PRODUCT MONOGRAPH

PrGILENYA®

Fingolimod (as fingolimod hydrochloride)

Oral capsules, 0.5 mg fingolimod (as fingolimod hydrochloride)

Sphingosine 1-phosphate receptor modulator

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Quebec
H9S 1A9

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Capsules / 0.5 mg fingolimod (as fingolimod hydrochloride)	Magnesium stearate, mannitol, gelatin, titanium dioxide, yellow iron oxide.

INDICATIONS AND CLINICAL USE

Adults: GILENYA® (fingolimod) is indicated as monotherapy for the treatment of patients with the relapsing-remitting form of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the progression of physical disability. GILENYA® is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for multiple sclerosis.

GILENYA® should only be prescribed by neurologists who are experienced in the treatment of multiple sclerosis, and are knowledgeable of the efficacy and safety profile of GILENYA® and are able to discuss benefits/risks with patients.

Geriatrics (> 65 years of age): Clinical studies of GILENYA® did not include sufficient numbers of patients aged 65 years and over to determine whether the safety and efficacy of GILENYA® differs in elderly patients compared to younger patients. Physicians who choose to treat geriatric patients should consider that treatment with GILENYA® in the context of a greater frequency of reduced hepatic, renal, immune, pulmonary and cardiovascular function, other concomitant diseases and concomitant drug therapy warrants caution and may necessitate additional or more frequent monitoring (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Pediatrics (< 18 years of age): Safety and efficacy of GILENYA® in patients below the age of 18 have not been studied. GILENYA® is not indicated in patients below 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to fingolimod or to any ingredient in the formulation of GILENYA® (fingolimod) or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

- Patients with increased risk for opportunistic infections, including those who are immunocompromised due to treatment (e.g. antineoplastic, immunosuppressive or immunomodulating therapies, total lymphoid irradiation or bone marrow transplantation) or disease (e.g. immunodeficiency syndrome).

- Patients with severe active infections including active chronic bacterial, fungal or viral infections (e.g., hepatitis, tuberculosis).

- Patients with known active malignancies, except for patients with basal cell carcinoma.

- Patients with severe hepatic impairment (Child-Pugh Class C) (see WARNINGS AND PRECAUTIONS, Special Populations; WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Special Populations and Conditions).

WARNINGS AND PRECAUTIONS

Varicella vaccination

There have been very rare fatal cases of varicella zoster virus (VZV) infections in patients taking GILENYA® (at recommended dose or higher doses used in clinical trials). These patients received prolonged concomitant corticosteroid use (more than 5 days) for treatment of multiple sclerosis relapses. Patients need to be assessed for their immunity to varicella (chickenpox) prior to GILENYA® treatment. It is recommended that patients without a health care professional confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo antibody testing to varicella zoster virus (VZV) before initiating GILENYA® therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended (if not contraindicated) prior to commencing treatment with GILENYA®. If vaccinated, treatment with GILENYA® should only be initiated 1 month after the patient has been vaccinated to allow full effect of vaccination to occur (see WARNINGS AND PRECAUTIONS, Herpetic infections).

SUMMARY OF IMPORTANT PRECAUTIONS TO BE TAKEN PRIOR TO INITIATING AND DURING TREATMENT WITH GILENYA®

Refer to the WARNINGS AND PRECAUTIONS – Immune, Cardiovascular, Ophthalmologic, Hepatic/Biliary/Pancreatic, Special Populations, DRUG INTERACTIONS, and TOXICOLOGY sections for more complete information.

GILENYA® should be used under the supervision of a neurologist experienced in the treatment of multiple sclerosis and familiar with the safety and efficacy of GILENYA®. All patients should have an electrocardiogram (ECG) performed prior to the first dose and 6 hours after the first dose. Patients should be monitored closely for signs and symptoms of bradyarrhythmia, with hourly pulse and blood pressure measurements, for at least 6 hours after the first dose.

Immune system effects

GILENYA® reduces circulating lymphocyte counts to 20-30% of baseline values via reversible retention in lymphoid organs and may increase the risk of infections.

- Delay the start of GILENYA® in patients with severe active infection until resolved.
- Check complete blood count (CBC) before starting therapy if no recent (i.e. within 6 months or after discontinuation of prior therapy) result is available.
- Instruct patients to promptly report symptoms of infection during treatment and for two months after discontinuation.
- Check varicella-zoster virus (VZV) antibody status before starting therapy if there is no health care professional confirmed history of chicken pox or vaccination with varicella vaccine; if negative, vaccination is recommended, with a delay in treatment initiation for 1 month after vaccination to allow full effect of vaccination to occur.
- Co-administration of anti-neoplastic, immunosuppressive or immune-modulating therapies is not recommended due to the risk of additive immune system effects.

Cardiovascular effects

Initiation of GILENYA® treatment results in reversible heart rate decrease and has also been associated with atrioventricular (AV) conduction delays, including isolated cases of spontaneously resolving complete AV block (see WARNINGS AND PRECAUTIONS, Bradyarrhythmia; ADVERSE REACTIONS Post Market Adverse Events).

Conditions when GILENYA® should not be used

- GILENYA® should not be used in patients with a history or currently experiencing second-degree Mobitz type II or higher AV block, sick-sinus syndrome, sino-atrial heart block, a history of recurrent syncope or symptomatic bradycardia, significant QT prolongation (QTc >470 msec in females or >450 msec in males) or in patients with relevant risk factors for QT prolongation (e.g. hypokalemia, hypomagnesemia or congenital QT prolongation), due to the risk of serious cardiac rhythm disturbances.

- GILENYA® should not be used in patients with known ischemic heart disease (including angina pectoris), history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea

since significant bradycardia may be poorly tolerated in these patients.

- Class Ia and Class III anti-arrhythmic drugs have been associated with cases of torsades de pointes in patients with bradycardia. Since initiation of GILENYA® treatment results in decreased heart rate, GILENYA® should not be used concomitantly with these drugs.

- GILENYA® should not be initiated in patients on concurrent therapy with beta-blockers, with heart-rate lowering calcium channel blockers or with other substances that may decrease heart rate because there is limited experience in situations of concomitant use and this may be associated with severe bradycardia and heart block. If treatment with GILENYA® is considered necessary, advice from a cardiologist should be sought regarding a switch to a non heart-rate-lowering drug or for appropriate monitoring (e.g., at least overnight monitoring) during treatment initiation, if such a switch cannot be implemented.

First dose monitoring

- For all patients, obtain an electrocardiogram (ECG) and measure blood pressure prior to and 6-hours after the first dose of GILENYA®.
- Monitor all patients for signs and symptoms of bradyarrhythmia, with hourly pulse and blood pressure measurements, for at least 6 hours after the first dose.
- If symptoms of bradyarrhythmia or atrioventricular (AV) block occur, initiate appropriate management, with continued monitoring (e.g., continuous ECG monitoring) until the symptoms have resolved.
- Should a patient require pharmacological intervention during the first dose observation period, continuous overnight monitoring (e.g., continuous ECG monitoring) in a medical facility should be instituted and the first dose monitoring strategy should be repeated when the second dose of GILENYA® is administered.

Extended monitoring, until the finding has resolved, is also required:

- if the heart rate at 6 hours post-dose is <45 bpm or is the lowest value post-dose, or
- if the ECG at 6 hours after the first dose shows new-onset second-degree or higher grade AV block.

If the ECG at 6 hours after the first dose shows a QTc interval ≥500 msec patients should be monitored overnight.

GILENYA® may lead to an increase in blood pressure. Measure blood pressure regularly in all patients.

Ophthalmologic effects

GILENYA® may cause macular edema with or without symptoms.

- An ophthalmic evaluation should be performed 3-4 months after treatment initiation in all patients, and at any time in any patient complaining of visual disturbances.
- Patients with diabetes mellitus or a history of uveitis are at increased risk of macular edema and should undergo an ophthalmic evaluation prior to initiating GILENYA®

therapy and have regular ophthalmic evaluations while receiving GILENYA® therapy.

Hepatic effects

GILENYA® may increase liver transaminases.

- Obtain transaminase and bilirubin levels prior to initiating treatment if no recent (i.e. within the last 6 months) result is available, every 3 months during the first year of treatment and periodically thereafter in the absence of symptoms or when symptoms suggestive of hepatic injury develop.

Pregnancy

- Women of childbearing potential should be counselled on the potential for serious risk to the fetus and the need for effective contraception during, and for 2 months after treatment with GILENYA®.

Cardiovascular

Initiation of GILENYA® treatment is associated with decreased heart rate, PR interval prolongation and AV conduction delays, requiring patients to be monitored for at least 6 hours after receiving the first dose of GILENYA® (see WARNINGS AND PRECAUTIONS - Bradyarrhythmia; - PR Interval Prolongation and Atrioventricular [AV] Block; - Monitoring During Re-initiation of Therapy Following Discontinuation). GILENYA® is also associated with QTc interval prolongation (see WARNINGS AND PRECAUTIONS - QTc interval prolongation).

Bradyarrhythmia

Decreased heart rate

Initiation of GILENYA® treatment results in a reversible decrease in heart rate. After the first 0.5 mg dose, the heart rate decrease is maximal within 6 hours post-dosing. The heart rate returns to baseline progressively over approximately one month during chronic treatment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics – Heart rate and rhythm). Patients who experienced bradycardia in controlled multiple sclerosis clinical trials were generally asymptomatic but some patients (0.5% receiving GILENYA® 0.5 mg and 0.2% of patients receiving placebo) experienced mild to moderate symptoms, including hypotension, dizziness, fatigue, palpitations, dyspnea, arrhythmia, and/or chest pain or chest discomfort, which resolved within the first 24 hours of treatment (see ADVERSE REACTIONS, ECG Findings and Bradyarrhythmia; DRUG INTERACTIONS, Pharmacodynamic Interactions, and ACTIONS AND CLINICAL PHARMACOLOGY, Cardiovascular).

Conditions when GILENYA® should not be used

Clinical trials in patients with multiple sclerosis excluded patients with several cardiovascular conditions and/or risk factors. Due to limited experience in patients with cardiovascular

conditions and/or risk factors and the known effects of GILENYA® on heart rate and cardiac conduction, GILENYA® should not be used in patients with the following conditions.

- GILENYA® should not be used in patients with a history or presence of second-degree Mobitz type II or higher AV block, sick-sinus syndrome, sino-atrial heart block, a history of recurrent syncope or symptomatic bradycardia, or significant QT prolongation (QTc >470 msec in females or >450 msec in males) or in patients with relevant risk factors for QT prolongation (e.g. hypokalemia, hypomagnesemia or congenital QT prolongation), due to the risk of serious cardiac rhythm disturbances. If a decision is made to undertake treatment, such patients should be evaluated by a cardiologist prior to initiation of treatment, to assess suitability and to determine the most appropriate monitoring strategy, which should be at least overnight.

- GILENYA® should not be used in patients with known ischemic heart disease (including angina pectoris), history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea because significant bradycardia may be poorly tolerated in these patients. If a decision is made to undertake treatment, such patients should be evaluated by a cardiologist prior to initiation of treatment, to assess suitability and to determine the most appropriate monitoring, strategy which should be at least overnight.

- GILENYA® has not been studied in patients with arrhythmias requiring treatment with Class Ia (e.g. quinidine, disopyramide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic drugs. Class Ia and Class III antiarrhythmic drugs have been associated with cases of torsades de pointes in patients with bradycardia. Because initiation of GILENYA® treatment results in decreased heart rate, GILENYA® should not be used concomitantly with these drugs.

- There is limited experience with GILENYA® in patients receiving concurrent therapy with beta blockers, heart-rate lowering calcium channel blockers (such as verapamil or diltiazem), or other substances that may decrease heart rate (e.g. digoxin, cholinesterase inhibitors or pilocarpine). Since the initiation of GILENYA® treatment is also associated with bradycardia (see "Decreased Heart Rate"), concomitant use of these substances during GILENYA® initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, GILENYA® should not be initiated in patients who are concurrently treated with these substances. If treatment with GILENYA® is considered necessary, advice from a cardiologist should be sought regarding a switch to drugs that do not lower heart rate or for appropriate monitoring (e.g., at least overnight monitoring) during treatment initiation, if the heart-rate-lowering drugs cannot be discontinued (see DRUG INTERACTIONS).

For patients with any of the above conditions, treatment should only be considered if the expected benefits outweigh the known risks.

First dose monitoring

- For all patients, obtain an ECG and measure blood pressure prior to and 6-hours after the first dose.
- Monitor all patients for signs and symptoms of bradyarrhythmia, with hourly pulse and blood pressure measurements, for at least 6 hours after the first dose.
- If symptoms of bradyarrhythmia or AV block occur, initiate appropriate management, with continued monitoring (e.g., continuous ECG monitoring) until the symptoms have resolved.
- Should a patient require pharmacological intervention during the first-dose observation period, continuous overnight monitoring (e.g., continuous ECG monitoring) in a medical facility should be instituted and the first-dose monitoring strategy should be repeated when the second dose of GILENYA® is administered.

Extended monitoring, until the finding has resolved, is also required

- if the heart rate at 6 hours post-dose is <45 bpm or is the lowest value post-dose (suggesting that the maximum pharmacodynamic effect on the heart has not yet manifested)
  or
- if the ECG at 6 hours after the first dose shows new-onset second-degree or higher grade AV block.

If the ECG at 6 hours after the first dose shows a QTc interval ≥500 msec patients should be monitored overnight.

PR Interval Prolongation and Atrioventricular (AV) Block

Initiation of GILENYA® treatment has been associated with PR interval prolongation and AV conduction delays. The maximum increase in the PR interval occurs at about 6 h post-dosing. In Phase III controlled clinical trials, the incidence of first degree AV block on ECG at 6 h after the first dose was 4.7% of patients receiving GILENYA® 0.5 mg and 1.5% of patients receiving placebo, while the incidence of 2nd-degree AV block Mobitz type 1 was 0.2% for GILENYA® 0.5 mg and 0 for placebo. On Holter monitoring 2nd-degree AV block, Mobitz type 1 (Wenckebach), was reported in 3.4% of patients receiving GILENYA® 0.5 mg and 2% of patients on placebo, while 2:1 AV block was reported in 1.7% of patients receiving GILENYA® 0.5 mg, but not in any patients receiving placebo. The conduction abnormalities typically were transient, asymptomatic, and resolved within the first 24-hours on treatment. Isolated cases of transient, spontaneously resolving complete AV block have been reported during post-marketing use of GILENYA® (see ADVERSE REACTIONS, ECG Findings and Bradyarrhythmia; DRUG INTERACTIONS, Pharmacodynamic Interactions; ACTION AND CLINICAL PHARMACOLOGY, Cardiovascular).

Monitoring During Re-initiation of Therapy Following Discontinuation

If GILENYA® therapy is discontinued for more than 2 weeks, 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 as for the first dose should apply (i.e., monitor for at least 6 hours after the first dose). Within the first 2 weeks of treatment, first-dose procedures are

recommended after an interruption of one day or more. During weeks 3 and 4 of treatment, first dose procedures are recommended after a treatment interruption of more than 7 days.

QTc Prolongation

GILENYA® is associated with QTc interval prolongation (see ADVERSE REACTIONS, ECG Findings; DRUG INTERACTIONS, Pharmacodynamic Interactions; and ACTIONS AND CLINICAL PHARMACOLOGY, Cardiovascular).

In a thorough QT interval study of doses of 1.25 mg 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 QTcI, with the upper limit of the 90% CI ≤13.0 ms. In the multiple sclerosis studies, clinically relevant effects on prolongation of the QTc-interval have not been observed. However, patients at risk for QT prolongation were excluded from clinical studies.

Since initiation of GILENYA® treatment results in decreased heart rate, and therefore a prolongation of the QT interval, GILENYA® should not be used in patients with significant QT prolongation (QTc >470 msec in females or >450 msec in males) or in patients with relevant risk factors for QT prolongation (e.g., hypokalemia, hypomagnesemia or congenital QT prolongation). If a decision is made to undertake treatment, such patients should be evaluated by a cardiologist prior to initiation of treatment, to assess suitability and to determine the most appropriate monitoring, which should be at least overnight.

GILENYA® has not been studied in patients treated with drugs that prolong the QT interval. Because the risk of QT interval prolongation is expected to be greater in patients who receive concomitant treatment with other drugs that prolong the QT interval, the use of GILENYA® with such drugs should be avoided. If a decision is made to undertake treatment such patients should be evaluated by a cardiologist prior to initiation of treatment, to assess suitability and to determine the most appropriate monitoring, which should be at least overnight.

Many drugs that cause QTc prolongation are suspected to increase the risk of torsade de pointes, a polymorphic ventricular tachyarrhythmia. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Blood pressure effects

In multiple sclerosis clinical trials, patients treated with GILENYA® 0.5 mg had an average increase of approximately 2 mmHg in systolic pressure, and approximately 1 mmHg in diastolic pressure, first detected after approximately 1 month of treatment initiation, and persisting with continued treatment. In controlled studies involving 854 multiple sclerosis patients on GILENYA® 0.5 mg and 511 multiple sclerosis patients on placebo, hypertension was reported as an adverse reaction in 5% of patients on GILENYA® 0.5 mg and in 3% of patients on placebo. Blood pressure should be monitored during treatment with GILENYA®.

Immune

Infections

A core pharmacodynamic effect of GILENYA® is a dose-dependent reduction of peripheral lymphocyte count to 20-30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues. Because elimination of fingolimod after discontinuation of GILENYA® may take up to 2 months, recovery of peripheral lymphocyte counts to baseline values is gradual (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). GILENYA® may therefore increase the risk of infections, including opportunistic infections (see ADVERSE REACTIONS) during treatment and for up to 2 months after discontinuation of treatment. Continue monitoring for infections during this period.

GILENYA® is contraindicated in patients at an increased risk of opportunistic infections and in patients with severe active infections including active chronic bacterial, fungal or viral infections (see CONTRAINDICATIONS).

Before initiating and during treatment with GILENYA®, the following precautions should be taken:

- Obtain a CBC before initiating treatment if no recent (i.e. within 6 months or after discontinuation of prior therapy) result is available. Treatment with GILENYA® should not be initiated when lymphocyte counts are consistently below the normal range.

- Treatment should not be initiated when there are signs and symptoms of a severe active bacterial, fungal or viral infection. Instruct patients to promptly report symptoms or signs suggestive of any infection, during and for up to 2 months after discontinuation of treatment, to facilitate early diagnosis and initiation of appropriate treatments (see WARNINGS AND PRECAUTIONS, Patient Counseling Information).

- Determine immunization status for VZV. Patients need to be assessed for their immunity to varicella (chickenpox) prior to GILENYA® treatment. It is recommended that patients without a health care professional confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo antibody testing to varicella zoster virus (VZV) before initiating GILENYA® therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with GILENYA®, if not contraindicated (see ADVERSE DRUG REACTIONS). For patients requiring vaccination, initiation of treatment with GILENYA® should be delayed for 1 month after the patient has been vaccinated, to allow the full effect of the vaccination to occur (see WARNINGS AND PRECAUTIONS, Varicella Zoster Vaccination; WARNINGS AND PRECAUTIONS, Vaccination).

In the 24-month placebo controlled multiple sclerosis clinical trial, the overall rate of infections (72%) and serious infections (2%) with GILENYA® 0.5 mg was similar to that of placebo. However, bronchitis and pneumonia were more common in GILENYA®-treated patients (see ADVERSE REACTIONS).

Physicians should advise patients about the potential for increased risk of infections and necessary vigilance during treatment and after discontinuation of treatment with GILENYA® (see

WARNINGS AND PRECAUTIONS, Immune System Effects Following Discontinuation of Treatment). For patients who develop serious infections, suspending treatment with GILENYA® should be considered, and the benefits and risks of treatment should be re-assessed prior to re-initiation of treatment.

Herpetic infections

Two patients died of herpetic infections during controlled trials. One death was due to a disseminated primary varicella zoster infection 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 prolonged (more than 5 days) concomitant 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, disseminated reactivation of varicella zoster virus in a patient that received prolonged concomitant corticosteroid therapy, was fatal.

Physicians should be vigilant for clinical symptoms that may be suggestive of serious herpetic infections. Disseminated herpetic infections should be included in the differential diagnosis when patients who are receiving GILENYA present with an atypical MS relapse or multiorgan failure. For cases of disseminated herpetic infections, antiviral therapy and discontinuation of GILENYA treatment is recommended. Treatment of zoster should follow current relevant guidelines.

Progressive Multifocal Leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in the post-marketing setting (see ADVERSE DRUG REACTIONS). PML is an opportunistic infection caused by JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to severe disability or death. In some of the reported cases, PML has occurred in patients who were not previously treated with natalizumab, which has a known association with PML, and in patients who had not previously taken or were not concomitantly taking any immunosuppressive or immunomodulatory medications. Other ongoing systemic medical conditions resulting in compromised immune system function were not reported in most of these cases. These cases of PML have occurred after approximately 2-3 years of treatment. The relationship between the risk of PML and duration of treatment is not known.

Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, GILENYA® treatment should be suspended until PML has been excluded. 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.

Cryptococcal Meningitis

Cases of cryptococcal meningitis have been reported in the post-marketing setting, generally after

approximately 2-3 years of treatment, but may occur earlier. The relationship between the risk of cryptoccoccal infection and the duration of treatment is not known (see ADVERSE REACTIONS). Patients with symptoms and signs consistent with cryptococcal meningitis should undergo prompt diagnostic evaluation and appropriate treatment should be initiated if cryptococcal meningitis is diagnosed.

Vaccination

- The use of live attenuated vaccines during GILENYA® treatment and for two months after discontinuing treatment is not recommended due to the risk of infection from the vaccine (see WARNINGS AND PRECAUTIONS, Infections).

- Vaccination may be less effective during and for up to two months after discontinuing treatment with GILENYA® (see WARNINGS AND PRECAUTIONS, Immune System Effects Following Discontinuation of Treatment; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics-Immune system).

- For patients with negative IgG antibody test results for VZV due to no previous exposure or vaccination and who do not have contraindications for the vaccine, a full course of vaccination with varicella vaccine is recommended prior to commencing treatment with GILENYA®. Initiation of GILENYA® therapy should be postponed for one month after vaccination to allow the full effect of vaccination to occur (see WARNINGS AND PRECAUTIONS, Varicella Zoster Vaccination).

- The immunization recommendations for adults (routine and specific risk groups) from the National Advisory Committee on Immunization (NACI) (http://www.phac-aspc.gc.ca/im/is-cv/index-eng.php) and local infectious disease experts should be considered when evaluating the need for other vaccinations, before commencing and during treatment with GILENYA®.

Immune System Effects Following Discontinuation of Treatment
If a decision is made to stop treatment with GILENYA®, the physician and patient need to be aware that fingolimod remains in the blood and has pharmacodynamic effects, such as decreased lymphocyte counts for up to two months, following the last dose. Lymphocyte counts typically return to the normal range within 2 months of stopping therapy (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics-Immune system). Physicians should advise patients about the potential for increased risk of infections and necessary vigilance for up to two months after discontinuation of treatment with GILENYA®.

Because of the continuing pharmacodynamic effects of fingolimod, starting other therapies during the 2 months following stopping GILENYA® warrants the same precautions as concomitant treatment with GILENYA®. Use of immunosuppressants soon after the discontinuation of GILENYA® may lead to an additive effect on the immune system and, therefore, caution should be applied (see DRUG INTERACTIONS).

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

Co-administration of anti-neoplastic, immunosuppressive or immune-modulating therapies is not recommended due to the risk of additive immune system effects (see DRUG INTERACTIONS). For the same reason, corticosteroids should be co-administered with caution and specific decisions as to the dosage and duration of concomitant treatment should be based on clinical judgment. Co-administration of a short course of corticosteroids (up to 5 days as per study protocols) did not increase the overall rate of infection in patients treated with fingolimod in the Phase III clinical trials, compared to placebo.

When switching to or from another disease modifying therapy with immunosuppressive or immune modulating effects, the half-life and mode of action of GILENYA® and the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimizing risk of disease reactivation. Prior to initiating the new treatment, a recent CBC should be available to ensure any immune effects (e.g. cytopenia) of the discontinued therapy have resolved.

Beta interferon, glatiramer acetate or dimethyl fumarate

GILENYA® can generally be started immediately after discontinuation of beta interferon, glatiramer acetate or dimethyl fumarate provided that immune effects (e.g. cytopenia) from these therapies have resolved.

Natalizumab or teriflunomide

Elimination of natalizumab usually takes up to 2-3 months following discontinuation. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take several months (average: 8 months) and up to 2 years. Due to the long half-life of natalizumab or teriflunomide, caution regarding potential additive immune effects is required when switching patients from these therapies to GILENYA®. A careful case-by-case assessment regarding the timing of the initiation of GILENYA® treatment is recommended.

Alemtuzumab

Due to the characteristics and duration of alemtuzumab immune suppressive effects described in its Product Monograph, initiating treatment with GILENYA® after alemtuzumab is not recommended unless the benefits of GILENYA® treatment clearly outweigh the risks for the individual patient.

Hepatic/Biliary/Pancreatic

Liver function

Increased hepatic enzymes, mostly alanine aminotransaminase (ALT) elevation, have been reported in multiple sclerosis patients treated with GILENYA®. In clinical trials, a 3-fold the upper limit of normal (ULN) or greater elevation in ALT occurred in 8% of patients treated with GILENYA® 0.5 mg, as compared to 2% of patients on placebo. Elevations 5-fold the ULN occurred in 2% of patients on GILENYA® 0.5 mg and 1% of patients on placebo. In clinical trials, GILENYA® was discontinued if the elevation exceeded 5 times the ULN. Recurrence of

ALT elevations occurred with re-challenge in some patients, supporting a relationship to fingolimod. The majority of elevations occurred within 6-9 months of initiating treatment and serum transaminase levels returned to normal within approximately 2 months after discontinuation of GILENYA® (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings-Liver function).

For all patients, recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with GILENYA®. During treatment, liver enzymes should be evaluated every 3 months for the first year and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurement. With repeated confirmation of liver transaminases above 5 times the ULN, treatment with GILENYA® should be interrupted and only re-commenced once liver transaminase values have normalized. The benefits and risks of treatment should be re-assessed prior to re-initiation of treatment.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine during treatment, should have liver enzymes checked and GILENYA® should be discontinued if significant liver injury is confirmed (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings, Liver function).

Patients with pre-existing liver disease may be at an increased risk of developing elevated liver enzymes during GILENYA® treatment (see WARNINGS AND PRECAUTIONS, Special Populations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Special Populations and Conditions).

Neoplasm

For patients treated with immunosuppressive or immune modulating drugs there is potential for an increased risk of lymphomas and other malignancies, particularly of the skin.

Cases of lymphoma have been reported in clinical trials and in the postmarketing setting with GILENYA® (see ADVERSE REACTIONS).

Basal cell carcinoma (BCC) and other skin cancers have been reported in patients receiving GILENYA® in clinical trials and in the postmarketing setting (see ADVERSE REACTIONS). Vigilance for skin cancer is recommended in patients receiving GILENYA®. Health care professionals and patients are advised to monitor for suspicious skin lesions before initiating treatment and regularly during treatment with GILENYA®. If a suspicious skin lesion is observed, it should be promptly evaluated.

Neurologic

Posterior reversible encephalopathy syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported at 0.5 mg dose in clinical trials and in the post-marketing setting. Symptoms reported included

sudden onset of severe headache, nausea, vomiting, 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.

Ophthalmologic

Macular Edema

Macular edema (see ADVERSE REACTIONS, Macular edema) with or without visual symptoms has been reported in 0.4% of patients treated with GILENYA® 0.5 mg compared to 0.1% of patients receiving placebo. Macular edema was diagnosed predominantly in the first 3-4 months of therapy. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmic examination. Macular edema generally improved or resolved with or without treatment after drug discontinuation, but some patients had residual visual acuity loss even after resolution of macular edema. In clinical trials, treatment with GILENYA® was discontinued when patients developed macular edema and was not re-initiated when the adverse event resolved.

An ophthalmic evaluation is recommended 3-4 months after treatment initiation. If patients report visual disturbances at any time while on GILENYA® therapy, an evaluation of the fundus, including the macula, should be carried out (see WARNINGS AND PRECAUTIONS, Patient Counseling Information).

It is recommended that GILENYA® be discontinued if a patient develops macular edema. Continuation of treatment in patients with macular edema has not been evaluated. A decision on whether or not GILENYA® therapy should be re-initiated after resolution of macular edema needs to take into account the potential benefits and risks for the individual patient.

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 (see ADVERSE REACTIONS, Macular edema). Multiple sclerosis patients with concomitant diabetes mellitus were excluded from the clinical trials with GILENYA®. In other clinical trials with GILENYA® that included diabetic patients, the rate of macular edema was several-fold greater in diabetic patients compared to non-diabetic patients, and macular edema was twice as frequent in patients treated with GILENYA® (diabetic and non-diabetic) compared to patients receiving control treatment.

In addition to an ophthalmic evaluation prior to initiating GILENYA® therapy and at 3-4 months after initiating treatment, regular follow-up evaluations are recommended for multiple sclerosis patients with diabetes mellitus or a history of uveitis while receiving GILENYA® therapy.

Respiratory

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 (see ADVERSE REACTIONS, Respiratory). The changes in FEV1 appear to be reversible after treatment discontinuation, but there is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation.

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

Multiple sclerosis patients with compromised respiratory function (e.g., pulmonary fibrosis, diagnosis of active pulmonary disease, abnormal pulmonary function tests) were excluded from GILENYA® clinical trials.

GILENYA® should be used with caution in patients with severe respiratory disease, pulmonary fibrosis, moderate and severe asthma or chronic obstructive pulmonary disease (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics-Pulmonary Function).

Metabolic

Total Cholesterol, LDL Cholesterol, and Triglycerides

GILENYA® treatment results in increased levels of total cholesterol, LDL cholesterol, and triglycerides (see ADVERSE REACTIONS, Cholesterol and Triglycerides). These observations should be taken into consideration when treating patients with–pre-existing hyperlipidemia, atherosclerosis, or ischemic heart disease.

Sexual Function/Reproduction

Labor and delivery

There are no data on the effects of fingolimod on labor and delivery.

Infertility

Data from preclinical studies does not suggest that fingolimod would be associated with an increased risk of reduced fertility.

Female reproductive toxicity

Based on animal data, GILENYA® is potentially teratogenic (see WARNINGS AND PRECAUTIONS, Special Populations-Pregnant women).

Male reproductive toxicity

Available data do not suggest that GILENYA® would be associated with an increased risk of male-mediated fetal toxicity.

Special Populations

Women of childbearing potential / Contraception: Before initiation of GILENYA® treatment, women of childbearing potential should be counselled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with GILENYA®. Since it takes approximately 2 months to eliminate the compound from the body after stopping treatment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics-Immune system), the potential risk to the fetus may persist and contraception should be continued during this period.

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. The use of GILENYA® in women who are or may become pregnant should only be considered if the potential benefit justifies the potential risk to the fetus.

Animal studies have shown that fingolimod induced reproductive toxicity including fetal loss and teratogenicity when given to pregnant animals. When fingolimod was administered orally to pregnant rats during the period of organogenesis, increased incidences of fetal malformations and embryo-fetal lethality were observed starting at doses corresponding to 2 times the exposure in humans at the recommended dose of 0.5 mg. The most common fetal visceral malformations in rats included persistent truncus arteriosus and ventricular septal defect. Oral administration of fingolimod to pregnant rabbits during organogenesis resulted in increased incidences of embryo-fetal lethality and fetal growth retardation starting at doses similar to the exposure in humans at the recommended dose of 0.5 mg (see TOXICOLOGY).

Pregnancy exposure registry: There is a registry that monitors pregnancy outcomes in women exposed to GILENYA® during pregnancy. If a patient becomes pregnant while taking GILENYA®, physicians are encouraged to report this event by calling the GILENYA® Pregnancy Registry at 1-855-788-5333 or visiting www.gilenyapregnancyregistry.com.

Nursing Women: Fingolimod is excreted in the milk of animals treated during lactation. There are no data on the effects of GILENYA® on the breastfed child or the effects of GILENYA® on milk production. Since many drugs are excreted in human milk and because of the potential for serious adverse drug reactions to fingolimod in nursing infants, women receiving GILENYA® should not breast feed.

Hepatic Impairment: GILENYA® is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) (see CONTRAINDICATIONS). Although no dose adjustments are needed in patients with mild or moderate hepatic impairment, caution should be exercised when initiating treatment with GILENYA® in these patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics - Special Populations and Conditions).

Patients with pre-existing liver disease were excluded from MS clinical trials and it is not known if these patients are at an increased risk of developing elevated liver function tests, more severe liver injury, or other adverse events during treatment with GILENYA® (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Renal Impairment: Caution is recommended when using GILENYA® in patients with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics - Special Populations and Conditions).

Pediatrics (< 18 years of age): GILENYA® is not indicated for use in pediatric patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics - Special Populations and Conditions).

Geriatrics (> 65 years of age): Clinical studies of GILENYA® did not include sufficient numbers of patients aged 65 years and over to assess efficacy and safety in this age group. Due to the greater frequency of reduced hepatic, renal, immune, pulmonary and cardiovascular function, other concomitant diseases and concomitant drug therapy, treatment with GILENYA® merits caution and may necessitate additional or more frequent monitoring in geriatric patients (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Patient Counseling Information

Consumer Information is included in the package of GILENYA® dispensed to the patient. Patients receiving GILENYA® should also be given the following information by the physician and /or pharmacist:

1. ***General***
   Summarize for patients the benefits and potential risks of treatment with GILENYA®.

   Tell patients to take GILENYA® once daily as prescribed. Tell patients not to discontinue GILENYA® without first discussing this with the prescribing physician.

2. ***First-dose cardiovascular effects and monitoring***
   Advise patients that initiation of GILENYA® treatment results in a decrease in heart rate. Inform patients that they will need to have their heart rate and blood pressure monitored in the doctor's office or other medical facility for at least 6 hours after the first dose, and that they will be required to have an ECG performed prior to dosing and at the end of the 6-hour monitoring period. Also inform patients that in case of abnormal ECG recording, very slow heart rate at the end of the 6-hour observation period, or symptoms of bradyarrhythmia they will need to be monitored longer, possibly overnight, until findings have resolved. Symptoms of bradyarrhythmia may include dizziness or palpitations. Advise patients that if GILENYA® is discontinued for more than two weeks, effects similar to those observed on treatment initiation may be seen and observation for at least 6 hours, including periodic assessment of heart rate, will be needed on treatment re-initiation.

3. ***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 there is the potential for additive immune system effects if corticosteroid therapy is required. Advise patients that the use of some vaccines should be avoided during treatment with GILENYA® and for 2 months after discontinuation. Advise patients who have not had chickenpox or vaccination with varicella vaccine that the vaccination is recommended prior to commencing treatment with GILENYA®.

4. ***Blood pressure increase***

Advise patients that an increase in blood pressure could occur during chronic treatment with GILENYA® and that regular monitoring of blood pressure should be undertaken.

5. ***Liver enzyme increases***
   Inform patients that GILENYA® may increase liver enzymes. Advise patients that regular blood testing will be performed and that they should contact their physician if they have any unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine during treatment.

6. ***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.

7. ***Respiratory effects***
   Advise patients that they should contact their physician if they experience new onset or worsening dyspnea.

8. ***Fetal risk***
   Inform patients that, based on animal studies, GILENYA® may cause fetal harm. Discuss the potential risks to the fetus 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.

9. ***Drug interactions***
   Advise patients that concomitant use of certain cardiac medications may increase the risk of bradyarrhythmia with first-dose administration of GILENYA® and ask them to provide information on all medications currently being taken.

   Advise patients that co-administration of anti-neoplastic, immunosuppressive or immune-modulating therapies is not recommended due to the risk of additive immune system effects.

10. ***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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A total of 1703 patients on GILENYA® (fingolimod) (0.5 or 1.25 mg dose) constituted the safety population in the two Phase III studies (D2301 and D2302) for approval in patients with relapsing-remitting multiple sclerosis (see CLINICAL TRIALS). Study D2301 (FREEDOMS) was a 2-year placebo-controlled clinical study involving 1272 multiple sclerosis patients treated with fingolimod (854: 425 on fingolimod 0.5 mg, 429 on fingolimod 1.25 mg) or placebo (418).

In this study, the most serious adverse events (AEs) for the 0.5 mg recommended therapeutic dose were infections, macular edema, and bradycardia or atrioventricular blocks on treatment initiation (see WARNINGS AND PRECAUTIONS). The most frequent AEs (incidence ≥10% and more frequent than with placebo) reported with the 0.5 mg dose were headache, influenza, diarrhea, back pain, liver enzyme elevations and cough. The only adverse event that led to more than 1% of patients receiving GILENYA® 0.5 mg to stop therapy was serum transaminase elevations, leading to drug discontinuation in 3.8% of patients.

Study D2302 (TRANSFORMS) was a 1-year controlled study using interferon beta-1a as comparator involving 1280 patients with multiple sclerosis treated with fingolimod (849: 429 on fingolimod 0.5 mg, 420 on fingolimod 1.25 mg) or interferon beta-1a (431). In Study D2302, the most frequently reported AEs (≥ 10%), serious AEs and AEs leading to discontinuation were generally similar to those reported in placebo-controlled studies, taking into account the differences in study duration.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Treatment emergent adverse events (AEs) are listed according to MedDRA system organ class.

Table 1 - Treatment emergent AEs occurring in ≥1% of patients in Study D2301, and reported for GILENYA® 0.5 mg at ≥1% higher rate than for placebo.

Primary system organ class Preferred Term	Placebo N=418 (%)	Fingolimod 0.5mg N=425 (%)
Infections		
Influenza viral infections	41 (9.8)	55 (12.9)
Bronchitis	15 (3.6)	34 (8.0)
Sinusitis	19 (4.5)	28 (6.6)
Gastroenteritis	13 (3.1)	19 (4.5)
Pneumonia*	1 (0.2)	2 (0.5)
Herpes viral infections*	33 (7.9)	37 (8.7)
Tinea infections	6 (1.4)	16 (3.8)
Cardiac Disorders		
Bradycardia	4 (1.0)	15 (3.5)
Nervous system disorders		

Table 1 - Treatment emergent AEs occurring in ≥1% of patients in Study D2301, and reported for GILENYA® 0.5 mg at ≥1% higher rate than for placebo.

Primary system organ class Preferred Term	Placebo N=418 (%)	Fingolimod 0.5mg N=425 (%)
Headache	96 (23.0)	107 (25.2)
Dizziness	23 (5.5)	31 (7.3)
Paresthesia	18 (4.3)	23 (5.4)
Migraine	6 (1.4)	20 (4.7)
Gastrointestinal disorders		
Diarrhea	31 (7.4)	50 (11.8)
General disorders and administration site conditions		
Asthenia	5 (1.2)	11 (2.6)
Musculoskeletal and connective tissue disorders		
Back pain	29 (6.9)	50 (11.8)
Skin and subcutaneous tissue disorders		
Eczema	8 (1.9)	14 (3.3)
Alopecia	10 (2.4)	15 (3.5)
Pruritus	5 (1.2)	11 (2.6)
Investigations		
Alanine transaminase (ALT) increased	16 (3.8)	43 (10.1)
Gamma-glutamyl transferase (GGT) increased	4 (1.0)	22 (5.2)
Hepatic enzyme increased	1 (0.2)	14 (3.3)
Weight decreased	14 (3.3)	20 (4.7)
Blood triglycerides increased	5 (1.2)	11 (2.6)
Liver function test abnormal	1 (0.2)	6 (1.4)
Respiratory, thoracic and mediastinal disorders		
Cough	34 (8.1)	43 (10.1)
Dyspnea	19 (4.5)	34 (8.0)
Psychiatric disorders		
Depression	28 (6.7)	33 (7.8)
Eye disorders		
Eye pain	6 (1.4)	11 (2.6)
Vision blurred	6 (1.4)	15 (3.5)
Vascular disorders		

Table 1 - Treatment emergent AEs occurring in ≥1% of patients in Study D2301, and reported for GILENYA® 0.5 mg at ≥1% higher rate than for placebo.

Primary system organ class Preferred Term	Placebo N=418 (%)	Fingolimod 0.5mg N=425 (%)
Hypertension	16 (3.8)	27 (6.4)
Blood and lymphatic system disorders		
Leucopenia	1 (0.2)	12 (2.8)
Lymphopenia	2 (0.5)	15 (3.5)

* Plausible relationship to study drug

Infections

In the two-year multiple sclerosis clinical trial, the overall rate of infections (72%) and serious infections (2%) at the 0.5 mg dose was similar to placebo. However, bronchitis and pneumonia were more common in GILENYA®-treated patients (Table 1).

There have been very rare fatal cases of VZV infections in patients taking GILENYA® (at the recommended dose or higher doses used in clinical trials). These patients received prolonged concomitant corticosteroid use (more than 5 days) for treatment of multiple sclerosis relapses.

There have been very rare cases of other herpes viral infections with fatal outcome. Some cases of disseminated herpes infections have been reported, including fatal cases, with one case at the 0.5 mg dose (see WARNINGS AND PRECAUTIONS, Herpetic Infections).

Macular Edema

In clinical trials, macular edema occurred in 0.4% of patients treated with the recommended GILENYA® dose of 0.5 mg, 1.1% of patients treated with the higher 1.25 mg dose, and in 0.1% of patients that received placebo.

The majority of cases in multiple sclerosis clinical trials occurred within the first 3-4 months of therapy. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmic examination. Treatment with GILENYA® was discontinued in all cases of macular edema. The macular edema generally improved or resolved spontaneously after drug discontinuation. The risk of recurrence after re-challenge has not been evaluated (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

Macular edema incidence is increased in multiple sclerosis patients with a history of uveitis (approximately 20% in those with a history of uveitis vs. 0.6% without a history of uveitis).

Patients with diabetes mellitus were excluded from multiple sclerosis clinical trials. In renal transplant clinical studies where patients with diabetes mellitus were included, the incidence of macular edema was several-fold greater in patients with diabetes compared to non-diabetic

patients. In addition, therapy with fingolimod 2.5 mg and 5 mg resulted in a 2-fold increase in the incidence of macular edema in those studies. Multiple sclerosis patients with diabetes mellitus are therefore expected to be at a higher risk for macular edema (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

ECG Findings

GILENYA® was associated with PR interval prolongation, QTc interval prolongation, and decreased heart rate (see WARNINGS AND PRECAUTIONS, Cardiovascular; DRUG INTERACTIONS, Pharmacodynamic Interactions; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics-Heart rate and rhythm, -Thorough QT Study).

Bradyarrhythmia

Initiation of GILENYA® treatment results in a reversible decrease in heart rate that may also be associated with AV conduction delays (see WARNINGS AND PRECAUTIONS, Cardiovascular; DRUG INTERACTIONS, Pharmacodynamic Interactions; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics-Heart rate and rhythm).

In multiple sclerosis clinical trials the mean maximum decrease in heart rate after taking the first dose was seen within 6 hours post-dose, with a decline in the mean heart rate of 8 beats per minute for GILENYA® 0.5 mg at 5 h post-dosing. The placebo-adjusted change in mean hourly heart rate at 6 h post-dosing was approximately 13 beats per minute according to 24 h Holter monitoring. The second dose may result in a slight further decrease. Patients who experienced bradycardia were generally asymptomatic but some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue, palpitations, and/or chest pain or chest discomfort, which resolved within the first 24 hours of treatment. Heart rate returned to baseline within 1 month of chronic dosing.

In the multiple sclerosis clinical trial program first-degree AV block (prolonged PR interval on ECG) was detected following drug initiation in 4.7% of patients receiving GILENYA® 0.5 mg, in 2.8% of patients receiving intramuscular interferon beta-1a and in 1.5% of patients receiving placebo. Second-degree AV block Mobitz type 1 (Wenckebach) was detected in 0.2% of patients on GILENYA® 0.5 mg.

Isolated reports of complete AV block during the 6 hour observation period and delayed onset cardiac events, including transient asystole and death within 24 hours of the first dose, have been reported during postmarketing experience and the relationship to GILENYA® cannot be excluded (see ADVERSE REACTIONS, Post-Market Adverse Events).

The conduction abnormalities observed both in clinical trials and post-marketing were typically transient, asymptomatic and resolved within 24 hours. Although most patients in clinical trials did not require medical intervention, one patient on the 0.5 mg dose received isoprenaline (isoproterenol) for an asymptomatic 2nd-degree Mobitz I AV block.

Blood pressure

GILENYA® is associated with a *decrease* of blood pressure after the first dose. Chronic treatment is associated with an *increase* in blood pressure.

On the first day of treatment in multiple sclerosis clinical trials, GILENYA® was associated with a decrease in systolic, diastolic, and mean arterial BP, starting at 1 hour post-dose, reaching its maximal decrease after 4-5 hours. The maximal decrease from pre-dose values in mean arterial BP was 3.5 mmHg (5 hours post-dose) in the GILENYA® 0.5 mg group compared to a maximal mean decrease of 1.8 mmHg (4 hours post-dose) in the placebo group (see WARNINGS AND PRECAUTIONS, Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics-Blood Pressure).

In multiple sclerosis clinical trials GILENYA® 0.5 mg was associated with increases of approximately 2 mmHg in systolic pressure, and 1 mmHg in diastolic pressure manifesting after approximately 1 month of treatment initiation. These increases persisted with continued treatment. In controlled studies involving 854 multiple sclerosis patients on GILENYA® 0.5 mg and 511 multiple sclerosis patients on placebo, hypertension was reported as an adverse reaction in 5% of patients on GILENYA® 0.5 mg and in 3% of patients on placebo.

Vascular events

Rare cases of ischemic stroke and hemorrhagic stroke have been reported in patients treated with GILENYA® in clinical trials and in the post-marketing setting. The relationship to GILENYA® remains uncertain. In phase III clinical trials, rare cases of peripheral arterial occlusive disease occurred in patients receiving fingolimod at doses of 1.25 mg (2.5 times the recommended dose) and 5.0 mg (10 times the recommended dose).

Neoplasms

In pooled data from the two placebo-controlled Phase III clinical trials, D2301 (FREEDOMS) and D2309 (FREEDOMS II), basal cell carcinoma has been reported in 14/783 (1.8%) patients receiving fingolimod, and in 5/773 (0.6%) patients on placebo.

There have been cases of other skin cancer and lymphoma in clinical studies and the post-marketing setting; however a causal relationship has not been established. The reported lymphoma cases were heterogeneous in nature, including B-cell and T-cell lymphomas (see WARNINGS AND PRECAUTIONS, Neoplasm).

Respiratory system

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 (see WARNINGS AND PRECAUTIONS, Respiratory). At Month 24, the reduction from baseline in the percent of predicted values for FEV1 was 3.1% for GILENYA® 0.5 mg and 2.0% for placebo, corresponding to a mean decrease of 150 mL/**s** and 120 mL/**s**, respectively. For DLCO, the reductions from baseline in percent of predicted values at Month 24 were 3.8% for GILENYA® 0.5 mg and 2.7% for placebo. The changes in FEV1 appear to be reversible after treatment discontinuation, but there is insufficient

information to determine the reversibility of the decrease of DLCO after drug discontinuation.

In the 24-month multiple sclerosis placebo-controlled trial, dyspnea was reported in 7.1% of patients receiving GILENYA® 0.5 mg and 4.5% of patients receiving placebo. Several patients discontinued GILENYA® because of unexplained dyspnea during the extension (uncontrolled) studies.

Other Adverse Events Observed During Double blind Controlled Clinical Trials in MS

The D2309 study (FREEDOMS II) was a 2-year prospective, double blind study designed to evaluate the efficacy, safety, and tolerability of two doses of fingolimod (1.25 mg and 0.5 mg) compared with placebo in patients with RRMS. This Phase III study was completed after the approval of the fingolimod. The three arms of the study were fingolimod 1.25 mg (n=370); fingolimod 0.5 mg (n=358) and placebo (n=355). The safety data from the study were very consistent with the D2301 study. In this study, the incidence of increased AST adverse events was higher for fingolimod (0.5 mg) than placebo (3.1% vs 1.4%).

Post-Market Adverse Reactions

The following adverse reactions have been reported during postmarketing experience:

Cardiac Disorders: Isolated reports of transient, spontaneously resolving complete AV block have been observed during the six-hour observation period with GILENYA®. Isolated delayed-onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose of GILENYA®. These cases have been confounded by concomitant medications and/or pre-existing disease, but the relationship to GILENYA® cannot be excluded.

Infections and Infestations: Hemophagocytic syndrome with fatal outcome has been reported with fingolimod treatment in the context of infection. Hemophagocytic syndrome is a rare condition that has been described in association with infections and a variety of autoimmune disease and cases have been reported in patients with MS.

Cases of infections with opportunistic viral (e.g. VZV, JCV causing PML, HSV), fungal (e.g. cryptococci including cryptococcal meningitis), or bacterial (e.g. atypical mycobacterium) pathogens, have been reported (see WARNINGS AND PRECAUTIONS, Immune).

Immune system disorders: Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation.

Gastrointestinal disorders: nausea

Because adverse reactions identified during post-marketing use are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Abnormal Hematologic and Clinical Chemistry Findings

Liver function

Increased hepatic enzymes (mostly ALT elevation) have been reported in multiple sclerosis patients treated with GILENYA®. In clinical trials, patients treated with GILENYA® experienced an asymptomatic elevation in serum levels of ALT, irrespective of adverse event reporting. Three-fold or greater increases in ALT were seen in 8.5% of patients receiving GILENYA® 0.5 mg compared to 1.7% of those on placebo while ≥5-fold elevations were seen in 1.9% and 1.0% of patients, respectively, in the two-year placebo-controlled multiple sclerosis clinical trial. The majority of ALT elevations occurred within 6-9 months of initiating treatment with GILENYA®. Findings were similar, but less frequent for AST and GGT.

ALT levels returned to normal after discontinuation of GILENYA® within approximately 2 months. In a small number of patients (2 patients on GILENYA® 0.5 mg), who experienced liver transaminase elevations of ≥5x ULN and who continued on GILENYA® therapy, the ALT levels returned to normal within approximately 5 months (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Cholesterol and Triglycerides

In the 24 month placebo-controlled multiple sclerosis clinical trial D2301, total cholesterol and triglyceride levels were increased during treatment with GILENYA® 0.5 mg from Week 2 to Month 24. The incidence of notable high cholesterol levels (> 6.21 mmol/L) was 39.6% for GILENYA® 0.5 mg and 31.9% for placebo. The incidence of notable high triglyceride levels (> 3.39 mmol/L) was 13.7% for GILENYA® 0.5 mg and 7.5% for placebo.

DRUG INTERACTIONS

Overview

Pharmacodynamic interactions

Anti-neoplastic, immunosuppressive or immune-modulating drugs: Co-administration of anti-neoplastic, immunosuppressive or immune modulating therapies is not recommended due to the risk of additive immune system effects. Caution should also be applied when switching patients from long-acting therapies with immune effects such as natalizumab, teriflunomide or mitoxantrone (see WARNINGS AND PRECAUTIONS, Immune).

Co-administration of a short course of corticosteroids (up to five days as per study protocol) to treat relapses did not increase the overall rate of infection in patients treated with fingolimod in the Phase III clinical trials, compared to placebo (see WARNINGS and PRECAUTIONS and ADVERSE REACTIONS). Patients should be reminded of the potential for increased risk of infection due to the risk of additive immune system effects of corticosteroids.

Heart rate lowering drugs: GILENYA® (fingolimod) treatment results in PR interval prolongation during the first week and heart rate decrease during the first month of treatment. Due to potential additive effects on heart rate or cardiac conduction, GILENYA® should not be used concomitantly with heart rate lowering drugs (e.g. antiarrhythmics, beta blockers, calcium

channel blockers) (see WARNINGS AND PRECAUTIONS, Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics-Heart rate and rhythm).

Fingolimod has been studied in combination with atenolol or diltiazem. When a single dose of fingolimod 5 mg/day was used with atenolol 50 mg/day (steady state) in an interaction study in healthy volunteers, there was an additional 15% reduction of heart rate at fingolimod treatment initiation, an effect not seen with diltiazem 240 mg/day (steady state).

GILENYA® should not be initiated in patients receiving beta-blockers, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem), or other substances that may decrease heart rate (e.g. digoxin, cholinesterase inhibitors, or pilocarpine) because of the potential additive effects on heart rate. If treatment with GILENYA® is considered necessary, advice from a cardiologist should be sought regarding the switch to a non heart-rate lowering drug or for appropriate monitoring (e.g., at least overnight monitoring) during treatment initiation, if the heart-rate-lowering drugs cannot be discontinued (see WARNINGS AND PRECAUTIONS, Cardiovascular).

QTc prolonging drugs: GILENYA® may result in QTc prolongation during the first month of treatment (See WARNINGS AND PRECAUTIONS, Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics-Thorough QT Study). GILENYA® has not been studied in patients treated with drugs that prolong the QT interval.

Class Ia antiarrhythmics (e.g., quinidine, disopyramide) and Class III antiarrhythmics (e.g., amiodarone, sotalol) may prolong the QTc interval and have been associated with cases of torsades de pointes in patients with bradycardia and these drugs were excluded from use in multiple sclerosis clinical trials. Since initiation of GILENYA® treatment results in both a decreased heart rate and a prolongation of QTc interval, GILENYA® should not be used concomitantly with Class Ia or Class III drugs (see WARNINGS AND PRECAUTIONS, Cardiovascular-Bradyarrhythmia).

The initiation of treatment with GILENYA® in a patient taking other types of QTc prolonging drugs should be avoided. If a decision is made to undertake treatment such patients should be evaluated by a cardiologist prior to initiation of treatment, to assess suitability and to determine the most appropriate monitoring, which should be at least overnight.

In addition to the Class Ia and Class III antiarrhythmic drugs, other drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples found below. Chemical/ pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc prolongation and/or torsade de pointes:

Class 1C antiarrhythmics (e.g., flecainide, propafenone); antipsychotics (e.g., chlorpromazine, haloperidol); antidepressants (e.g., fluoxetine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline); opioids (e.g., methadone); macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, tacrolimus); quinolone antibiotics (e.g., ciprofloxacin); antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole); domperidone; 5-HT3 receptor antagonists (e.g., ondansetron); tyrosine kinase inhibitors (e.g.,

sunitinib); histone deacetylase inhibitors (e.g., vorinostat); beta-2 adrenoceptor agonists (e.g., salmeterol).

Current information sources should be consulted for newly approved drugs that prolong the QT/QTc interval as well as for older drugs for which this effect has recently been established.

Vaccines: During and for up to 2 months after treatment with GILENYA® vaccination may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided (see WARNINGS AND PRECAUTIONS, Immune - Vaccination).

Pharmacokinetic interactions

Fingolimod is primarily cleared *via* human cytochrome P450 4F2 (CYP4F2) and possibly other CYP4F isoenzymes. *In vitro* studies in hepatocytes indicated that CYP3A4 may contribute to fingolimod metabolism in the case of strong induction of CYP3A4.

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 demonstrated that fingolimod and fingolimod-phosphate have little or no capacity to inhibit the activity of CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11 (fingolimod only)). Therefore, fingolimod and fingolimod-phosphate are unlikely to reduce the clearance of drugs that are mainly cleared through metabolism by the major CYP isoenzymes.

Potential of fingolimod and fingolimod-phosphate to induce its own and/or the metabolism of co-medications

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2, and ABCB1 (P-gp or 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 ABCB1 with respect to the vehicle control. Therefore, no clinically relevant induction of the tested CYP enzymes or ABCB1 (P-gp) by fingolimod is expected at therapeutic concentrations. *In vitro* experiments did not provide an indication of CYP induction by fingolimod-phosphate.

Potential of fingolimod and fingolimod-phosphate to inhibit the active transport of co-medications

Based on *in vitro* data, fingolimod as well as fingolimod-phosphate are not expected to inhibit the uptake of co-medications and/or biologics transported by the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1, OATP1B3) or the sodium taurocholate co-transporting polypeptide (NTCP). Similarly, they are not expected to inhibit the efflux of co-medications 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.

Drug-Drug Interactions

Oral contraceptives

In an open label two-period study, healthy female volunteers (n=31) on a steady regimen of oral contraceptive (ethinylestradiol and levonorgestrel) received the oral contraceptive alone for 14 days, followed by co-administration of the oral contraceptive and fingolimod 0.5 mg/day for an additional 14 days. The steady state co-administration of fingolimod and the oral contraceptive did not elicit any change in oral contraceptive exposure. Fingolimod and fingolimod-phosphate exposure were consistent with those from previous studies.

No interaction studies have been performed with oral contraceptives containing other progestogens, however an effect of fingolimod on their exposure is not expected.

Cyclosporine

The pharmacokinetics of single-dose fingolimod were not altered during co-administration with cyclosporine at steady-state, nor were cyclosporine (CYP3A4 substrate) steady-state pharmacokinetics altered by single-dose, or multi-dose (28 days) fingolimod administration. These data suggest that fingolimod is not likely to reduce or increase the clearance of drugs mainly cleared by CYP3A4 and that inhibition of CYP3A4 is unlikely to reduce the clearance of fingolimod. Potent inhibition of transporters P-gp, MRP2 and OATP1B1 does not influence fingolimod disposition.

Ketoconazole

In an open-label, two-period crossover study, healthy volunteers (N=22) received a single dose of 5 mg fingolimod on Day 1 of the first period and ketoconazole 200 mg twice daily for 9 days during the second period, with a single 5 mg dose of fingolimod administered on the fourth day of ketoconazole treatment. The co-administration of ketoconazole 200 mg twice daily at steady-state and a single dose of fingolimod 5 mg led to a 1.7-fold increase in the AUC of fingolimod and fingolimod-phosphate by inhibition of CYP4F2. This study did not evaluate the effect of chronic co-administration of ketoconazole, a potent inhibitor of CYP3A and CYP4F2, on fingolimod pharmacokinetics. Therefore, caution should be exercised during chronic co-administration of GILENYA® and systemic ketoconazole and patients should be closely monitored as the risk of adverse events may be increased.

Isoproterenol and atropine

Single-dose fingolimod and fingolimod-phosphate exposure was not altered by co-administered isoproterenol, or atropine.

Carbamazepine

The co-administration of carbamazepine 600 mg twice daily at steady-state and a single dose of fingolimod 2 mg decreased the AUC of fingolimod and fingolimod-phosphate by approximately

40%. The clinical relevance of this decrease is unknown; however, the co-administration of carbamazepine may decrease the efficacy of fingolimod treatment.

Drug-Laboratory Interactions

Since fingolimod reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilized to evaluate the lymphocyte subset status of a patient treated with GILENYA®.

Laboratory tests requiring the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes.

DOSAGE AND ADMINISTRATION

Dosing Considerations

See WARNINGS AND PRECAUTIONS, Cardiovascular for complete information on patients with certain cardiovascular conditions in which GILENYA® should not be used or which may require additional monitoring.

Conditions when GILENYA® should not be used

- GILENYA® should not be initiated in patients on concurrent therapy with beta-blockers, with heart-rate lowering calcium channel blockers or with other substances that may decrease heart rate. If treatment with GILENYA® is considered necessary, advice from a cardiologist should be sought regarding a switch to drugs that do not lower heart rate or for appropriate monitoring during treatment initiation, if the heart-rate-lowering drugs cannot be discontinued (see WARNINGS AND PRECAUTIONS, Cardiovascular-Bradyarrhythmia; DRUG INTERACTIONS-Heart rate lowering drugs).

- The use of GILENYA® with drugs that prolong the QT interval should be avoided. If a decision is made to undertake treatment such patients should be evaluated by a cardiologist prior to initiation of treatment, to assess suitability and to determine the most appropriate monitoring, which should be at least overnight (see WARNINGS AND PRECAUTIONS, Cardiovascular-QTc prolongation; DRUG INTERACTIONS-QTc prolonging drugs).

See WARNINGS AND PRECAUTIONS, Cardiovascular-Bradyarrhythmia for other conditions when GILENYA® should not be used.

First dose monitoring

- For all patients, obtain an ECG and measure blood pressure prior to dosing and 6-hours after the first dose.
- Monitor all patients for signs and symptoms of bradyarrhythmia, with hourly pulse and blood pressure measurements, for at least 6 hours after the first dose.

- If symptoms of bradyarrhythmia or AV block occur, initiate appropriate management, with continued monitoring (e.g., continuous ECG) until the symptoms have resolved (see WARNINGS AND PRECAUTIONS, Cardiovascular, Bradyarrhythmia).

See WARNINGS AND PRECAUTIONS, Cardiovascular-Bradyarrhythmia for additional recommendations for extended monitoring.

- Patients should be advised that the ability to drive an automobile or operate dangerous equipment may be impaired during the first day of treatment.

- Re-initiation of GILENYA® after a treatment interruption of more than 2 weeks after the first month of treatment may produce the same effect on heart rate as the initial dose. Patients should be monitored as for the first dose. Within the first 2 weeks of treatment, first-dose procedures are recommended after an interruption of one day or more. During week 3 and 4 of treatment, first dose procedures are recommended after a treatment interruption of more than 7 days (see WARNINGS AND PRECAUTIONS, Cardiovascular-Re-initiation of therapy following discontinuation).

Dosing in special populations

- *Renal impairment*: GILENYA® should be used with caution in patients with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Special Populations and Conditions).

- *Hepatic impairment*: GILENYA® is contraindicated in patients with severe hepatic impairment (Child-Pugh class C) (see CONTRAINDICATIONS). Although dose adjustments are not needed in patients with mild and moderate hepatic impairment, caution should be exercised when initiating GILENYA® treatment in these patients (ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Special Populations and Conditions; WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic-Liver Function).

- *Pediatric patients*: GILENYA® is not indicated for use in pediatric patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Special Populations and Conditions).

- *Geriatric patients*: GILENYA® should be used with caution in patients aged 65 years and over due to the greater frequency of reduced hepatic, renal, immune, pulmonary and cardiovascular function, other concomitant diseases and concomitant drug therapy (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Special Populations; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Special Populations and Conditions).

- *Ethnicity*: No GILENYA® dose adjustments are needed based on ethnic origin (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Special Populations and Conditions).

- *Gender*: No GILENYA® dose adjustments are needed based on gender (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Special Populations and Conditions).

- *Diabetic patients*: GILENYA® should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular edema (see ADVERSE REACTIONS, Macular Edema). Multiple sclerosis patients with concomitant diabetes mellitus were excluded from the clinical trials with GILENYA®.

Recommended Dose and Dosage Adjustment

The recommended dose of GILENYA® is one 0.5 mg capsule taken orally once daily, which can be taken with or without food.

Patients already on beta interferon or glatiramer acetate therapy can switch directly to GILENYA® if they do not display signs of treatment-related abnormalities such as cytopenia. Caution is advised when switching patients from natalizumab or teriflunomide to GILENYA®. For recommendations related to switching patients from other disease modifying therapies to GILENYA®, see WARNINGS AND PRECAUTIONS: Immune - Prior treatment with immunosuppressive or immune-modulating therapies.

Missed Dose

If a dose is missed, treatment should be continued with the next dose as planned.

If the treatment is interrupted for one day or more during the first two weeks of treatment, first dose procedures are recommended upon reinitiation (see WARNINGS AND PRECAUTIONS, Cardiovascular – Re-initiation Therapy Following discontinuation).

Administration

GILENYA® is taken orally, with or without food.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Single doses of fingolimod up to 40 mg (80-fold the recommended dose of 0.5mg) were well tolerated in healthy volunteers. Fingolimod doses of 5 mg to 40 mg were associated with a mild to moderate, dose dependent decrease in FEV1. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with small airway reactivity.

Fingolimod can induce bradycardia. The decline in heart rate usually starts within one hour of the first dose, and is maximal within 6 hours. There have been reports of slow atrioventricular conduction with isolated reports of transient, spontaneously resolving complete AV block (see WARNINGS AND PRECAUTIONS-Cardiovascular; and ADVERSE DRUG REACTIONS-

Bradyarrhythmia, -Post Market Adverse Events).

In case of GILENYA® overdosage, observe patients overnight with continuous ECG monitoring in a medical facility and obtain regular measurements of pulse rate and blood pressure (see DOSAGE AND ADMINISTRATION-Dosing Considerations; and WARNINGS AND PRECAUTIONS-Cardiovascular).

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fingolimod is metabolized by sphingosine kinase to the active metabolite fingolimod-phosphate. Fingolimod-phosphate, binds with high affinity to sphingosine 1-phosphate (S1P) receptors 1, 3, 4, and 5. Fingolimod-phosphate binding to S1P receptors on lymphocytes induces S1P receptor down-regulation on lymphocytes, and 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 not known, but may involve reduction of lymphocyte migration into the central nervous system.

Pharmacodynamics

Immune system

Effects on immune cell numbers in the blood. In a study in which 12 subjects were treated with GILENYA® (fingolimod) 0.5 mg/day for 28 days, the mean lymphocyte count was decreased to approximately 70% of baseline within 4 hours after the first dose and approximately 50% within 8 hours. With continued daily dosing, the lymphocyte count continued to decrease over a 2-week period, reaching a nadir count of approximately 500 cells/µL or approximately 30% of baseline. Low lymphocyte counts are maintained with chronic daily dosing.

In the 2-year placebo-controlled multiple sclerosis clinical trial in which 425 patients were treated with GILENYA® 0.5 mg and 418 patients received placebo, 18% of patients on 0.5 mg fingolimod reached a nadir below 200 cells/µL on at least one occasion. Approximately 4% of patients on 0.5 mg fingolimod had lymphocyte counts below 200 cells/µL on two or more consecutive tests separated by approximately 3 months, and for the majority of these patients lymphocyte counts remained at this level for at least 180 days. Treatment was interrupted when patients had confirmed lymphocyte counts below 200 cells/µL and lymphocyte counts were monitored frequently until levels returned to 600 cells/µL.

Peripheral lymphocyte count increases are evident within days of stopping fingolimod treatment. Because elimination of fingolimod after discontinuation of GILENYA® may take up to 2 months (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics), recovery of peripheral lymphocyte counts to baseline values is gradual. For patients in multiple sclerosis clinical trials who had lymphocyte count results available both at the end of treatment and during the 3-month

interval following discontinuation of treatment, lymphocyte counts returned to normal values within 3 months of discontinuing treatment. Delayed recovery, beyond 3 months, of lymphocyte counts was uncommon and showed a potential correlation with higher doses of fingolimod, the occurrence of lymphocyte counts < 0.2 x 10^9/L while on treatment, and longer duration of exposure to fingolimod.

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

Effect on antibody response. Immunologic responses are decreased during treatment with GILENYA® 0.5 mg. 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, respectively, in subjects on GILENYA® 0.5 mg. Similarly, IgG titers were decreased by 45% and 50%, in response to KLH and PPV, 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 multiple sclerosis).

Heart rate and rhythm

Fingolimod causes a reversible prolongation of PR interval and reduction in heart rate upon treatment initiation (see ADVERSE REACTIONS). The maximum decline in heart rate is seen in the first 6 hours post dose, with 70% of the negative chronotropic effect achieved on the first day. Heart rate progressively returns to baseline values within 1 month of chronic treatment.

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

With initiation of fingolimod treatment there is an increase in atrial premature contractions, but there is no increased rate of atrial fibrillation/flutter, ventricular arrhythmias or ectopy. Fingolimod treatment is not associated with a decrease in cardiac output.

The decrease in heart rate induced by fingolimod can be reversed by atropine, isoproterenol (isoprenaline) or salmeterol.

Thorough QT Study

In a placebo-controlled, double-blind, parallel group study, healthy volunteers were randomized to receive placebo (N=55), fingolimod 1.25 mg (N=53), or fingolimod 2.5 mg (N=61) for 7 days. A loading dose procedure was used to enable steady-state to be reached more quickly. The

therapeutic 0.5 mg dose was not studied. Serial ECG recordings were performed for 12 h at baseline and on day 7. Fingolimod was associated with statistically significant QTc prolongation at all time points on day 7, with a maximum effect of 10.9 msec (90% CI 7.88, 13.91) at 6 h post-dosing in the fingolimod 1.25 mg group and 11.1 ms (90% CI 7.56, 14.62) at 6 h post-dosing in the fingolimod 2.5 mg group.

Blood Pressure

Acute dosing with fingolimod resulted in statistically significant decreases in standing systolic and diastolic blood pressure from 2-14 h on Day 1 dosing. The maximum decrease in standing systolic and diastolic blood pressure was -9.5 and -7.6 mmHg respectively at 6 h post-dosing in the fingolimod 1.25 mg treatment group. The therapeutic 0.5 mg dose was not studied. *Chronic dosing* led to statistically significant increases in systolic and diastolic blood pressure on day 28. (see WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, Blood Pressure).

Pulmonary function

Single doses of fingolimod ≥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 placebo-controlled study of subjects with moderate asthma but without multiple sclerosis given fingolimod at doses 0.5mg, 1.25 mg and 2.5 mg or placebo for 10 days (n=9 subjects/group), a significant 10% reduction in mean time-matched, baseline-corrected AUEC FEV1 for the period of 0 to 6 hours after dosing on Day 10 was observed in patients receiving fingolimod 1.25 mg (2.5-times the recommended dose). Changes in FEV1 in the fingolimod 0.5mg and 2.5mg dose groups were, however, not statistically different from those observed in the placebo group. Fingolimod 1.25 mg however was associated with a 5-fold increase in the use of rescue short acting beta-agonists. There was a 2-fold increase (not statistically significant) in the use of rescue short-acting agonists in the fingolimod 0.5 mg group.

Pharmacokinetics

Absorption: The pharmacokinetic parameters of GILENYA® 0.5 mg after a single dose and at steady-state are displayed in the table below.

	Fingolimod		Fingolimod-P	
	Single dose	Steady-state	Single dose	Steady-state
Tmax, h	12	12	6	6
Cmax, ng/mL	0.42	3.66	0.45	1.81
$AUC_{0\text{-}24h}$, ng.h/mL	7.84	76.1	6.1	33.1

Values are mean, except Tmax (median)

Fingolimod absorption is slow (T_{max} of 12-16 hours) and extensive (≥85%, based on the amount of radioactivity excreted in urine and the amount of metabolites in feces extrapolated to infinity). The apparent absolute oral bioavailability is 93%.

Food intake does not alter C_{max} or exposure (AUC) of fingolimod or fingolimod-phosphate. The time to reach maximum drug concentration in blood plasma (T_{max}) is increased when GILENYA® is taken with food. GILENYA® may be taken without regard to meals (see DOSAGE AND ADMINISTRATION).

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

Distribution: Fingolimod highly distributes in red blood cells, with the fraction in blood cells of 86%. Fingolimod-phosphate has a smaller uptake in blood cells of <17%. Fingolimod and fingolimod-phosphate are highly protein bound (>99.7%). 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 three main pathways; by reversible stereoselective phosphorylation to the pharmacologically active (*S*)-enantiomer of fingolimod-phosphate, by oxidative biotransformation catalyzed mainly by CYP4F2 and possibly other CYP4F isoenzymes and subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive non-polar ceramide analogs of fingolimod.

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 radio-labeled 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%)).

Excretion: Fingolimod blood clearance is 6.3±2.3 L/h, and the average apparent terminal half-life ($t_{1/2}$) is 6-9 days. Blood levels of fingolimod-phosphate decline in parallel with fingolimod in the terminal phase yielding similar half-life 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 representing less than 2.5% of the dose each. After 34 days, the recovery of the administered dose is 89%.

Special Populations and Conditions

Pediatrics: The safety and efficacy of GILENYA® in patients below the age of 18 have not been studied. GILENYA® is not indicated for use in pediatric patients.

Geriatrics: Clinical studies of GILENYA® did not include sufficient numbers of patients aged 65 years and over to determine whether the safety and efficacy of GILENYA® differs in elderly patients compared to younger patients. Due to the greater frequency of reduced hepatic, renal, immune, pulmonary and cardiovascular function, other concomitant diseases and concomitant drug therapy, treatment with GILENYA® merits caution and may necessitate additional or more frequent monitoring in geriatric patients.

Gender: Gender has no influence on fingolimod and fingolimod-phosphate pharmacokinetics.

Race: The effects of ethnic origin on fingolimod and fingolimod phosphate pharmacokinetics are not of clinical relevance.

Hepatic Insufficiency: The pharmacokinetics of single-dose fingolimod (1 or 5 mg), when assessed in subjects with mild, moderate or severe hepatic impairments (Child-Pugh class A, B, and C), showed no change on fingolimod $C_{max,}$ but an increase in AUC by 12%, 44% and 103%, respectively. The apparent elimination half-life is unchanged in mild hepatic impairment but is prolonged by 49-50% in moderate and severe hepatic impairment. The rate of lymphocyte count recovery was approximately 4-fold slower in the subjects with severe hepatic impairment compared to subjects with normal hepatic function. GILENYA® is contraindicated in patients with severe hepatic impairment (Child-Pugh class C) (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations). GILENYA® should be used with caution in patients with mild and moderate hepatic impairment (Child-Pugh classes A and B). It is not known if patients with hepatic impairment are at increased risk of developing elevated liver function tests, more severe liver injury or other adverse events during treatment with GILENYA®.

Renal Insufficiency: Severe renal impairment increases fingolimod C_{max} and AUC by 32% and 43%, respectively, and fingolimod-phosphate C_{max} and AUC by 25% and 14%, respectively. The apparent elimination half-life is unchanged for both analytes. Exposure to fingolimod metabolites was markedly increased, as shown by a 14-fold increase in AUC for the metabolite M3. The clinical significance of such increase in exposure is not known because the toxicity of this metabolite has not been fully characterized.

Caution is recommended when using GILENYA® in patients with severe renal impairment (see WARNINGS AND PRECAUTIONS, Special Populations).

The pharmacokinetics of fingolimod and its metabolites in subjects with mild or moderate renal impairment have not been evaluated.

STORAGE AND STABILITY

Store at 15 - 25°C; protect from moisture.

GILENYA® (fingolimod) must be kept out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

GILENYA® (fingolimod) is supplied as hard capsules containing 0.5 mg fingolimod (as hydrochloride).

The capsules have a white opaque body and bright yellow opaque cap; radial imprint with black ink, "FTY 0.5 mg" on cap and two radial bands imprinted on the body with yellow ink. Available in cartons of 7 (1 blister card of 7 capsules) or 28 capsules (2 blisters cards of 14 capsules).

Non-medicinal ingredients: magnesium stearate, mannitol; capsule shell contain: gelatin, titanium dioxide, yellow iron oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

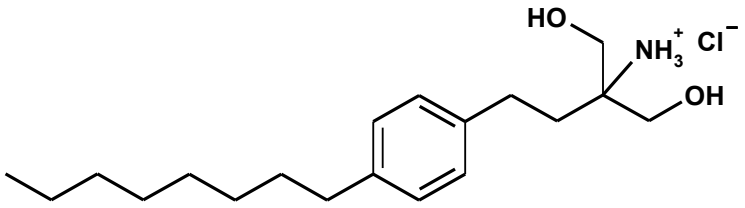
Drug Substance

Common name: Fingolimod hydrochloride

Chemical name: 2-amino-2[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride

Molecular formula and molecular mass: $C_{19}H_{33}NO_2 \cdot HCl$
343.93

Structural formula:



Physicochemical properties: Description: White to practically white powder

Solubility: Freely soluble in water.

pH value: pH of 1% solution in water at 22° to 25°C is 4.0.

CLINICAL TRIALS

Study demographics and trial design

Table 2 –Summary of patient demographics for clinical trials in RRMS

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Study D2301 (FREEDOMS)	Randomized, double-blind, placebo-controlled study.	GILENYA® 0.5 mg or 1.25 mg, or placebo, once-daily (oral). 2-year study.	GILENYA® 0.5 mg: n=425 GILENYA® 1.25 mg: n=429 Placebo: n=418	37.1 (17-55 years)	Male: 30.1 % Female: 69.9 %

Study D2302 (TRANSFORMS)	Randomized, double-blind, double-dummy, active (interferon beta-1a, 30 µg IM once weekly, Avonex®)-controlled study.	GILENYA® 0.5 mg or 1.25 mg, once-daily (oral), or Avonex® 30µg, once-weekly (IM). 1-year study.	GILENYA® 0.5 mg: n=429 GILENYA® 1.25 mg: n=420 Avonex®: n=431	36.2 (18-55 years)	Male: 32.7 % Female: 67.3 %

The efficacy of GILENYA® (fingolimod) has been demonstrated in two studies evaluating once daily doses of GILENYA® 0.5 mg and 1.25 mg in patients with relapsing-remitting multiple sclerosis. 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 between 0 to 5.5.

Study D2301 (FREEDOMS)

The FREEDOMS study was a 2-year randomized, double-blind, placebo-controlled Phase III study in patients with relapsing-remitting multiple sclerosis 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 the 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 (ARR).

Median age was 37 years, median disease duration was 6.7 years and median EDSS score at baseline was 2.0. Approximately 40% of patients had received treatment with other disease modifying therapies prior to entering the study, with interferon-beta being the most commonly used prior treatment (used by 29% of all patients). Patients were randomized to receive fingolimod 0.5 mg (n=425) or fingolimod 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 718.5 days on placebo.

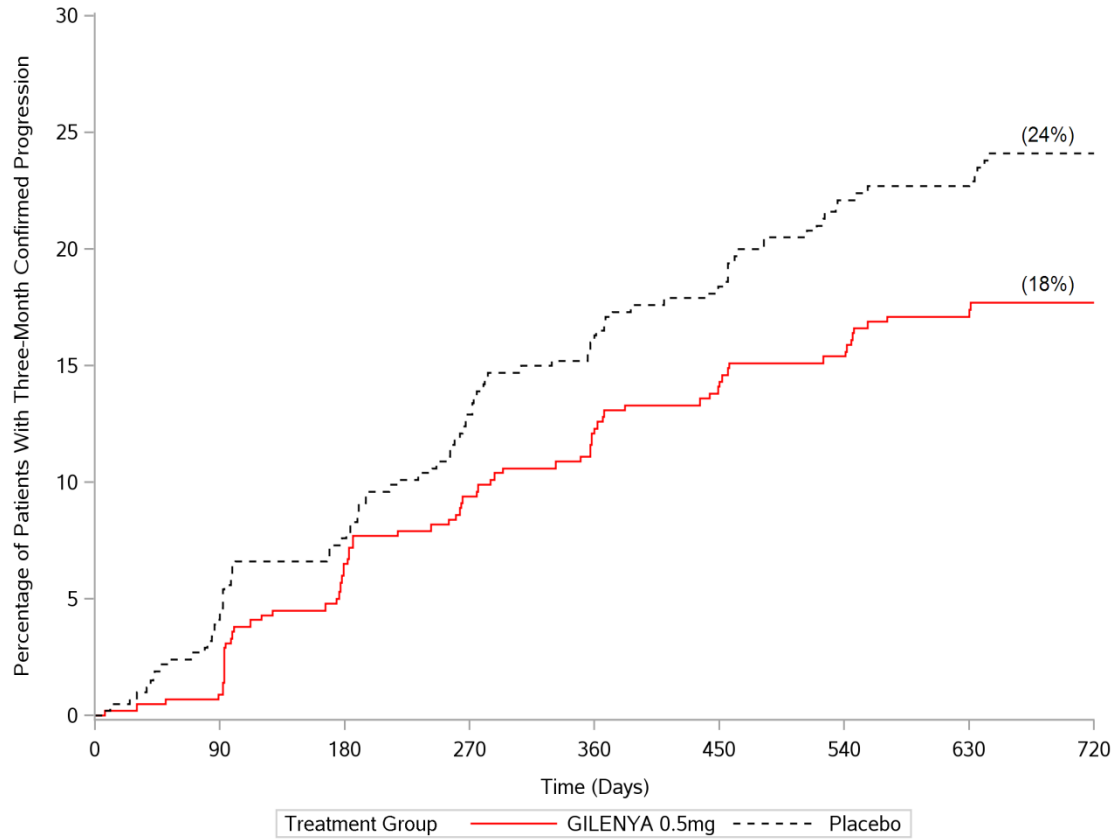
The primary endpoint, the annualized relapse rate was significantly lower in patients treated with GILENYA® than in patients who received placebo, with a relative reduction in relapse of 54% for patients treated with GILENYA® 0.5 mg. The key secondary endpoint was the time to 3-month confirmed disability progression, as measured by 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 sustained disability progression was significantly delayed with GILENYA® treatment compared to placebo. The 1.25 mg dose did not provide additional benefit over the 0.5 mg dose. Results for the Intent to Treat (ITT) analysis of primary and key secondary endpoints of the FREEDOMS study are shown in Table 3 and Figure 1.

Table 3. FREEDOMS study results

	GILENYA® 0.5 mg N=425	Placebo N=418	p-value
Primary endpoint			
Annualized relapse rate†	0.18	0.40	<0.001
Key secondary endpoint			
Kaplan-Meier estimate of percentage (SE) of patients free of 3-month confirmed disability progression at Month 24	82.3 (1.89)	75.9 (2.17)	0.026
Hazard ratio of disability progression (95% CI)	0.70 (0.52, 0.96)		0.024

† Based on confirmed relapses. Relapse was defined as neurologic symptoms together with an increase ≥ 0.5 in the total EDSS score, or an increase of 1 point in each of two EDSS functional system scores, or an increase of two points in one EDSS functional system score (excluding bowel-bladder or cerebral functional systems). P-value determined by negative binomial regression adjusting for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS.

Figure 1 Time to 3-month confirmed disability progression – Study D2301 (ITT population)



p = 0.026 for GILENYA® vs. placebo.

The time to disability progression was significantly longer with GILENYA® vs. placebo.

Secondary MRI endpoints included new and enlarging (active) T2 lesion counts, T1 Gadolinium (Gd)-enhancing lesion count and the rate of brain atrophy. The mean number of active T2 lesions over 24 months was 2.5 for GILENYA® 0.5 mg and 9.8 for placebo ($p<0.001$), representing a 74% relative reduction. The mean number of Gd-enhancing lesions at Month 24 was 0.2 for GILENYA® compared to 1.1 for placebo ($p<0.001$), a relative reduction of 81%. The rate of brain atrophy (mean % change in total brain volume) was less with GILENYA® (-0.8%) than with placebo (-1.3%) over 24 months ($p<0.001$). Changes in brain volume were also significant at Months 6 and 12.

Study D2302 (TRANSFORMS)

The TRANSFORMS study was a 1-year randomized, double-blind, double-dummy, active (interferon beta-1a)-controlled Phase III study in patients with relapsing-remitting multiple sclerosis who had not received any natalizumab in the previous 6 months. Prior treatment 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. Approximately 57% of patients had received treatment with other disease modifying therapies prior to entering the study, with interferon-beta being the most commonly used prior treatment (used by 49% of all patients). Patients were randomized to receive fingolimod 0.5 mg (n=429) or 1.25 mg (n=420) or interferon beta-1a 30 micrograms via the intramuscular route once weekly (n=431) for up to 12 months. Median time on study drug was 365 days on 0.5 mg, 364 days on 1.25 mg and 361 days on interferon beta-1a.

The annualized relapse rate was significantly lower in patients treated with GILENYA® than in patients who received interferon beta-1a, with a relative reduction in relapse of 52% for patients treated with GILENYA®. The 1.25 mg dose did not provide additional benefit over the 0.5 mg dose.

The key secondary endpoints were the number of new or newly enlarging T2 lesions and the 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 or newly enlarging T2 lesions was significantly lower in patients treated with GILENYA® than in patients who received interferon beta-1a. 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. There were no significant differences between the 0.5 mg and the 1.25 mg doses on either endpoint. Results for the primary and key secondary endpoints of this study are shown in Table 4.

Table 4. TRANSFORMS study results

	GILENYA® 0.5 mg N=429	Interferon-beta-1a 30 µg N=431	p-value
Primary endpoint Annualized relapse rate[1]	0.16	0.33	<0.001
Key secondary endpoints ***MRI*** Mean (median) number of new or newly enlarging T2 lesions over 12 months[2]	1.6 (0)	2.6 (1.0)	0.002
3-month confirmed disability progression Kaplan-Meier estimate of percentage (SE) of patients free of 3-month confirmed disability progression at Month 12	94.1 (1.25)	92.1 (1.33)	0.24
Hazard ratio of disability progression (95% CI)	0.71 (0.42, 1.21)		0.21

[1] Based on confirmed relapses. Relapse was defined as neurologic symptoms together with an increase $\geq$ 0.5 in the total EDSS score, or an increase of 1 point in each of two EDSS functional system scores, or an increase of two points in one EDSS functional system score (excluding bowel-bladder or cerebral functional systems). P-value determined by negative binomial regression adjusting for treatment, country, number of relapses in previous 2 years and baseline EDSS.
[2] Statistical analysis using negative binomial regression adjusted for treatment, country, number of relapses in previous 2 years and baseline EDSS.

Other secondary endpoints included the proportion of patients remaining relapse-free, T1 Gd-enhancing lesion count and the rate of brain atrophy. The proportion of patients remaining relapse-free after 12 months was 83% for GILENYA® 0.5mg and 70% for those receiving interferon beta-1a ($p<0.001$). The mean number of Gd-enhancing lesions at Month 12 was 0.2 for GILENYA® compared to 0.5 for interferon beta-1a ($p<0.001$), a relative reduction of 60%. The rate of brain atrophy (mean % change in total brain volume) was less with GILENYA® (-0.3%) than with interferon beta-1a (-0.5%) over 12 months ($p<0.001$).

Pooled results of studies D2301 and D2302 showed a consistent reduction of annualized relapse rate compared to comparator in subgroups defined by gender, age, prior multiple sclerosis therapy, disease activity or disability levels at baseline.

DETAILED PHARMACOLOGY

Mechanism of Action

Fingolimod-phosphate binding to S1P receptors on lymphocytes causes internalization and functional antagonism of S1P receptors. This reduces S1P-dependent egress of lymphocytes from lymphoid organs and, in animals reduces the numbers of autoreactive cells that invade the CNS. Studies in animals and *in vitro* studies indicate that fingolimod can penetrate the CNS and may

also act via interaction with S1P receptors on neural cells.

Non-Clinical Pharmacokinetics

Pharmacokinetics and disposition of fingolimod, its metabolites, and fingolimod-phosphate (in the form of its *(S)*- and *(R)*-enantiomers AML629 and AML627, respectively) were investigated in mice, rats, rabbits, dogs and cynomolgus monkeys.

Fingolimod and fingolimod-phosphate were major drug-related components across all species including human. The fate of fingolimod and fingolimod-phosphate appears to be similar in all species investigated including man. Fingolimod-phosphate was present exclusively in the form of the (*S*)-enantiomer. The absolute oral bioavailability of fingolimod was high or up to complete in animals and humans. Systemic exposure to fingolimod was generally dose proportional with no gender differences. Fingolimod accumulated in the brain of rats, and dogs, and in the brain and lung of cynomolgus monkeys after multiple oral dosing. After discontinuation of dosing, fingolimod was slowly eliminated from the rat and monkey brain.

The biotransformation of fingolimod in animals and human occurred by three main pathways: *(i)* by reversible stereoselective phosphorylation to the (*S*)-enantiomer of fingolimod-phosphate, *(ii)* by hydroxylation at the terminal methyl group of the octyl chain (catalyzed predominantly by CYP4F2), followed by rapid further oxidation to the carboxylic acid metabolite which undergoes further biotransformation by β-oxidation-like losses of two carbon units to other carboxylic acid metabolites, *(iii)* formation of non-polar ceramide analogs of fingolimod. Essentially the same metabolites of fingolimod in humans were formed by at least one of the animal species *in vivo* and/or *in vitro*, supporting the selection of the toxicological test species.

Fingolimod was eliminated predominantly by oxidative metabolism (CYP4F2). Fingolimod-phosphate appeared to be eliminated mainly by de-phosphorylation back to fingolimod. Direct oxidation of fingolimod-phosphate does not appear to occur to a significant extent across species including human. Renal excretion of unchanged fingolimod was not observed. Fecal excretion of unchanged fingolimod and fingolimod-phosphate was minor.

The involvement of multiple cytochrome P450 isoenzymes in the oxidation of fingolimod suggests that the metabolism of fingolimod may not be readily inhibited completely by a single specific CYP inhibitor. The potential for drug-drug interactions between fingolimod and co-medications *via* cytochrome P450 enzymes, and *via* hepatic uptake and efflux transport systems appears low. Fingolimod and AML629 are not expected to inhibit cytochrome P450-mediated metabolic clearance of co-medications. Fingolimod does not induce its own liver drug metabolizing enzymes or those of potential co-medications.

Safety Pharmacology

A slight inhibition of hERG (25% or 18%) was present at the solubility limit of fingolimod or of the pharmacologically active S-enantiomer (0.5 μM or 0.4 μM) in stably transfected HEK293 cells.

In the Langendorff perfused rabbit heart model, fingolimod-phosphate increased cycle length and

reduced coronary perfusion at target concentrations between 10 nM and 100 nM.

Oral fingolimod at 10 mg/kg induced significant decreases in heart rate, and increases in systolic and diastolic blood pressure in conscious, free-moving male cynomolgus monkeys.

Intravenous administration of the pharmacologically active S-enantiomer of fingolimod-phosphate decreased heart rate, decreased blood pressure, prolonged the PR interval, and caused sinus arrhythmias at doses of 0.01 and 0.1 mg/kg in anesthetized guinea pigs. The decrease in heart rate and prolongation of the PR interval caused by the S-enantiomer of fingolimod-phosphate were inhibited by pertussis toxin, suggesting the involvement of a Gαi/o-coupled S1P receptor.

In anesthetized rats intravenous fingolimod-phosphate decreased the heart rate and produced sinus arrhythmias at 0.3 mg/kg, prolonged the PR interval and decreased the respiratory tidal volume at doses greater than 0.03 mg/kg, and decreased respiratory minute volume at 0.03 mg/kg. Pertussis toxin inhibited the fingolimod-phosphate-induced decrease in heart rate, prolongation in PR interval, AV block and decrease in respiratory tidal volume.

Dyspnea, bradycardia and ECG findings of sino-atrial block, atrioventricular block, findings resembling left bundle branch block, atrial premature complexes, and ventricular premature complexes were present at 0.1 and/or 0.5 mg/kg in rats intravenously administered the pharmacologically active S-enantiomer of fingolimod-phosphate.

In dogs, by step-wise increasing the daily oral dose of fingolimod from 0.1 to 10 mg/kg, the decrease in heart rate and increase in blood pressure were less pronounced compared with giving an oral dose of ≥2.5 mg/kg on Day 1. An increase in frequency of AV block and ventricular premature contractions occurred in dogs given 10 mg/kg fingolimod orally.

Intravenous fingolimod (3 and 10 mg/kg) induced a marked and long-lasting increase in airway resistance in anesthetized rats. Pretreatment with *B. pertussis* toxin resulted in a reduction of the acute bronchoconstriction suggesting that the acute effects caused by fingolimod occur via signaling pathways involving Gi-GTP-binding protein.

Bronchoconstriction induced in anesthetized rats by IV injection of fingolimod was reversed by injection of the beta-2 adrenoceptor agonist, salbutamol.

TOXICOLOGY

The preclinical safety profile of fingolimod was assessed in mice, rats, dogs and monkeys.

Fingolimod had a moderate level of acute toxicity. Deaths occurred following single dose IV administration of 50 mg/kg in mice and ≥25 mg/kg IV in rats, and following single dose oral administration of ≥300 mg/kg in rats. No deaths occurred in dogs after single oral doses of 1000 or 2000 mg/kg. Signs of acute toxicity were referable to respiratory, CNS and gastrointestinal

systems and included dyspnea, uncoordination, tremors, convulsions, sedation and decreased locomotor activity and forestomach ulcers in rodents, and vomiting and loose stools in dogs.

The major target organs in repeat-dose oral studies were lungs, and blood vessels with findings at administered dose levels and systemic exposures in animals that, in some instances, were without a defined margin compared with the human oral dose (0.5 mg/day) and associated systemic exposure.

Effects on the lymphoid system consisting of lymphopenia, lymphoid depletion (thymus cortex, spleen, lymph nodes), and increased size and density of staining of thymus medulla, were consistently observed across a wide range of doses in all animal species tested and essentially represent anticipated effects based on fingolimod pharmacology. Gastrointestinal protozoan infection was considered to reflect increased susceptibility to infection secondary to immunosuppression in monkeys administered 0.5 or 3 mg/kg. Granulomatous inflammation in lungs of mice and pneumonia observed in rats and dogs may also be secondary to immunosuppression.

Lung was a sensitive target organ in all animal species tested. Findings included increased lung weight and insufficient or lack of pulmonary collapse at necropsy. Microscopic lung changes included smooth muscle hypertrophy/hyperplasia and/or interstitial collagenization at the bronchoalveolar junction; hyperdistension of alveoli; and increased alveolar macrophage infiltrates. Lung pathologic changes occurred at ≥0.1 mg/kg in rats, ≥0.01 mg/kg in dogs, and ≥0.5 mg/kg in monkeys. In the 52-week monkey study respiratory distress was associated with ketamine administration at fingolimod doses of 3 and 10 mg/kg.

Vasculopathy in Wistar rats involved vessels in multiple organs including kidney, spleen, mesentery and brain. The lowest effect dose levels were 1.5 mg/kg in the 26-week study and 0.15 mg/kg in the 104-week carcinogenicity study. Vascular lesions in heart of dogs administered ≥1 mg/kg were considered related to hemodynamic effects of fingolimod.

Treatment-related kidney findings (nephropathy, tubular basophilia and/or hyaline casts) occurred in rodent studies (5 mg/kg in 13-week and ≥0.25 mg/kg in 104-week studies in mice; ≥0.3 mg/kg in 26-week and ≥0.05 mg/kg in 104-week studies in rats).

Pathologic changes were present in the nervous system in dogs at relatively high dose levels. Mononuclear cell infiltrates or perivascular mononuclear cells were present in brain or spinal cord at 10 mg/kg (26-week study) and 30 mg/kg (4-week study).

Treatment-related findings in repeat-dose toxicology studies generally showed evidence of potential reversibility following treatment withdrawal, although recovery was incomplete in some instances.

Effects on liver (increased transaminases in rats and dogs), pituitary (vacuolation and/or atrophy of anterior pituitary cells in rats and dogs), adrenal medulla (vacuolation and decrease in number of cells and fibrosis in dogs) and gastrointestinal tract (forestomach erosion in rats, stomach ulcers in dogs) mainly occurred at relatively high dose levels and inconsistently across species.

There were no treatment-related ophthalmoscopic findings in toxicology studies. Vasculopathy was present in eyes histopathologically for a small number of treated animals at ≥0.5 mg/kg in the 104-week rat study.

No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of fingolimod up to the maximum tolerated dose of 2.5 mg/kg, representing an approximate 50-fold margin based on human systemic exposure (AUC) at the 0.5 mg dose. Vasculopathy and nephropathy were the main lesions contributing to the increased mortality at 0.5 and 2.5 mg/kg. In a 2-year mouse study, an increased incidence of malignant lymphoma was seen at doses of 0.25 mg/kg and higher, representing an approximate 6-fold margin based on human systemic exposure (AUC) at a daily dose of 0.5 mg.

Fingolimod was not mutagenic in an Ames test and in a L5178Y mouse lymphoma cell line in vitro. No clastogenic effects were seen in vitro in V79 Chinese hamster lung cells. Fingolimod induced numerical (polyploidy) chromosomal aberrations in V79 cells at concentrations of 3.7 µg/mL and above. Fingolimod was not clastogenic in the in vivo micronucleus tests in mice and rats.

Fingolimod had no effect on sperm count or motility, nor on fertility in male and female rats up to the highest dose tested (10 mg/kg), representing an approximate 150-fold margin based on human systemic exposure (AUC) at a daily dose of 0.5 mg.

Fingolimod was teratogenic at doses of 0.1 mg/kg or higher (corresponding to 2 or more times the exposure in humans at the recommended dose of 0.5 mg) when given to pregnant rats during the period of organogenesis. The most common fetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. The receptor affected by fingolimod (sphingosine -1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. An increase in post-implantation loss was observed in rats at doses of 1 mg/kg and higher and a decrease in viable fetuses at 3 mg/kg. Fingolimod was not teratogenic in the rabbit, but an increased incidence of embryo-fetal mortality was seen starting at doses of 1.5 mg/kg (corresponding to similar exposure in humans at the recommended dose of 0.5 mg), and a decrease in viable fetuses as well as fetal growth retardation at 5 mg/kg.

In rats, F1 generation pup survival was decreased in the early postpartum period at doses administered during pregnancy and lactation that did not cause maternal toxicity (0.05, 0.15 and 0.5 mg/kg). However, F1 body weights, development, behavior, and fertility were not affected by treatment with fingolimod. In a toxicity study in juvenile rats, no additional target organs of toxicity were observed compared to adult rats. Repeated stimulations with Keyhole Limpet Hemocyanin (KLH) showed a moderately decreased response during the treatment period, but fully functional immune reactions at the end of an 8-week recovery period.

Fingolimod was excreted in the milk of treated animals during lactation. Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

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PART III: CONSUMER INFORMATION

PrGILENYA®
Fingolimod (as fingolimod hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when GILENYA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GILENYA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

GILENYA® is used to treat adult patients with the relapsing and remitting form of multiple sclerosis (MS). GILENYA® is generally recommended for MS patients who have not responded well to, or cannot tolerate one or more of the other therapies for multiple sclerosis.

What it does:

GILENYA® does not cure MS, but it helps to reduce the number of attacks (relapses) that occur, reduce inflammation in the brain (brain lesions identified seen on MRI scans), and slow the build-up of physical problems due to MS (disability progression).

GILENYA® changes how the body's immune system works by decreasing the ability of lymphocytes to move freely within the body. This lowers the number of lymphocytes in the blood and prevents them from reaching the brain and spinal cord. This may reduce the inflammation and nerve damage that happens in MS.

When it should not be used:

You should not take GILENYA® if:

- you are allergic (hypersensitive) to fingolimod or to any of the other ingredients listed in this leaflet.
- your immune system is weakened (immunocompromised) due to disease (immunodeficiency syndrome) or medicines or treatments that suppress the immune system, such as medicines used to treat cancer or bone marrow transplantation.
- you have a severe active infection or an active chronic infection such as hepatitis or tuberculosis.
- you have an active cancer (except for a type of skin cancer called basal cell carcinoma).
- you have severe liver disease.

What the medicinal ingredient is:

The active substance of GILENYA® is fingolimod.

What the nonmedicinal ingredients are:
The nonmedicinal ingredients of GILENYA® hard capsules are: gelatin, magnesium stearate, mannitol, titanium dioxide and yellow iron oxide.

What dosage forms it comes in:

GILENYA® is supplied as hard capsules. Each hard capsule contains 0.5 mg of fingolimod (as fingolimod hydrochloride).

WARNINGS AND PRECAUTIONS

Chickenpox vaccine
Patients who have not had chickenpox or have not had the chickenpox vaccine are at risk of having a serious and life-threatening chickenpox infection during treatment with GILENYA®. There have been very rare fatal cases of chickenpox infection reported in patients treated with GILENYA®, who also received a relatively long course of corticosteroid therapy.

If you are not protected against chickenpox, your doctor may recommend that you receive the chickenpox vaccine 1 month before starting treatment with GILENYA®.

BEFORE you use GILENYA® talk to your doctor or pharmacist if:

- you have heart problems, such as **an irregular or abnormal heartbeat, a heart disease, high blood pressure, a history of stroke or other diseases related to blood vessels in the brain, severe untreated sleep apnea, or if you are at risk for, or if you have heart rhythm disturbances**.
- **you are taking medicines for an irregular heartbeat** such as quinidine, procainamide, amiodarone or sotalol.
- **you suffer from slow heart rate, you are already taking other medicines that slow your heart rate or you have a history of sudden loss of consciousness (fainting)**.
- you have a weakened immune system (due to a disease or medicines that suppress the immune system).
- you have been vaccinated within 1 month before you start taking GILENYA® or you plan to receive a vaccine. You should not receive certain types of vaccines (called "live attenuated vaccines") during and for up to 2 months after treatment with GILENYA®.
- you have never had chickenpox or have not been vaccinated for chickenpox.
- you have or have had visual disturbances or other signs of swelling in the central vision area at the back of the eye (a condition known as macular edema), inflammation or infection of the eye (uveitis).
- you have diabetes. Diabetes increases the risk of having macular edema during GILENYA® treatment.
- you have liver problems. GILENYA® may affect your liver function.
- you have low or high blood pressure. GILENYA® causes a mild increase in blood pressure.
- you have high cholesterol or triglyceride levels. GILENYA® may increase blood levels of cholesterol and triglycerides.
- you have kidney problems.
- you have breathing problems. GILENYA® has a slight effect on lung function.
- you are pregnant, think you may be pregnant or are trying to become pregnant.
- you are breast feeding.

Monitoring: Before you start treatment and periodically during treatment, your doctor may want you to undergo several tests to help monitor side-effects of GILENYA®. These will include:
blood tests (to check your white blood cell counts, liver function), eye examination (to monitor for macular edema), checks of your heart rhythm and blood pressure, and possibly lung function.

Slow heart rate and irregular heart beat

GILENYA® causes the heart rate to slow down, especially during the first month of treatment. GILENYA® can also cause an irregular heartbeat, especially after the first dose. Irregular heartbeat usually returns to normal in less than one day. Slow heart rate usually returns to normal within one month. These heart rhythm disturbances may be more likely in patients with risk factors, such as heart disease, or when certain interacting drugs are taken. In general, people more than 65 years of age are at higher risk.

If you have an irregular or abnormal heartbeat or a history of sudden loss of consciousness (fainting), your condition may worsen temporarily with GILENYA®. The same applies if you have a slow heart rate or if you are taking medicines which slow the heartbeat.

If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, at any time during treatment with GILENYA®, you should seek immediate medical attention.

Because GILENYA® has side effects on the heart, you will be required to have an electrocardiogram (ECG) to check the health of your heart before you start GILENYA®. Your doctor will ask you to stay in the clinic or office for at least 6 hours after taking the first dose of GILENYA® so your heart rate and blood pressure can be checked each hour and appropriate measures can be taken if heart-related side effects occur at the start of treatment. A second ECG will be done 6 hours after taking the first dose. Depending on the results of the ECG, blood pressure checks and how you are feeling, you may need to be observed for longer, possibly overnight, in a health care facility. The same observation process may apply if you are starting treatment again after a break from GILENYA® therapy.

Infections

The effects of GILENYA® on your body's immune system may reduce your body's ability to fight infections and you may get infections more easily while you are taking GILENYA® (and for up to 2 months after you stop taking it). If you have an infection, tell your doctor before you take GILENYA®. Any infection that you already have may get worse. Infections could be serious and sometimes life-threatening. Before you start taking GILENYA®, your doctor will confirm whether you have enough white blood cells in your blood. **During your treatment** with GILENYA®, if you think you have an infection, have fever, feel like you have the flu, or have a headache with a stiff neck, sensitivity to light, nausea, and/or confusion (these may be symptoms of meningitis), contact your doctor right away. If you believe your MS is getting worse (e.g. weakness or visual changes) or if you notice any new or unusual symptoms, talk to your doctor as soon as possible, because these may be the symptoms of a rare brain disorder caused by infection and called progressive multifocal leukoencephalopathy (PML).

The use of other medications and treatments that suppress or change how the immune system works is not recommended during treatment with GILENYA® because the risk of infections can be increased further.

Macular edema
A problem with your vision, called macular edema, can occur during treatment with GILENYA®. Macular edema can cause some of the same vision symptoms as an MS attack (optic neuritis), but you also may not notice any symptoms. Macular edema usually starts in the first 3 to 4 months after you start taking GILENYA®. Your doctor should therefore test your vision 3 to 4 months after you start taking GILENYA®, or any time you notice vision changes during treatment.

Your risk of macular edema may be higher if you have diabetes or have had an inflammation of your eye called uveitis. If you have or have had visual disturbances or other signs of swelling in the central vision area (macula) at the back of the eye, uveitis or diabetes, your doctor should test your vision before you start taking GILENYA®.

Other warnings you should know about:
The effects of GILENYA® on the body's immune system may increase the risk of developing lymphoma and other cancers such as skin cancer. Lymphoma and skin cancer, mostly basal cell carcinoma, have been reported in patients treated with GILENYA®.

If you already have moles or open sores before starting treatment with GILENYA®, pay attention for changes in the size, shape or color of moles or the healing of open sores (not healing within weeks) after you start treatment. These may be signs of skin cancer that you should talk to your doctor about.

A type of skin cancer called basal cell carcinoma (BCC) has been reported in MS patients treated with GILENYA®. During treatment with GILENYA® you should check your skin regularly for unusual changes. Talk to your doctor if you notice any skin nodules (e.g. shiny pearly nodules), patches or open sores that do not heal within weeks (these may be signs of BCC). Your doctor will also do regular skin examinations during your treatment with GILENYA®.

Older people (over 65 years old)
GILENYA® was studied in very few MS patients over 65 years old. Treatment with GILENYA® requires extra caution in older patients due to the greater likelihood of having other medical problems in addition to MS.

Children and adolescents (under 18 years old)

GILENYA® should not be used in children and adolescents as it has not been studied in MS patients aged under 18.

Pregnancy and breast-feeding

Before you start treatment with GILENYA® your doctor may ask you to have a pregnancy test to ensure that you are not pregnant.

You should avoid becoming pregnant while taking GILENYA® or in the two months after you stop taking it because of the risk of harming your unborn child. Talk with your doctor about the associated risk and about reliable methods of birth control that you should use during treatment and for 2 months after you stop treatment.

If you do become pregnant while taking GILENYA® tell your doctor right away. You and your doctor will decide what is best for you and your baby. If you become pregnant while taking GILENYA®, you can call the GILENYA® Pregnancy Registry at 1-855-788-5333.

You should not breast-feed while you are taking GILENYA®. GILENYA® can pass into breast milk and there is a risk of serious side effects for a breast-fed baby.

Driving and using machines

After the first dose of GILENYA®, you will need to stay at the doctor's office or clinic for at least 6 hours to have your heart rate checked. Your ability to drive and use machines may be affected during and potentially after this period.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking or have recently taken any of the following medicines:

- **Medicines for heart problems or high blood pressure**.
- **Medicines for an irregular heartbeat** such as, quinidine, procainamide, amiodarone or sotalol.
- **Medicines that slow down heartbeat** such as atenolol or metoprolol (called beta-blockers), such as verapamil, or diltiazem (called calcium channel blockers) or digoxin.
- **Medicines that suppress or modulate the immune system including other medicines used to treat MS** (beta-interferon, glatiramer acetate, natalizumab, mitoxantrone, dimethyl fumarate, teriflunomide, alemtuzumab or corticosteroids) **or medicines used to treat cancer**. GILENYA® should not be started while you are on these medications or for several months after you have stopped taking some of these medications due to a possible added effect on the immune system and potential for increased risk of serious infections. However, starting treatment with GILENYA® after alemtuzumab is not recommended.

  When corticosteroids were used for a few days to treat relapses in the multiple sclerosis studies with GILENYA® this did not result in increased infections. However, because there is the potential for increased risk of infection, extra caution is recommended if corticosteroids are used.

- **Vaccines.** If you need to receive a vaccine, seek your doctor's advice first. During and for up to 2 months after stopping treatment with GILENYA®, administration of some vaccines containing live virus (live attenuated vaccines) may result in the infection that the vaccination should prevent, while other vaccines may not work well enough to protect you.
- **Antifungal drugs** (such as ketoconazole).
- **Antibiotics** (such as erythromycin).
- **Drugs to treat HIV infection.**
- **Asthma drugs**.

PROPER USE OF THIS MEDICATION

Always take GILENYA® exactly as your doctor has told you.

Usual adult dose:

The dose is one capsule per day (0.5 mg of fingolimod) taken orally (by mouth).

Take GILENYA® once a day, at the same time each day with half a glass of water. GILENYA® can be taken with or without food.

Do not stop taking GILENYA® or change your dose without talking with your doctor.

GILENYA® will stay in your body for up to 2 months after you stop taking it, the side effects described in this leaflet may still occur during that time.

Overdose:

If you have taken more GILENYA® than your doctor has recommended contact the regional Poison Control Centre and a health care practitioner immediately, or go to the nearest hospital emergency department, even if there are no symptoms. Take the medication package with you when you go to the hospital.

Missed Dose:

If you forget a dose, take the next dose as planned. Do not take a double dose to make up for a forgotten dose.

If you have been taking GILENYA® for less than 2 weeks and you forget to take a dose for one day, or if you stop taking GILENYA® for more than 7 days during weeks 3 and 4 of treatment, contact your doctor right away. Your doctor may decide to observe you at the time you take the next dose.

If you start GILENYA® again after stopping for 2 weeks or more, you will start taking GILENYA® again in your doctor's office or clinic. Do not restart GILENYA® after stopping it for more than two weeks without seeking advice from your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, patients treated with GILENYA® may experience side effects, although not everybody gets them.
Very common side effects (affect more than 1 in 10 patients):

- Flu virus infection

- Headache
- Diarrhea
- Back pain
- Cough

Common side effects (affect between 1 and 10 in every 100 patients):

- Sinusitis
- Fungal infections affecting skin, nails or hair
- Dizziness
- Migraine
- Weakness
- Mild increase in blood pressure
- Skin rash
- Hair loss
- Itchy skin
- Weight loss
- Blurred vision
- Breathlessness
- Tingling or numbness
- Depression
- Eye pain

Uncommon side effects (affect between 1 and 10 in every 1,000 patients):

- Depressed mood.

Frequency not known:

- Allergic reactions, including symptoms of rash or itchy hives, swelling of lips, tongue or face, which are more likely to occur on the day you start GILENYA® treatment.
- A rare brain disorder caused by infection and called progressive multifocal leukoencephalopathy (PML). The symptoms of PML may be similar to MS (e.g. weakness or visual changes).
- Nausea.

If any of these side effects affects you severely, tell your doctor.

If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency help
		Only if severe	In all cases	
Common	Symptoms of bronchitis such as cough with phlegm, chest pain, fever		✓	
	Symptoms of gastroenteritis such as vomiting, nausea, diarrhea, fever			
	Symptoms of shingles (or herpes zoster) such as blisters, burning, itching or pain of the skin, typically on the upper body or the face. Other symptoms may be fever followed by numbness, itching or red patches with severe pain		✓	
	Symptoms of slow heartbeat (bradycardia) such as feeling dizzy, tired, awareness of own heartbeat, decrease in blood pressure		✓	
	Symptoms of a type of skin cancer called basal cell carcinoma (BCC), which often appears as a pearly nodule, though it can also take other forms		✓	
	Symptoms of low level of white blood cells such as fever, sore throat or mouth ulcers due to infections		✓	
Uncommon	Symptoms of pneumonia such as fever, cough, difficulty breathing		✓	
	Symptoms of macular edema (swelling in the central vision area of the retina at the		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency help
		Only if severe	In all cases	
	back of the eye) such as shadows or blind spot in the center of the vision, blurred vision, problems seeing colors or fine details			
	Liver disorder (symptoms include nausea, vomiting, loss of appetite, swelling and/or pain in the abdomen, fatigue, itching, yellowing of the skin or eyes, dark urine)		✓	
	Trouble breathing		✓	
Rare	Stroke (symptoms include weakness and/or loss of sensation of limbs or face, difficulty speaking, clumsiness, visual loss)			✓
	Peripheral artery disease (symptoms include cold, painful, discolored digits or limb)			✓
	Posterior reversible encephalopathy syndrome (PRES) (symptoms may include sudden severe headache, nausea, vomiting, confusion, drowsiness, personality change paralysis, abnormal speech, convulsions and vision changes)			✓
	Cancer of the lymphatic system (lymphoma) (symptoms may include painless swelling of lymph node, enlarged tonsils, fever, chills, night sweats, fatigue, itching, unexplained weight loss, loss of appetite, persistent coughing/ breathlessness and headache)		✓	
Isolated cases	Temporary but serious irregularity in heart beat			✓
	Cryptococcal infections (a type of fungal infection), including meningitis with symptoms such as headache with a stiff neck, sensitivity to light, nausea, and/or confusion		✓	
	Progressive multifocal leukoencephalopathy (PML), a rare brain infection (symptoms may include weakness or visual changes)		✓	

This is not a complete list of side effects. For any unexpected effects while taking GILENYA®, contact your doctor or pharmacist.

HOW TO STORE IT

- Do not use GILENYA® after the expiry date shown on the box.
- Store at 15-25°C.
- Store in the original package, protect from moisture.
- Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.novartis.ca

or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at:

1-800-363-8883

If you become pregnant while taking GILENYA®, talk to your doctor about registering with the GILENYA® Pregnancy Registry. You can enroll in this registry by calling:

1-855-788-5333.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc., 385 Bouchard Blvd., Dorval, Quebec, H9S 1A9.

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