cutaneous malignancies: Suspicious skin lesions should be evaluated. (5.11)

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

Most common adverse reactions (incidence ≥ 10% and > placebo): Headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. (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----------

- Systemic ketoconazole: Monitor during concomitant use. (7.2, 12.3)
- Vaccines: Avoid live attenuated vaccines during, and for 2 months after stopping GILENYA treatment. (5.2, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 10/2018

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 relapsing forms of multiple sclerosis (MS) in patients 10 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Assessment Prior to Initiating GILENYA

Cardiac Evaluation

Obtain a cardiac evaluation in patients with certain preexisting conditions *[see Warnings and Precautions (5.1)]*.

Prior to starting treatment, determine whether patients are taking drugs that could slow heart rate or atrioventricular conduction *[see Dosage and Administration (2.4) and Drug Interactions (7.5)]*.

Complete Blood Count (CBC)

Review results of a recent CBC *[see Warnings and Precautions (5.2) and Drug Interactions (7.6)]*.

Prior Medications

If patients are taking antineoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with GILENYA *[see Warnings and Precautions (5.2) and Drug Interactions (7.4)]*.

Vaccinations

Test patients for antibodies to varicella zoster virus (VZV) before initiating GILENYA; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with GILENYA *[see Warnings and Precautions (5.2)]*. It is recommended that pediatric patients if possible, complete all immunizations in accordance with current immunization guidelines prior to initiating GILENYA therapy.

2.2 Important Administration Instructions

Patients who initiate GILENYA and those who reinitiate treatment after discontinuation for longer than 14 days require first-dose monitoring. This monitoring is also recommended when the dose is increased in pediatric patients *[see Dosage and Administration (2.4, 2.5)]*.

GILENYA can be taken with or without food.

2.3 Recommended Dosage

In adults and pediatric patients 10 years of age and older weighing more than 40 kg, the recommended dosage of GILENYA is 0.5 mg orally once-daily.

In pediatric patients 10 years of age and older weighing less than or equal to 40 kg, the recommended dosage of GILENYA is 0.25 mg orally once daily.

Fingolimod doses higher than 0.5 mg are associated with a greater incidence of adverse reactions without additional benefit.

2.4 First-Dose Monitoring

Initiation of GILENYA treatment results in a decrease in heart rate, for which monitoring is recommended *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]*. Prior to dosing and at the end of the observation period, obtain an electrocardiogram (ECG) in all patients.

First 6-Hour Monitoring

Administer the first dose of GILENYA in a setting in which resources to appropriately manage symptomatic bradycardia are available. Monitor all patients for 6 hours after the first dose for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement.

Additional Monitoring after 6-Hour Monitoring

Continue monitoring until the abnormality resolves if any of the following are present (even in the absence of symptoms) after 6 hours:

- The heart rate 6 hours postdose is less than 45 bpm in adults, less than 55 bpm in pediatric patients 12 years of age and older, or less than 60 bpm in pediatric patients 10 or 11 years of age
- The heart rate 6 hours postdose is at the lowest value postdose suggesting that the maximum pharmacodynamic effect on the heart may not have occurred
- The ECG 6 hours postdose shows new onset second degree or higher atrioventricular (AV) block.

If postdose symptomatic bradycardia occurs, initiate appropriate management, begin continuous ECG monitoring, and continue monitoring until the symptoms have resolved if no pharmacological treatment is required. If pharmacological treatment is required, continue monitoring overnight and repeat 6-hour monitoring after the second dose.

Overnight Monitoring

Continuous overnight ECG monitoring in a medical facility should be instituted:

- in patients that require pharmacologic intervention for symptomatic bradycardia. In these patients, the first dose monitoring strategy should be repeated after the second dose of GILENYA
- in patients with some preexisting heart and cerebrovascular conditions *[see Warnings and Precautions (5.1)]*
- in patients with a prolonged QTc interval before dosing or during 6-hour observation, or at additional risk for QT prolongation, or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes *[see Warnings and Precautions (5.1), Drug Interactions (7.1)]*
- in patients receiving concurrent therapy with drugs that slow heart rate or atrioventricular conduction *[see Drug Interactions (7.5)]*.

2.5 Monitoring After Reinitiation of Therapy Following Discontinuation

When restarting GILENYA after discontinuation for more than 14 days after the first month of treatment, perform first- dose monitoring, because effects on heart rate and AV conduction may recur on reintroduction of GILENYA treatment *[see Dosage and Administration (2.4)]*. The same precautions (first-dose monitoring) as for initial dosing are applicable. Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of 1 day or more; during weeks 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:

- 0.25 mg hard capsules with an ivory opaque body and cap, with black radial imprint “FTY 0.25mg” on the cap and a black radial band on the capsule body.
- 0.5 mg hard capsules with a white opaque body and bright yellow cap imprinted with “FTY 0.5 mg” on the cap and 2 radial bands imprinted on the capsule body with yellow ink.

4 CONTRAINDICATIONS

GILENYA is contraindicated in patients who have:

- in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization or Class III/IV heart failure
- a 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 *[see Warnings and Precautions (5.1)]*
- a baseline QTc interval ≥ 500 msec

- concomitant treatment with Class Ia or Class III anti-arrhythmic drugs
- had a hypersensitivity reaction to fingolimod or any of the excipients in GILENYA. Observed reactions include rash, urticaria and angioedema upon treatment initiation *[see Warnings and Precautions (5.13)]*.

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 (2.4)]*.

Reduction in Heart Rate

After the first dose of GILENYA, the heart rate decrease starts within an hour. On Day 1, the maximum decline in heart rate generally occurs within 6 hours and recovers, although not to baseline levels, by 8 to 10 hours postdose. 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 in adults, and below 50 beats per minute in pediatric patients occurred rarely. In controlled clinical trials in adult patients, 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. Patients who experienced bradycardia were generally asymptomatic, but some patients experienced hypotension, dizziness, fatigue, palpitations, and/or chest pain that usually resolved within the first 24 hours on treatment.

Patients with some preexisting conditions (e.g., ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, history of symptomatic bradycardia, history of recurrent syncope, severe untreated sleep apnea, AV block, sinoatrial 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.

Since initiation of GILENYA treatment, results in decreased heart rate and may prolong the QT interval, patients with a prolonged QTc interval (> 450 msec adult and pediatric males, > 470 msec adult females, or > 460 msec pediatric 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

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 1 month of chronic treatment. 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 to 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.

Atrioventricular Blocks

Initiation of GILENYA treatment has resulted in transient AV conduction delays. In controlled clinical trials in adult patients, first-degree AV block after the first dose occurred in 4.7% of patients receiving GILENYA and 1.6% of patients on placebo. In a study of 697 patients with available 24-hour Holter monitoring data after their first dose (N = 351 receiving GILENYA and N = 346 on placebo), second-degree AV blocks (Mobitz Types I [Wenckebach] or 2:1 AV blocks) occurred in 4% (N = 14) of patients receiving GILENYA and 2% (N = 7) of patients on placebo. Of the 14 patients receiving GILENYA, 7 patients had 2:1 AV block (5 patients within the first 6 hours postdose and 2 patients after 6 hours postdose). All second degree AV blocks on placebo were Mobitz Type I and occurred after the first 12 hours postdose. 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.

DOCKET ALARM

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