

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

Warnings and Precautions (5.1, 5.2, 5.3, 5.5, 5.6) 5/2015

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- Recommended dose: 0.5 mg orally once-daily, with or without food (2)
- First Dose Monitoring:
 - Observe all patients for bradycardia for at least 6 hours after first dose with hourly pulse and blood pressure measurement. Obtain electrocardiogram (ECG) prior to dosing and at end of observation period.
 - Patients who develop heart rate <45 bpm, 2nd degree or higher atrioventricular (AV) block, or in whom lowest postdose heart rate is at the end of the observation period should be monitored until resolution.
 - If symptomatic bradycardia occurs, begin continuous ECG monitoring until resolved. If pharmacological intervention is required, continue this monitoring overnight, and repeat first-dose monitoring for the second dose.
 - Patients at higher risk of symptomatic bradycardia or heart block, or prolonged QTc interval, or taking drugs with known risk of torsades de pointes should be observed overnight. (2, 7)

DOSAGE FORMS AND STRENGTHS

0.5 mg hard capsules (3)

CONTRAINDICATIONS

- 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 (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)

WARNINGS AND PRECAUTIONS

- Bradycardia and/or atrioventricular conduction after first dose: Monitor patients. (2, 5.1)
- Infections: GILENYA may increase the risk of infections. A recent CBC should be available before initiating treatment. Monitor for infection during treatment and for 2 months after discontinuation. Do not start in patients with active infections. (5.2)
- Macular edema: Perform an examination of the fundus including the macula before and 3–4 months after treatment initiation. Patients with diabetes mellitus or a history of uveitis are at increased risk. (5.3)
- Posterior reversible encephalopathy syndrome (PRES): If suspected, discontinue GILENYA. (5.4)
- Decrease in pulmonary function tests (PFT): Obtain PFT when clinically indicated. (5.5)
- Liver injury: Liver enzyme results should be available before initiation. Discontinue if significant liver injury occurs. (5.6)
- Women of childbearing potential should use effective contraception during and for 2 months after stopping GILENYA. (5.7)
- Blood pressure (BP): Monitor BP during treatment. (5.8)

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

- Ketoconazole: Closely monitor during concomitant use with systemic ketoconazole. (7, 12.3)
- Vaccines: Avoid live attenuated vaccines during, and for 2 months after stopping GILENYA treatment. (5.2, 7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Hepatic impairment: Closely monitor patients with severe hepatic impairment. (5.6, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 5/2015

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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 (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 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. 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

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.

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 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.

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 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 0.5 mg 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.

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. In the combined clinical trial experience with all doses of fingolimod, the rate of macular edema was approximately 20% in MS patients with a history of uveitis versus 0.6% in those without a history of uveitis. GILENYA has not been tested in MS patients with diabetes mellitus. 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.

5.4 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.

5.5 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. In 2-year placebo-controlled trials, the reduction from baseline in the percent of predicted values for FEV1 at the time of last assessment on drug was 2.8% for GILENYA 0.5 mg and 1.0% for placebo. For DLCO, the reduction from baseline in percent of predicted values at the time of last assessment on drug was 3.3% for GILENYA 0.5 mg and 0.5% 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 placebo-controlled trials, dyspnea was reported in 9% of patients receiving GILENYA 0.5 mg and 7% 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.

5.6 Liver Injury

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.

In 2-year placebo-controlled clinical trials, elevation of liver transaminases to 3-fold the upper limit of normal (ULN) or greater occurred in 14% of patients treated with GILENYA 0.5 mg and 3% of patients on placebo. Elevations 5-fold the ULN or greater occurred in 4.5% of patients on GILENYA and 1% of patients on placebo. The majority of elevations occurred within 6 to 9 months. In clinical trials, GILENYA was discontinued if the elevation exceeded 5 times the ULN. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of GILENYA. Recurrence of liver transaminase elevations occurred with rechallenge in some patients.

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 preexisting 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)*, *Clinical Pharmacology (12.3)*].

5.7 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.

5.8 Blood Pressure Effects

In MS controlled clinical trials, patients treated with GILENYA 0.5 mg had an average increase over placebo of approximately 3 mmHg in systolic pressure, and approximately 2 mmHg in diastolic pressure, first detected after approximately 1 month of treatment initiation, and persisting with continued treatment. Hypertension was reported as an adverse reaction in 8% of patients on GILENYA 0.5 mg and in 4% of patients on placebo. Blood pressure should be monitored during treatment with GILENYA.

5.9 Immune System Effects Following GILENYA Discontinuation

Fingolimod remains in the blood and has pharmacodynamic effects, including decreased lymphocyte counts, for up to 2 months following the last dose of GILENYA. Lymphocyte counts generally return to the normal range within 1–2 months of stopping therapy [see *Clinical Pharmacology (12.2)*]. Because of the continuing pharmacodynamic effects of fingolimod, initiating other drugs during this period warrants the same considerations needed for concomitant administration (e.g., risk of additive immunosuppressant effects) [see *Drug Interactions (7)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Bradyarrhythmia and Atrioventricular Blocks [see *Warnings and Precautions (5.1)*]
- Infections [see *Warnings and Precautions (5.2)*]
- Macular Edema [see *Warnings and Precautions (5.3)*]
- Posterior Reversible Encephalopathy Syndrome [see *Warnings and Precautions (5.4)*]
- Respiratory Effects [see *Warnings and Precautions (5.5)*]
- Liver Injury [see *Warnings and Precautions (5.6)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials (Studies 1, 2, and 3), a total of 1212 patients with relapsing forms of multiple sclerosis received GILENYA 0.5 mg. This included 783 patients who received GILENYA 0.5 mg in the 2-year placebo-controlled trials (Studies 1 and 3) and 429 patients who received GILENYA 0.5 mg in the 1 year active-controlled trial (Study 2). The overall exposure in the controlled trials was equivalent to 1716 person-years. Approximately 1000 patients 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 was approximately 4119 person-years.

In placebo-controlled trials, the most frequent adverse reactions (incidence $\geq 10\%$ and $>$ placebo) for GILENYA 0.5 mg were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. Adverse events that led to treatment discontinuation and occurred in more than 1% of patients taking GILENYA 0.5 mg were serum transaminase elevations (4.7% compared to 1% on placebo) and basal cell carcinoma (1% compared to 0.5% on placebo).

Table 1 lists adverse reactions that occurred in $\geq 1\%$ of GILENYA-treated patients and $\geq 1\%$ higher rate than for placebo.

Table 1 Adverse Reactions Reported in Studies 1 and 3 (Occurring in $\geq 1\%$ of Patients and Reported for GILENYA 0.5 mg at $\geq 1\%$ Higher Rate than for Placebo)

Primary System Organ Class Preferred Term	GILENYA 0.5 mg N=783 %	Placebo N=773 %
Infections		
Influenza	11	8
Sinusitis	11	8
Bronchitis	8	5
Herpes zoster	2	1
Tinea versicolor	2	<1
Cardiac Disorders		
Bradycardia	3	1
Nervous system disorders		
Headache	25	24
Migraine	6	4
Gastrointestinal disorders		
Nausea	13	12
Diarrhea	13	10
Abdominal pain	11	10
General disorders and administration site conditions		
Asthenia	2	1
Musculoskeletal and connective tissue disorders		
Back pain	10	9
Pain in extremity	10	7
Skin and subcutaneous tissue disorders		
Alopecia	3	2
Actinic keratosis	2	1
Investigations		
Liver transaminase elevations (ALT/GGT/AST)	15	4
Blood triglycerides increased	3	1
Respiratory, thoracic, and mediastinal disorders		
Cough	12	11
Dyspnea	9	7
Eye disorders		
Vision blurred	4	2
Vascular disorders		

Hypertension	8	4
Blood and lymphatic system disorders		
Lymphopenia	7	<1
Leukopenia	2	<1
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Skin papilloma	3	2
Basal cell carcinoma	2	1

Adverse reactions of dizziness, pneumonia, eczema and pruritus were also reported in Studies 1 and 3 but did not meet the reporting rate criteria for inclusion in Table 1 (difference was less than 1%).

Adverse reactions with GILENYA 0.5 mg in Study 2, the 1-year active-controlled (versus interferon beta-1a) study were generally similar to those in Studies 1 and 3.

Vascular Events

Vascular events, including ischemic and hemorrhagic strokes, and peripheral arterial occlusive disease were reported in premarketing clinical trials in patients who received GILENYA doses (1.25–5 mg) higher than recommended for use in MS. Similar events have been reported with GILENYA 0.5 mg in the postmarketing setting although a causal relationship has not been established.

Lymphomas

Cases of lymphoma have occurred in premarketing clinical trials and in the postmarketing setting. The relationship to GILENYA remains uncertain.

7 DRUG INTERACTIONS

QT Prolonging Drugs

GILENYA has not been studied in patients treated with drugs that prolong the QT interval. Drugs that prolong the QT interval have been associated with cases of torsades de pointes in patients with bradycardia. Since initiation of GILENYA treatment results in decreased heart rate and may prolong the QT interval, patients on 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 *Dosage and Administration* (2) and *Warnings and Precautions* (5.1)].

Ketoconazole

The blood levels of fingolimod and fingolimod-phosphate are increased by 1.7-fold when used concomitantly with ketoconazole. Patients who use GILENYA and systemic ketoconazole concomitantly should be closely monitored, as the risk of adverse reactions is greater.

Vaccines

GILENYA reduces the immune response to vaccination. Vaccination may be less effective during and for up to 2 months after discontinuation of treatment with GILENYA [see *Clinical Pharmacology* (12.2)]. Avoid the use of live attenuated vaccines during and for 2 months after treatment with GILENYA because of the risk of infection.

Antineoplastic, Immunosuppressive, or Immune-Modulating Therapies

Antineoplastic, immune-modulating, or immunosuppressive therapies, (including corticosteroids) are expected to increase the risk of immunosuppression, and the risk of additive immune system effects must be considered if these therapies are coadministered with GILENYA. When switching from drugs with prolonged immune effects, such as natalizumab, teriflunomide or mitoxantrone, the duration and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects when initiating GILENYA [see *Warnings and Precautions* (5.2)].

Drugs That Slow Heart Rate or Atrioventricular Conduction (e.g., beta blockers or diltiazem)

Experience with GILENYA in patients receiving concurrent therapy with drugs that slow the heart rate or atrioventricular conduction (e.g., beta blockers, digoxin, or heart rate-slowing calcium channel blockers such as diltiazem or verapamil) is

limited. Because initiation of GILENYA treatment may result in an additional decrease in heart rate, concomitant use of these drugs during GILENYA initiation may be associated with severe bradycardia or heart block. Seek advice from the prescribing physician regarding the possibility to switch to drugs that do not slow the heart rate or atrioventricular conduction before initiating GILENYA. Patients who cannot switch, should have overnight continuous ECG monitoring after the first dose [see *Dosage and Administration* (2) and *Warnings and Precautions* (5.1)].

Laboratory Test Interaction

Because GILENYA reduces blood lymphocyte counts via redistribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilized to evaluate the lymphocyte subset status of a patient treated with GILENYA. A recent CBC should be available before initiating treatment with GILENYA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. In oral studies conducted in rats and rabbits, fingolimod demonstrated developmental toxicity, including teratogenicity (rats) and embryoletality, when given to pregnant animals. In rats, the highest no-effect dose was less than the recommended human dose (RHD) of 0.5 mg/day on a body surface area (mg/m^2) basis. The most common fetal visceral malformations in rats included persistent truncus arteriosus and ventricular septal defect. The receptor affected by fingolimod (sphingosine 1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. Because it takes approximately 2 months to eliminate fingolimod from the body, potential risks to the fetus may persist after treatment ends [see *Warnings and Precautions* (5.7, 5.9)]. GILENYA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Registry

A pregnancy registry has been established to collect information about the effect of GILENYA use during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the GILENYA pregnancy registry by calling Outcome at 1-877-598-7237, sending an email to gpr@outcome.com or visiting www.gilenyapregnancyregistry.com.

Animal Data

When fingolimod was orally administered to pregnant rats during the period of organogenesis (0, 0.03, 0.1, and 0.3 mg/kg/day or 0, 1, 3, and 10 mg/kg/day), increased incidences of fetal malformations and embryo-fetal deaths were observed at all but the lowest dose tested (0.03 mg/kg/day), which is less than the RHD on a mg/m^2 basis. Oral administration to pregnant rabbits during organogenesis (0, 0.5, 1.5, and 5 mg/kg/day) resulted in increased incidences of embryo-fetal mortality and fetal growth retardation at the mid and high doses. The no-effect dose for these effects in rabbits (0.5 mg/kg/day) is approximately 20 times the RHD on a mg/m^2 basis.

When fingolimod was orally administered to female rats during pregnancy and lactation (0, 0.05, 0.15, and 0.5 mg/kg/day), pup survival was decreased at all doses and a neurobehavioral (learning) deficit was seen in offspring at the high dose. The low-effect dose of 0.05 mg/kg/day is similar to the RHD on a mg/m^2 basis.

8.2 Labor and Delivery

The effects of GILENYA on labor and delivery are unknown.

8.3 Nursing Mothers

Fingolimod is excreted in the milk of treated rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from GILENYA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of GILENYA in pediatric patients with MS below the age of 18 years have not been established.

In a study in which fingolimod (0.3, 1.5, or 7.5 mg/kg/day) was orally administered to young rats from weaning through sexual maturity, changes in bone mineral density and persistent neurobehavioral impairment (altered auditory startle) were observed at all doses. Delayed sexual maturation was noted in females at the highest dose tested and in males at all doses. The bone changes observed in fingolimod-treated juvenile rats are consistent with a reported role of S1P in the regulation of bone mineral homeostasis.

When fingolimod (0.5 or 5 mg/kg/day) was orally administered to rats from the neonatal period through sexual maturity, a marked decrease in T-cell dependent antibody response was observed at both doses. This effect had not fully recovered by 6-8 weeks after the end of treatment.

8.5 Geriatric Use

Clinical MS studies of GILENYA did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. GILENYA should be used with caution in patients aged 65 years and over, reflecting the greater frequency of decreased hepatic, or renal, function and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Because fingolimod, but not fingolimod-phosphate, exposure is doubled in patients with severe hepatic impairment, patients with severe hepatic impairment should be closely monitored, as the risk of adverse reactions may be greater [see *Warnings and Precautions* (5.6) and *Clinical Pharmacology* (12.3)].

No dose adjustment is needed in patients with mild or moderate hepatic impairment.

8.7 Renal Impairment

The blood level of some GILENYA metabolites is increased (up to 13-fold) in patients with severe renal impairment [see *Clinical Pharmacology* (12.3)]. The toxicity of these metabolites has not been fully explored. The blood level of these metabolites has not been assessed in patients with mild or moderate renal impairment.

10 OVERDOSAGE

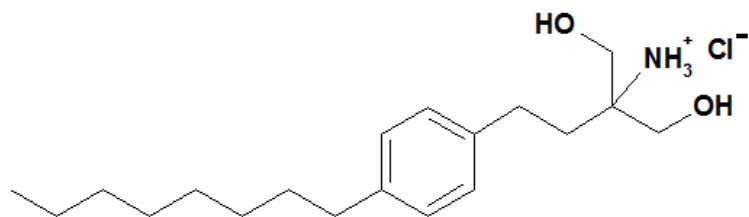
GILENYA can induce bradycardia as well as AV conduction blocks (including complete AV block). The decline in heart rate usually starts within 1 hour of the first dose and is maximal within 6 hours in most patients [see *Warnings and Precautions* (5.1)]. In case of GILENYA overdose, observe patients overnight with continuous ECG monitoring in a medical facility, and obtain regular measurements of blood pressure [see *Dosage and Administration* (2)].

Neither dialysis nor plasma exchange results in removal of fingolimod from the body.

11 DESCRIPTION

Fingolimod is a sphingosine 1-phosphate receptor modulator.

Chemically, fingolimod is 2-amino-2-[2-(4-octylphenyl)ethyl]propan-1,3-diol hydrochloride. Its structure is shown below:



Fingolimod hydrochloride is a white to practically white powder that is freely soluble in water and alcohol and soluble in propylene glycol. It has a molecular weight of 343.93.

GILENYA is provided as 0.5 mg hard gelatin capsules for oral use. Each capsule contains 0.56 mg of fingolimod hydrochloride, equivalent to 0.5 mg of fingolimod.

Each GILENYA 0.5 mg capsule contains the following inactive ingredients: gelatin, magnesium stearate, mannitol, titanium dioxide, yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fingolimod is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate. Fingolimod-phosphate is a sphingosine 1-phosphate receptor modulator, and binds with high affinity to sphingosine 1-phosphate receptors 1, 3, 4, and 5. Fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which fingolimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

12.2 Pharmacodynamics

Heart Rate and Rhythm

Fingolimod causes a transient reduction in heart rate and AV conduction at treatment initiation [*see Warnings and Precautions (5.1)*].

Heart rate progressively increases after the first day, returning to baseline values within 1 month of the start of chronic treatment.

Autonomic responses of the heart, including diurnal variation of heart rate and response to exercise, are not affected by fingolimod treatment.

Fingolimod treatment is not associated with a decrease in cardiac output.

Potential to Prolong the QT Interval

In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTc, with the upper boundary of the 90% confidence interval (CI) of 14.0 msec. There is no consistent signal of increased incidence of QTc outliers, either absolute or change from baseline, associated with fingolimod treatment. In MS studies, there was no clinically relevant prolongation of the QT interval, but patients at risk for QT prolongation were not included in clinical studies.

Immune System

Effects on Immune Cell Numbers in the Blood

In a study in which 12 subjects received GILENYA 0.5 mg daily, the lymphocyte count decreased to approximately 60% of baseline within 4 to 6 hours after the first dose. With continued daily dosing, the lymphocyte count continued to decrease over a 2-week period, reaching a nadir count of approximately 500 cells/mcL or approximately 30% of baseline. In a placebo-controlled study in 1272 MS patients (of whom 425 received fingolimod 0.5 mg daily and 418 received placebo), 18% (N=78) of patients on fingolimod 0.5 mg reached a nadir of <200 cells/mcL on at least 1 occasion. No patient on placebo reached a nadir of <200 cells/mcL. Low lymphocyte counts are maintained with chronic daily dosing of GILENYA 0.5 mg daily.

Chronic fingolimod dosing leads to a mild decrease in the neutrophil count to approximately 80% of baseline. Monocytes are unaffected by fingolimod.

Peripheral lymphocyte count increases are evident within days of stopping fingolimod treatment and typically normal counts are reached within 1 to 2 months.

Effect on Antibody Response

GILENYA reduces the immune response to vaccination, as evaluated in 2 studies.

In the first study, the immunogenicity of keyhole limpet hemocyanin (KLH) and pneumococcal polysaccharide vaccine (PPV-23) immunization were assessed by IgM and IgG titers in a steady-state, randomized, placebo-controlled study in healthy volunteers. Compared to placebo, antigen-specific IgM titers were decreased by 91% and 25% in response to KLH and PPV-23, respectively, in subjects on GILENYA 0.5 mg. Similarly, IgG titers were decreased by 45% and 50%, in response to KLH and PPV-23, respectively, in subjects on GILENYA 0.5 mg daily compared to placebo. The responder rate for GILENYA 0.5 mg as measured by the number of subjects with a >4-fold increase in KLH IgG was comparable to placebo and 25% lower for PPV-23 IgG, while the number of subjects with a >4 fold increase in KLH and PPV-23 IgM was 75% and 40% lower, respectively, compared to placebo. The capacity to mount a skin delayed-type hypersensitivity reaction to *Candida* and tetanus toxoid was decreased by approximately 30% in subjects on GILENYA

0.5 mg daily, compared to placebo. Immunologic responses were further decreased with fingolimod 1.25 mg (a dose higher than recommended in MS) [see *Warnings and Precautions* (5.2)].

In the second study, the immunogenicity of Northern hemisphere seasonal influenza and tetanus toxoid vaccination was assessed in a 12-week steady-state, randomized, placebo-controlled study of GILENYA 0.5 mg in multiple sclerosis patients (n=136). The responder rate 3 weeks after vaccination, defined as seroconversion or a ≥ 4 -fold increase in antibody directed against at least 1 of the 3 influenza strains, was 54% for GILENYA 0.5 mg and 85% in the placebo group. The responder rate 3 weeks after vaccination, defined as seroconversion or a ≥ 4 -fold increase in antibody directed against tetanus toxoid was 40% for GILENYA 0.5 mg and 61% in the placebo group.

Pulmonary Function

Single fingolimod doses ≥ 5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance. In a 14-day study of 0.5, 1.25, or 5 mg/day, fingolimod was not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Subjects on fingolimod treatment had a normal bronchodilator response to inhaled beta-agonists.

In a 14-day placebo-controlled study of patients with moderate asthma, no effect was seen for GILENYA 0.5 mg (recommended dose in MS). A 10% reduction in mean FEV1 at 6 hours after dosing was observed in patients receiving fingolimod 1.25 mg (a dose higher than recommended for use in MS) on Day 10 of treatment. Fingolimod 1.25 mg was associated with a 5-fold increase in the use of rescue short acting beta-agonists.

12.3 Pharmacokinetics

Absorption

The T_{max} of fingolimod is 12–16 hours. The apparent absolute oral bioavailability is 93%.

Food intake does not alter C_{max} or exposure (AUC) of fingolimod or fingolimod-phosphate. Therefore GILENYA may be taken without regard to meals.

Steady-state blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10-fold greater than with the initial dose.

Distribution

Fingolimod highly (86%) distributes in red blood cells. Fingolimod-phosphate has a smaller uptake in blood cells of $< 17\%$. Fingolimod and fingolimod-phosphate are $> 99.7\%$ protein bound. Fingolimod and fingolimod-phosphate protein binding is not altered by renal or hepatic impairment.

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1200 ± 260 L.

Metabolism

The biotransformation of fingolimod in humans occurs by 3 main pathways: by reversible stereoselective phosphorylation to the pharmacologically active (*S*)-enantiomer of fingolimod-phosphate, by oxidative biotransformation catalyzed mainly by the cytochrome P450 4F2 (CYP4F2) and possibly other CYP4F isoenzymes with subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive non-polar ceramide analogs of fingolimod.

Inhibitors or inducers of CYP4F2 and possibly other CYP4F isozymes might alter the exposure of fingolimod or fingolimod-phosphate. In vitro studies in hepatocytes indicated that CYP3A4 may contribute to fingolimod metabolism in the case of strong induction of CYP3A4.

Following single oral administration of [14 C] fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the AUC up to 816 hours post-dose of total radiolabeled components, are fingolimod itself (23.3%), fingolimod-phosphate (10.3%), and inactive metabolites [M3 carboxylic acid metabolite (8.3%), M29 ceramide metabolite (8.9%), and M30 ceramide metabolite (7.3%)].

Elimination

Fingolimod blood clearance is 6.3 ± 2.3 L/h, and the average apparent terminal half-life ($t_{1/2}$) is 6 to 9 days. Blood levels of fingolimod-phosphate decline in parallel with those of fingolimod in the terminal phase, yielding similar half-lives for both.

After oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod-phosphate are not excreted intact in urine but are the major components in the feces with amounts of each representing less than 2.5% of the dose.

Specific Populations

Geriatric Patients

The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in elderly patients. However, clinical experience in patients aged above 65 years is limited.

Gender

Gender has no clinically significant influence on fingolimod and fingolimod-phosphate pharmacokinetics.

Race

The effects of race on fingolimod and fingolimod-phosphate pharmacokinetics cannot be adequately assessed due to a low number of non-white patients in the clinical program.

Renal Impairment

In patients with severe renal impairment, fingolimod C_{max} and AUC are increased by 32% and 43%, respectively, and fingolimod-phosphate C_{max} and AUC are increased by 25% and 14%, respectively, with no change in apparent elimination half-life. Based on these findings, the GILENYA 0.5 mg dose is appropriate for use in patients with renal impairment. The systemic exposure of 2 metabolites (M2 and M3) is increased by 3- and 13-fold, respectively. The toxicity of these metabolites has not been fully characterized.

A study in patients with mild or moderate renal impairment has not been conducted.

Hepatic Impairment

In subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, and C), no change in fingolimod C_{max} was observed, but fingolimod $AUC_{0-\infty}$ was increased respectively by 12%, 44%, and 103%. In patients with severe hepatic impairment (Child-Pugh class C), fingolimod-phosphate C_{max} was decreased by 22% and $AUC_{0-96 \text{ hours}}$ was decreased by 29%. The pharmacokinetics of fingolimod-phosphate was not evaluated in patients with mild or moderate hepatic impairment. The apparent elimination half-life of fingolimod is unchanged in subjects with mild hepatic impairment, but is prolonged by about 50% in patients with moderate or severe hepatic impairment.

Patients with severe hepatic impairment (Child-Pugh class C) should be closely monitored, as the risk of adverse reactions is greater [see *Warnings and Precautions* (5.6)].

No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh class A and B).

Drug Interactions

Ketoconazole

The coadministration of ketoconazole (a potent inhibitor of CYP3A and CYP4F) 200 mg twice-daily at steady-state and a single dose of fingolimod 5 mg led to a 70% increase in AUC of fingolimod and fingolimod-phosphate. Patients who use GILENYA and systemic ketoconazole concomitantly should be closely monitored, as the risk of adverse reactions is greater [see *Drug Interactions* (7)].

Carbamazepine

The coadministration of carbamazepine (a potent CYP450 enzyme inducer) 600 mg twice-daily at steady-state and a single dose of fingolimod 2 mg decreased blood concentrations (AUC) of fingolimod and fingolimod-phosphate by approximately 40%. The clinical impact of this decrease is unknown.

Other strong CYP450 enzyme inducers, e.g., rifampicin, phenytoin, phenobarbital, and St. John's wort, may also reduce AUC of fingolimod and fingolimod-phosphate. The clinical impact of this potential decrease is unknown.

Potential of Fingolimod and Fingolimod-phosphate to Inhibit the Metabolism of Comedications

In vitro inhibition studies using pooled human liver microsomes and specific metabolic probe substrates demonstrate that fingolimod has little or no capacity to inhibit the activity of the following CYP enzymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11 (fingolimod only), and similarly fingolimod-phosphate has little or no capacity to inhibit the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 at concentrations up to 3 orders of magnitude of therapeutic concentrations. Therefore, fingolimod and fingolimod-phosphate are unlikely to reduce the clearance of drugs that are mainly cleared through metabolism by the major CYP isoenzymes described above.

Potential of Fingolimod and Fingolimod-phosphate to Induce its Own and/or the Metabolism of Comedications

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2, and MDR1 (P-glycoprotein) mRNA and CYP3A, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP4F2 activity in primary human hepatocytes. Fingolimod did not induce mRNA or activity of the different CYP enzymes and MDR1 with respect to the vehicle control; therefore, no clinically relevant induction of the tested CYP enzymes or MDR1 by fingolimod are expected at therapeutic concentrations. Fingolimod-phosphate was also examined for its potential to induce mRNA and/or activity of human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, CYP4F2, CYP4F3B, and CYP4F12. Fingolimod-phosphate is not expected to have clinically significant induction effects on these enzymes at therapeutic dose of fingolimod. In vitro experiments did not provide an indication of CYP induction by fingolimod-phosphate.

Transporters

Based on in vitro data, fingolimod as well as fingolimod-phosphate are not expected to inhibit the uptake of comedications and/or biologics transported by the organic anion transporting polypeptides OATP1B1, OATP1B3, or the sodium taurocholate co-transporting polypeptide (NTCP). Similarly, they are not expected to inhibit the efflux of comedications and/or biologics transported by the breast cancer resistance protein (BCRP), the bile salt export pump (BSEP), the multidrug resistance-associated protein 2 (MRP2), or P-glycoprotein (P-gp) at therapeutic concentrations.

Oral Contraceptives

The coadministration of fingolimod 0.5 mg daily with oral contraceptives (ethinylestradiol and levonorgestrel) did not elicit any clinically significant change in oral contraceptives exposure. Fingolimod and fingolimod-phosphate exposure were consistent with those from previous studies. No interaction studies have been performed with oral contraceptives containing other progestagens; however, an effect of fingolimod on their exposure is not expected.

Cyclosporine

The pharmacokinetics of single-dose fingolimod was not altered during coadministration with cyclosporine at steady-state, nor was cyclosporine steady-state pharmacokinetics altered by fingolimod. These data indicate that GILENYA is unlikely to reduce or increase the clearance of drugs cleared mainly by CYP3A4. Potent inhibition of transporters MDR1 (P-gp), MRP2, and OATP-1B1 does not influence fingolimod disposition.

Isoproterenol, Atropine, Atenolol, and Diltiazem

Single-dose fingolimod and fingolimod-phosphate exposure was not altered by coadministered isoproterenol or atropine. Likewise, the single-dose pharmacokinetics of fingolimod and fingolimod-phosphate and the steady-state pharmacokinetics of both atenolol and diltiazem were unchanged during the coadministration of the latter 2 drugs individually with fingolimod.

Population Pharmacokinetics Analysis

A population pharmacokinetics evaluation performed in MS patients did not provide evidence for a significant effect of fluoxetine and paroxetine (strong CYP2D6 inhibitors) on fingolimod or fingolimod-phosphate predose concentrations. In addition, the following commonly coprescribed substances had no clinically relevant effect (<20%) on fingolimod or fingolimod-phosphate predose concentrations: baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin, and corticosteroids.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral carcinogenicity studies of fingolimod were conducted in mice and rats. In mice, fingolimod was administered at oral doses of 0, 0.025, 0.25, and 2.5 mg/kg/day for up to 2 years. The incidence of malignant lymphoma was increased in males and females at the mid and high dose. The lowest dose tested (0.025 mg/kg/day) is less than the recommended human dose (RHD) of 0.5 mg/day on a body surface area (mg/m²) basis. In rats, fingolimod was administered at oral doses of 0, 0.05, 0.15, 0.5, and 2.5 mg/kg/day. No increase in tumors was observed. The highest dose tested (2.5 mg/kg/day) is approximately 50 times the RHD on a mg/m² basis.

Fingolimod was negative in a battery of in vitro (Ames, mouse lymphoma thymidine kinase, chromosomal aberration in mammalian cells) and in vivo (micronucleus in mouse and rat) assays.

When fingolimod was administered orally (0, 1, 3, and 10 mg/kg/day) to male and female rats prior to and during mating, and continuing to Day 7 of gestation in females, no effect on fertility was observed up to the highest dose tested (10 mg/kg), which is approximately 200 times the RHD on a mg/m² basis.

13.2 Animal Toxicology and/or Pharmacology

Lung toxicity was observed in 2 different strains of rats and in dogs and monkeys. The primary findings included increase in lung weight, associated with smooth muscle hypertrophy, hyperdistension of the alveoli, and/or increased collagen. Insufficient or lack of pulmonary collapse at necropsy, generally correlated with microscopic changes, was observed in all species. In rats and monkeys, lung toxicity was observed at all oral doses tested in chronic studies. The lowest doses tested in rats (0.05 mg/kg/day in the 2-year carcinogenicity study) and monkeys (0.5 mg/kg/day in the 39-week toxicity study) are similar to and approximately 20 times the RHD on a mg/m² basis, respectively.

In the 52-week oral study in monkeys, respiratory distress associated with ketamine administration was observed at doses of 3 and 10 mg/kg/day; the most affected animal became hypoxic and required oxygenation. As ketamine is not generally associated with respiratory depression, this effect was attributed to fingolimod. In a subsequent study in rats, ketamine was shown to potentiate the bronchoconstrictive effects of fingolimod. The relevance of these findings to humans is unknown.

14 CLINICAL STUDIES

The efficacy of GILENYA was demonstrated in 2 studies that evaluated once-daily doses of GILENYA 0.5 mg and 1.25 mg in patients with relapsing-remitting MS (RRMS). Both studies included patients who had experienced at least 2 clinical relapses during the 2 years prior to randomization or at least 1 clinical relapse during the 1 year prior to randomization, and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.5. Study 1 was a 2-year randomized, double-blind, placebo-controlled study in patients with RRMS who had not received any interferon-beta or glatiramer acetate for at least the previous 3 months and had not received any natalizumab for at least the previous 6 months. Neurological evaluations were performed at screening, every 3 months and at time of suspected relapse. MRI evaluations were performed at screening, Month 6, Month 12, and Month 24. The primary endpoint was the annualized relapse rate.

Median age was 37 years, median disease duration was 6.7 years and median EDSS score at baseline was 2.0. Patients were randomized to receive GILENYA 0.5 mg (N=425), 1.25 mg (N=429), or placebo (N=418) for up to 24 months. Median time on study drug was 717 days on 0.5 mg, 715 days on 1.25 mg and 719 days on placebo.

The annualized relapse rate was significantly lower in patients treated with GILENYA than in patients who received placebo. The secondary endpoint was the time to 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for patients with baseline EDSS of 5.5) sustained for 3 months. Time to onset of 3-month confirmed disability progression was significantly delayed with GILENYA treatment compared to placebo. The 1.25 mg dose resulted in no additional benefit over the GILENYA 0.5 mg dose. The results for this study are shown in Table 2 and Figure 1.

Table 2 Clinical and MRI Results of Study 1

	GILENYA 0.5 mg N=425	Placebo N=418	p-value
Clinical Endpoints			

Annualized relapse rate (primary endpoint)	0.18	0.40	<0.001
Percentage of patients without relapse	70%	46%	<0.001
Hazard ratio [‡] of disability progression (95% CI)	0.70 (0.52, 0.96)		0.02

MRI Endpoint

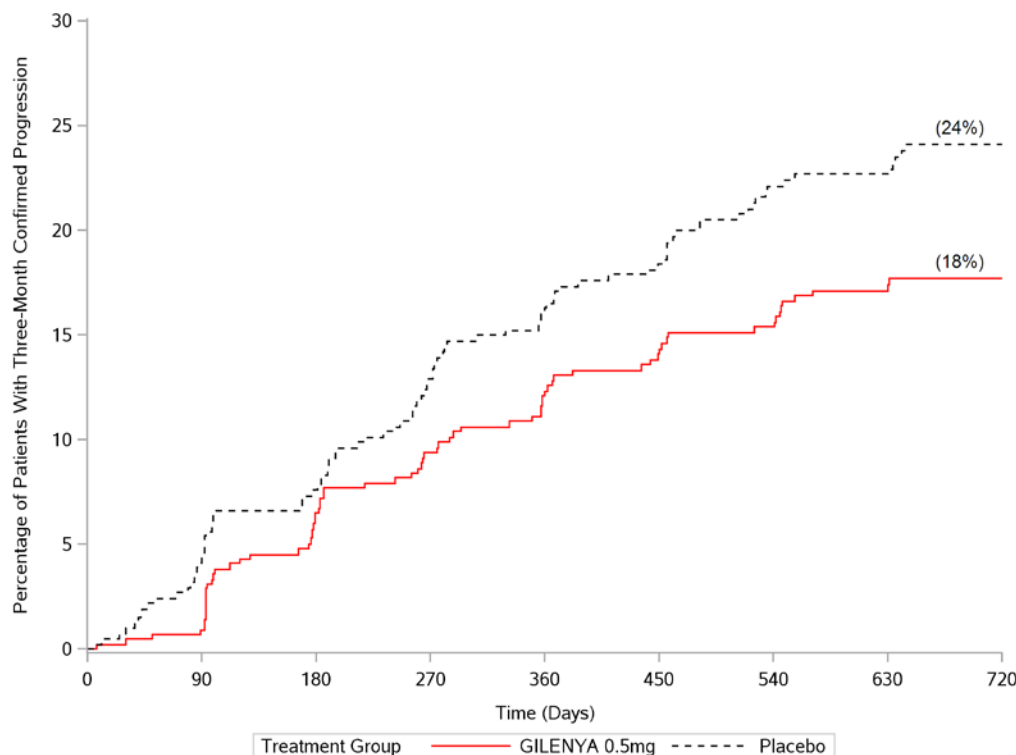
Mean (median) number of new or newly enlarging T2 lesions over 24 months	2.5 (0)	9.8 (5.0)	<0.001
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Mean (median) number of T1 Gd-enhancing lesions at Month 24	0.2 (0)	1.1 (0)	<0.001
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All analyses of clinical endpoints were intent-to-treat. MRI analysis used evaluable dataset.

[‡]Hazard ratio is an estimate of the relative risk of having the event of disability progression on GILENYA as compared to placebo.

Figure 1 Time to 3-Month Confirmed Disability Progression – Study 1 (ITT population)



Study 2 was a 1-year randomized, double-blind, double-dummy, active-controlled study in patients with RRMS who had not received any natalizumab in the previous 6 months. Prior therapy with interferon-beta or glatiramer acetate up to the time of randomization was permitted.

Neurological evaluations were performed at screening, every 3 months, and at the time of suspected relapses. MRI evaluations were performed at screening and at month 12. The primary endpoint was the annualized relapse rate.

Median age was 36 years, median disease duration was 5.9 years, and median EDSS score at baseline was 2.0. Patients were randomized to receive GILENYA 0.5 mg (N=431), 1.25 mg (N=426), or interferon beta-1a, 30 mcg via the intramuscular route (IM) once-weekly (N=435) for up to 12 months. Median time on study drug was 365 days on GILENYA 0.5 mg, 354 days on 1.25 mg, and 361 days on interferon beta-1a IM.

The annualized relapse rate was significantly lower in patients treated with GILENYA 0.5 mg than in patients who received interferon beta-1a IM. The key secondary endpoints were number of new and newly enlarging T2 lesions and time to onset of 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for those with baseline EDSS of 5.5) sustained for 3 months. The number of new and newly enlarging T2 lesions was significantly lower in patients treated with GILENYA than in patients who received interferon beta-1a IM. There was no significant difference in the time to 3-month confirmed disability progression between

GILENYA and interferon beta-1a-treated patients at 1 year. The 1.25 mg dose resulted in no additional benefit over the GILENYA 0.5 mg dose. The results for this study are shown in Table 3.

Table 3 Clinical and MRI Results of Study 2

	GILENYA 0.5 mg N=429	Interferon beta-1a IM 30 mcg N=431	p-value
Clinical Endpoints			
Annualized relapse rate (primary endpoint)	0.16	0.33	<0.001
Percentage of patients without relapse	83%	70%	<0.001
Hazard ratio [‡] of disability progression (95% CI)	0.71 (0.42, 1.21)		0.21
MRI Endpoint			
Mean (median) number of new or newly enlarging T2 lesions over 12 months	1.6 (0)	2.6 (1.0)	0.002
Mean (median) number of T1 Gd-enhancing lesions at Month 12	0.2 (0)	0.5 (0)	<0.001

All analyses of clinical endpoints were intent-to-treat. MRI analysis used evaluable dataset.

[‡] Hazard ratio is an estimate of the relative risk of having the event of disability progression on GILENYA as compared to control.

Pooled results of study 1 and study 2 showed a consistent and statistically significant reduction of annualized relapse rate compared to comparator in subgroups defined by gender, age, prior MS therapy, and disease activity.

16 HOW SUPPLIED/STORAGE AND HANDLING

0.5 mg GILENYA capsules are hard gelatin 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.

GILENYA capsules are supplied as follows:

Bottle of 30 capsules	NDC 0078-0607-15
Carton of 28 capsules containing 2 folded blister cards of 14 capsules per blister card	NDC 0078-0607-51
Carton of 7 capsules containing 1 blister card of 7 capsules per blister card	NDC 0078-0607-89

GILENYA capsules should be stored at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F). Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Tell patients not to discontinue GILENYA without first discussing this with the prescribing physician. Advise patients to contact their physician if they accidentally take more GILENYA than prescribed.

Cardiac Effects

Advise patients that initiation of GILENYA treatment results in a transient decrease in heart rate. Inform patients that they will need to be observed in the doctor's office or other facility for at least 6 hours after the first dose. Advise patients that if GILENYA is discontinued for more than 14 days, effects similar to those observed on treatment initiation may be seen and observation for at least 6 hours will be needed on treatment reinitiation, and that the same precautions will be taken if treatment is interrupted for more than 1 day within the first 2 weeks of treatment, or for more than 7 days during week 3 and 4 of treatment.

Risk of Infections

Inform patients that they may be more likely to get infections when taking GILENYA, and that they should contact their physician if they develop symptoms of infection. Advise patients that the use of some vaccines should be avoided during treatment with GILENYA and for 2 months after discontinuation. Recommend to patients that they delay treatment with GILENYA until after VZV vaccination if they have not had chickenpox or a previous VZV vaccination. Inform patients that prior or concomitant use of drugs that suppress the immune system may increase the risk of infection.

Macular Edema

Advise patients that GILENYA may cause macular edema, and that they should contact their physician if they experience any changes in their vision. Inform patients with diabetes mellitus or a history of uveitis that their risk of macular edema is increased.

Respiratory Effects

Advise patients that they should contact their physician if they experience new onset or worsening of dyspnea.

Hepatic Effects

Inform patients that GILENYA may increase liver enzymes. Advise patients that they should contact their physician if they have any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine.

Fetal Risk

Inform patients that, based on animal studies, GILENYA may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant or are trying to become pregnant. Advise women of childbearing age of the need for effective contraception during GILENYA treatment and for 2 months after stopping GILENYA. Advise the patient that if she should nevertheless become pregnant, she should immediately inform her physician.

Persistence of GILENYA Effects after Drug Discontinuation

Advise patients that GILENYA remains in the blood and continues to have effects, including decreased blood lymphocyte counts, for up to 2 months following the last dose.

T201x-xx
May 2015

MEDICATION GUIDE
GILENYA® (je-LEN-yah)
(fingolimod)
capsules

Read this Medication Guide before you start using GILENYA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your health problem or treatment.

What is the most important information I should know about GILENYA?

GILENYA may cause serious side effects, including:

1. Slow heart rate (bradycardia or bradyarrhythmia) when you start taking GILENYA.

GILENYA can cause your heart rate to slow down, especially after you take your first dose. You will have a test to check the electrical activity of your heart (ECG) before you take your first dose of GILENYA.

You will be observed by a healthcare professional for at least 6 hours after you take your first dose of GILENYA.

After you take your first dose of GILENYA:

- Your pulse and blood pressure should be checked every hour.
- You should be observed by a healthcare professional to see if you have any serious side effects. If your heart rate slows down too much, you may have symptoms such as:
 - dizziness
 - tiredness
 - feeling like your heart is beating slowly or skipping beats
- If you have any of the symptoms of slow heart rate, they will usually happen during the first 6 hours after your first dose of GILENYA. Symptoms can happen up to 24 hours after you take your first GILENYA dose.
- 6 hours after you take your first dose of GILENYA you will have another ECG. If your ECG shows any heart problems or if your heart rate is still too low or continues to decrease, you will continue to be observed.
- If you have any serious side effects after your first dose of GILENYA, especially those that require treatment with other medicines, you will stay in the medical facility to be observed overnight. You will also be observed for any serious side effects for at least 6 hours after you take your second dose of GILENYA the next day.
- If you have certain types of heart problems, or if you are taking certain types of medicines that can affect your heart, you will be observed overnight after you take your first dose of GILENYA.

Your slow heart rate will usually return to normal within 1 month after you start taking GILENYA. Call your doctor or go to the nearest hospital emergency room right away if you have any symptoms of a slow heart rate.

If you miss 1 or more doses of GILENYA you may need to be observed by a healthcare professional when you take your next dose. Call your doctor if you miss a dose of GILENYA. See **"How should I take GILENYA?"**

2. Infections. GILENYA can increase your risk of serious infections and decrease the way vaccines work in your body to prevent certain diseases, especially the chicken pox vaccine. GILENYA lowers the number of white blood cells (lymphocytes) in your blood. This will usually go back to normal within 2 months of stopping treatment. Your doctor may do a blood test before you start taking GILENYA. Call your doctor right away if you have any of these symptoms of an infection:

- fever
- tiredness
- body aches
- chills
- nausea
- vomiting

3. A problem with your vision called macular edema. Macular edema can cause some of the same vision symptoms as an MS attack (optic neuritis). You may not notice any symptoms with macular edema. If macular edema happens, it usually starts in the first 3 to 4 months after you start taking GILENYA. Your doctor should test your vision before you start taking GILENYA and 3 to 4 months after you start taking GILENYA, or any time you notice vision changes during treatment with GILENYA. Your risk of macular edema may be higher if you have diabetes or have had an inflammation of your eye called uveitis.

Call your doctor right away if you have any of the following:

- blurriness or shadows in the center of your vision
- a blind spot in the center of your vision
- sensitivity to light
- unusually colored (tinted) vision

What is GILENYA?

GILENYA is a prescription medicine used to treat relapsing forms of multiple sclerosis (MS) in adults. GILENYA can decrease the number of MS flare-ups (relapses). GILENYA does not cure MS, but it can help slow down the physical problems that MS causes.

It is not known if GILENYA is safe and effective in children under 18 years of age.

Who should not take GILENYA?

Do not take GILENYA if you:

- have had a heart attack, unstable angina, stroke or warning stroke or certain types of heart failure in the last 6 months
- have certain types of irregular or abnormal heartbeat (arrhythmia), including patients in whom a heart finding called prolonged QT is seen on ECG before starting GILENYA
- are taking certain medicines that change your heart rhythm

If any of the above situations apply to you, tell your doctor.

What should I tell my doctor before taking GILENYA?

Before you take GILENYA, tell your doctor about all your medical conditions, including if you had or now have:

- an irregular or abnormal heartbeat (arrhythmia)
- a history of stroke or warning stroke

- heart problems, including heart attack or angina
- a history of repeated fainting (syncope)
- a fever or infection, or you are unable to fight infections due to a disease or taking medicines that lower your immune system. Tell your doctor if you have had chicken pox or have received the vaccine for chicken pox. Your doctor may do a blood test for chicken pox virus. You may need to get the full course of the vaccine for chicken pox and then wait 1 month before you start taking GILENYA.
- eye problems, especially an inflammation of the eye called uveitis.
- diabetes
- breathing problems, including during your sleep
- liver problems
- high blood pressure
- Are pregnant or plan to become pregnant. GILENYA may harm your unborn baby. Talk to your doctor if you are pregnant or are planning to become pregnant.
 - Tell your doctor right away if you become pregnant while taking GILENYA or if you become pregnant within 2 months after you stop taking GILENYA.
 - If you are a female who can become pregnant, you should use effective birth control during your treatment with GILENYA and for at least 2 months after you stop taking GILENYA.

Pregnancy Registry: There is a registry for women who become pregnant during treatment with GILENYA. If you become pregnant while taking GILENYA, talk to your doctor about registering with the GILENYA Pregnancy Registry. The purpose of this registry is to collect information about your health and your baby's health.

For more information, contact the GILENYA Pregnancy Registry by calling Outcome at 1-877-598-7237, by sending an email to gpr@outcome.com, or go to www.gilenyapregnancyregistry.com.

- Are breastfeeding or plan to breastfeed. It is not known if GILENYA passes into your breast milk. You and your doctor should decide if you will take GILENYA or breastfeed. You should not do both.

Tell your doctor about all the medicines you take or have recently taken, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take medicines that affect your immune system, including corticosteroids, or have taken them in the past.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

Using GILENYA and other medicines together may affect each other causing serious side effects.

Especially tell your doctor if you take vaccines. Tell your doctor if you have been vaccinated within 1 month before you start taking GILENYA. You should not get certain vaccines, called live attenuated vaccines, while you take GILENYA and for at least 2 months after you stop taking GILENYA. If you take certain vaccines, you may get the infection the vaccine should have prevented. Vaccines may not work as well when given during GILENYA treatment.

How should I take GILENYA?

- You will be observed by a healthcare professional for at least 6 hours after your first dose of GILENYA. See **“What is the most important information I should know about GILENYA?”**
- Take GILENYA exactly as your doctor tells you to take it.
- Take GILENYA 1 time each day.
- If you take too much GILENYA, call your doctor or go to the nearest hospital emergency room right away.
- Take GILENYA with or without food.
- Do not stop taking GILENYA without talking with your doctor first.
- Call your doctor right away if you miss a dose of GILENYA. You may need to be observed by a healthcare professional for at least 6 hours when you take your next dose. If you need to be observed by a healthcare professional when you take your next dose of GILENYA you will have:
 - an ECG before you take your dose
 - hourly pulse and blood pressure measurements after you take the dose
 - an ECG 6 hours after your dose
- If you have certain types of heart problems, or if you are taking certain types of medicines that can affect your heart, you will be observed overnight by a healthcare professional in a medical facility after you take your dose of GILENYA.
- If you have serious side effects after taking a dose of GILENYA, especially those that require treatment with other medicines, you will stay in the medical facility to be observed overnight. If you were observed overnight, you will also be observed for any serious side effects for at least 6 hours after you take your second dose of GILENYA. See **“What is the most important information I should know about GILENYA?”**

What are possible side effects of GILENYA?

GILENYA can cause serious side effects.

See **“What is the most important information I should know about GILENYA?”**

Serious side effects include:

- **swelling and narrowing of the blood vessels in your brain.** A condition called PRES (Posterior reversible encephalopathy syndrome) has occurred rarely in patients taking GILENYA. Symptoms of PRES usually get better when you stop taking GILENYA. However, if left untreated it may lead to a stroke. Call your doctor right away if you have any of the following symptoms:
 - sudden headache
 - confusion
 - seizures
 - loss of vision
 - weakness

- **breathing problems.** Some people who take GILENYA have shortness of breath. Call your doctor right away if you have trouble breathing.
- **liver problems.** GILENYA may cause liver problems. Your doctor should do blood tests to check your liver before you start taking GILENYA. Call your doctor right away if you have any of the following symptoms of liver problems:
 - nausea
 - vomiting
 - stomach pain
 - loss of appetite
 - tiredness
 - your skin or the whites of your eyes turn yellow
 - dark urine

The most common side effects of GILENYA include:

- headache
- abnormal liver tests
- diarrhea
- cough
- flu
- sinusitis
- back pain
- abdominal pain
- pain in arms or legs

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of GILENYA. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store GILENYA?

- Store GILENYA in the original bottle or blister pack in a dry place.
- Store GILENYA at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep GILENYA and all medicines out of the reach of children.

General information about GILENYA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use GILENYA for a condition for which it was not prescribed. Do not give GILENYA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about GILENYA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about GILENYA that is written for healthcare professionals.

For more information, go to www.pharma.US.Novartis.com or call 1-888-669-6682.

What are the ingredients in GILENYA?

Active ingredient: fingolimod

Inactive ingredients: gelatin, magnesium stearate, mannitol, titanium dioxide, yellow iron oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

GILENYA is a registered trademark of Novartis AG.

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Novartis Pharma Stein AG
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