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----------

Contraindications (4)	2/2016
Warnings and Precautions (5.1, 5.4, 5.6)	5/2015
Warnings and Precautions (5.2, 5.3, 5.7, 5.10, 5.12)	2/2016

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

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

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

- Recommended dose: 0.5 mg orally once-daily, with or without food (2)
- First Dose Monitoring (including re-initiation after discontinuation >14 days):
  - 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)
  - Monitor until resolution if heart rate <45 bpm, atrioventricular (AV) block, or if lowest postdose heart rate is at the end of the observation period. (2)
  - Monitor symptomatic bradycardia with ECG until resolved. Continue overnight if intervention is required; repeat first-dose monitoring for second dose. (2)
  - 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, 7)

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

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)
- Increased blood pressure (BP): Monitor BP during treatment. (5.9)
- Basal cell carcinoma: suspicious skin lesions should be evaluated. (5.10)

----------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, 12.3)
- Vaccines: Avoid live attenuated vaccines during, and for 2 months after stopping GILENYA treatment. (5.2, 7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 2/2016

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. Patients who initiate GILENYA and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring *[see Reinitiation of Therapy Following Discontinuation]*.

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 (ECG) 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 postdose is <45 bpm
- 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

Should postdose 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 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. 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 decreases 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. Patients who cannot switch should have overnight continuous ECG monitoring after the first dose *[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 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.

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. 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 0.5 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

- 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 msec
- Treatment with Class Ia or Class III anti-arrhythmic drugs
- Patients who have 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 (5.12)]*.

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 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 were rarely observed. 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. 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.

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.

Atrioventricular Blocks

Initiation of GILENYA treatment has resulted in transient AV conduction delays. In controlled clinical trials, 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.

Postmarketing Experience

In the postmarketing setting, third-degree AV block and AV block with junctional escape have been observed during the first-dose 6-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 preexisting 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 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. Because the elimination of fingolimod after discontinuation may take up to 2 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.

In MS placebo-controlled trials, the overall rate of infections (72%) with GILENYA was similar to placebo. However, bronchitis, herpes zoster, influenza, sinusitis, and pneumonia were more common in GILENYA-treated patients. Serious infections occurred at a rate of 2.3% in the GILENYA group versus 1.6% in the placebo group.

In the postmarketing setting, serious infections with opportunistic pathogens including viruses (e.g., John Cunningham virus (JCV), herpes simplex viruses 1 and 2, varicella-zoster virus), fungi (e.g., cryptococci), and bacteria (e.g., atypical mycobacteria) have been reported with GILENYA. Patients with symptoms and signs consistent with any of these infections should undergo prompt diagnostic evaluation and appropriate treatment.

Herpes Viral Infections

In placebo-controlled trials, the rate of herpetic infections was 9% in patients receiving GILENYA 0.5 mg and 7% on placebo.

Two patients died of herpetic infections during controlled trials. One death was due to disseminated primary herpes zoster and the other to herpes simplex encephalitis. In both cases, the patients were taking a 1.25 mg dose of fingolimod (higher than the recommended 0.5 mg dose) and had received high-dose corticosteroid therapy to treat suspected MS relapses.

Serious, life-threatening events of disseminated varicella zoster and herpes simplex infections, including cases of encephalitis and multiorgan failure, have occurred with GILENYA 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.

Cases of Kaposi's sarcoma have been reported in the postmarketing setting. Kaposi's sarcoma is an angioproliferative disorder that is associated with infection with human herpes virus 8 (HHV-8). Patients with symptoms or signs consistent with Kaposi's sarcoma should be referred for prompt diagnostic evaluation and management.

Cryptococcal infections

Cryptococcal infections, including cases of cryptococcal meningitis and disseminated cryptococcal infections, have been reported with GILENYA in the postmarketing setting. Cryptococcal infections have generally occurred after approximately 2 years of GILENYA treatment, but may occur earlier. The relationship between the risk of cryptococcal

infection and the duration of treatment is unknown. Patients with symptoms and signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment.

Prior and Concomitant Treatment with Antineoplastic, Immunosuppressive, or Immune-Modulating Therapies

In clinical studies, patients who received GILENYA did not receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of GILENYA with any of these therapies, and also with corticosteroids, would be expected to increase the risk of immunosuppression *[see Drug Interactions (7)]*.

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

Varicella Zoster Virus Antibody Testing/Vaccination

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 1 month to allow the full effect of vaccination to occur.

5.3 Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients with MS who received GILENYA in the postmarketing setting. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML has occurred in patients who had not been treated previously with natalizumab, which has a known association with PML, and who were also not taking any immunosuppressive or immunomodulatory medications concomitantly. The patients had no other ongoing identified systemic medical conditions resulting in compromised immune system function, although one patient had a history of cancer treated with chemotherapy several years prior to taking Gilenya. The cases have occurred in patients treated with GILENYA for at least 2 years. The relationship between the risk of PML and the duration of treatment is unknown.

At the first sign or symptom suggestive of PML, withhold GILENYA and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

5.4 Macular Edema

Fingolimod increases the risk of macular edema. Perform an examination of the fundus including the macula in all patients before starting treatment, again 3–4 months after starting treatment, and again at any time after a patient reports visual disturbances while on GILENYA therapy.

A dose-dependent increase in the risk of macular edema occurred in the GILENYA clinical development program.

In 2-year, double-blind, placebo-controlled studies in patients with multiple sclerosis, macular edema with or without visual symptoms occurred in 1.5% of patients (11/799) treated with fingolimod 1.25 mg, 0.5% of patients (4/783) treated with GILENYA 0.5 mg and 0.4% of patients (3/773) treated with placebo. Macular edema occurred predominantly during the first 3 to 4 months of therapy. These clinical trials excluded patients with diabetes mellitus, a known risk factor for macular edema (see below *Macular Edema in Patients with History of Uveitis or Diabetes Mellitus).* Symptoms of macular edema included blurred vision and decreased visual acuity. 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. Macular edema has also been reported in patients taking GILENYA in the postmarketing setting, usually within the first 6 months of treatment.

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.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.