PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Teva-Fingolimod

Fingolimod Capsules

Capsule, 0.5 mg Fingolimod (as fingolimod hydrochloride), Oral

Sphingosine 1-phosphate receptor modulator

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

Date of Initial Authorization:
March 11, 2019

Date of Revision:
April 20, 2022

Submission Control Number: 259158

RECENT MAJOR LABEL CHANGES

2 Contraindications	02/2020
4 Dosage and Administration	04/2022
7 Warnings and Precautions	04/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Teva-Fingolimod (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. Teva-Fingolimod 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.

Teva-Fingolimod 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 Teva-Fingolimod and are able to discuss benefits/risks with patients.

1.1 Pediatrics

Pediatrics (<18 years of age): Teva-Fingolimod is not indicated in patients below 18 years of age.

1.2 Geriatrics

Geriatrics (>65 years of age): Clinical studies of fingolimod did not include sufficient numbers of patients aged 65 years and over to determine whether the safety and efficacy of fingolimod differs in elderly patients compared to younger patients. Physicians who choose to treat geriatric patients should consider that treatment with fingolimod 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 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to fingolimod or to any ingredient in the formulation of Teva-Fingolimod including any non-medical ingredient, or component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, 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). Initiate treatment with Teva-Fingolimod only

when the infection has resolved.

- Patients with known active malignancies, except for patients with basal cell carcinoma.
- Patients with severe hepatic impairment (Child-Pugh Class C) (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; and 10.3 Pharmacokinetics, Special Populations and Conditions).
- Patients who in the last 6 months had myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure.
- Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular**).**
- Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not have a pacemaker (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
- Patients with a baseline QTc interval ≥500 msec (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
- Women (including female adolescents) who are pregnant or of childbearing potential not using effective contraception (see 7 WARNINGS AND PRECAUTIONS). Pregnancy must be excluded before start of treatment as Teva-Fingolimod may cause fetal harm.

4 DOSAGE AND ADMINISTRATION

Teva-Fingolimod should be used under the supervision of a neurologist experienced in the treatment of multiple sclerosis and familiar with the safety and efficacy of Teva-Fingolimod.

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.

4.1 Dosing Considerations

Prior to initiating treatment with Teva-Fingolimod, the following assessments should be done to guide patient selection and treatment.

Refer to the 7 WARNINGS AND PRECAUTIONS – Immune, Cardiovascular, Ophthalmologic, Hepatic/Biliary/Pancreatic, Special Populations, 9 DRUG INTERACTIONS, and 16 NON-TOXICOLOGY sections for more complete information.

Immune system effects

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

- 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. Treatment with Teva-Fingolimod should not be initiated when lymphocyte counts are consistently below the normal range.

- Check varicella-zoster virus (VZV) antibody status before starting therapy if there is no health 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.

- Vaccination against human papilloma virus should be considered before initiating treatment with Teva-Fingolimod (see 7 WARNINGS AND PRECAUTIONS, Immune – Human Papilloma Virus).

- A recent cerebral MRI should be available before initiating treatment with Teva-Fingolimod to evaluate for findings suggestive of progressive multifocal leukoencephalopathy (PML) (see 7 WARNINGS AND PRECAUTIONS, Immune – Progressive Multifocal Leukoencephalopathy).

Cardiovascular effects

Initiation of Teva-Fingolimod 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 8.5 Post Market Adverse Reactions).

- Obtain an electrocardiogram (ECG) for all patients to determine whether pre-existing conduction abnormalities are present.
- Determine whether patients are taking concomitant medications that reduce heart rate or atrioventricular conduction.
- If treatment with Teva-Fingolimod is considered in the context of certain cardiac conditions, an evaluation from a cardiologist should be sought prior to initiating treatment, to assess suitability of treatment and to determine the most appropriate strategy for monitoring cardiac effects.

See 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 2 CONTRAINDICATIONS for more complete information regarding patients with certain cardiovascular conditions in which Teva-

Fingolimod should not be used or may require additional monitoring. All patients require at least 6 hours of cardiovascular monitoring during administration of the first dose of Teva-Fingolimod (see 4.4 Administration).

Ophthalmologic effects

Teva-Fingolimod may cause macular edema with or without symptoms. 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 Teva-Fingolimod therapy (see 7 WARNINGS AND PRECAUTION, Ophthalmologic)

Hepatic effects

Teva-Fingolimod is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C). Obtain transaminase and bilirubin levels prior to initiating treatment if no recent (i.e. within the last 6 months) results are available (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Skin cancer

Skin cancers have been reported in MS patients treated with fingolimod. Monitor for suspicious skin lesions before initiating treatment with Teva-Fingolimod, particularly in patients with risk factors for skin cancer (see 7 WARNINGS AND PRECAUTIONS, Neoplasm).

Pregnancy

Teva-Fingolimod is contraindicated in women (including female adolescents) who are pregnant or of childbearing potential not using effective contraception (see 7.1.1 Pregnant Women).

- A negative pregnancy test must be obtained before initiation of treatment in women of childbearing potential.

Current or prior medications

For patients taking antineoplastic, immunosuppressive, or immune-modulating therapies, including other disease modifying treatments for multiple sclerosis and corticosteroids, or if there is a history a prior use of such drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with Teva-Fingolimod (for more complete information, see 7 WARNINGS AND PRECAUTIONS, Immune and 9.2 Drug Interactions Overview).

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of Teva-Fingolimod is 0.5 mg once daily.

Patients already on beta interferon or glatiramer acetate therapy can switch directly to Teva-Fingolimod if they do not display signs of treatment-related abnormalities such as cytopenia. Caution is advised when switching patients from natalizumab or teriflunomide to Teva-Fingolimod. For recommendations related to switching patients from other disease modifying therapies to Teva-Fingolimod, see 7 WARNINGS AND PRECAUTIONS: Immune - Prior treatment with immunosuppressive or immune-modulating therapies.

Dosing in special populations

- *Renal impairment*: Teva-Fingolimod should be used with caution in patients with severe renal impairment (see 10.3 Pharmacokinetics, Special Populations and Conditions).

- *Hepatic impairment*: Teva-Fingolimod is contraindicated in patients with severe hepatic impairment (Child-Pugh class C) (see 2 CONTRAINDICATIONS). Although dose adjustments are not needed in patients with mild and moderate hepatic impairment, caution and monitoring should be exercised when initiating and during Teva-Fingolimod treatment in these patients (10.3 Pharmacokinetics, Special Populations and Conditions; 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic-Liver Function).

- *Pediatric patients*: Teva-Fingolimod is not indicated for use in pediatric patients.

- *Geriatric patients*: Teva-Fingolimod 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 2 CONTRAINDICATIONS; 7.1.4 Geriatrics; 10.3 Pharmacokinetics, Special Populations and Conditions).

- *Ethnicity*: No Teva-Fingolimod dose adjustments are needed based on ethnic origin (see 10.3 Pharmacokinetics, Special Populations and Conditions).

- *Gender*: No Teva-Fingolimod dose adjustments are needed based on gender (see 10.3 Pharmacokinetics, Special Populations and Conditions).

- *Diabetic patients*: Teva-Fingolimod should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular edema (see 8.2 Clinical Trial Adverse Reactions, Macular Edema). Multiple sclerosis patients with concomitant diabetes mellitus were excluded from the clinical trials with Teva-Fingolimod.

4.4 Administration

- Teva-Fingolimod is taken orally, with or without food.

- Patients should be advised that Teva-Fingolimod remains in the blood and continues to have effects, including decreased blood lymphocyte counts, for up to 2 months following the last dose.

First dose monitoring of fingolimod
Because initiation of Teva-Fingolimod treatment is associated with reversible heart rate decrease and atrioventricular (AV) conduction delays, patients must be closely monitored for cardiac effects during the administration of the first dose.

- For all patients, obtain an electrocardiogram (ECG) and measure blood pressure prior to and 6 hours after the first dose of fingolimod.

- 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 fingolimod is administered.

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

- if the heart rate at 6 hours post-dose is <45 bpm in adults, <55 bpm in pediatric patients aged 12 years and above, or <60 bpm in pediatric patients aged 10 to below 12 years, 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.

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

See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests **for recommendations regarding monitoring that should be performed during therapy with Teva-Fingolimod.**

4.5 Missed Dose

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

Because the effects on heart rate and AV conduction may recur on re-introduction of fingolimod, the same precautions as for the first dose should apply (i.e., monitor for at least 6 hours after the first dose) if fingolimod therapy is discontinued:

- For one day or more within the first 2 weeks of treatment
- For more than 7 days during weeks 3 and 4 of treatment
- For more than 2 weeks, after the first month of treatment

5 OVERDOSAGE

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 7 WARNINGS AND PRECAUTIONS, Cardiovascular; and 8.2 Clinical trial Adverse Reactions and 8.5 Post Market Adverse Reactions).

In case of Teva-Fingolimod overdosage, observe patients overnight with continuous ECG monitoring in a medical facility and obtain regular measurements of pulse rate and blood pressure (see 4.1 Dosing Considerations; and 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/ Composition	Nonmedicinal Ingredients
Oral	Capsules / 0.5 mg fingolimod (as fingolimod hydrochloride)	Gelatin, iron oxide yellow, pregelatinized starch, sodium lauryl sulphate and titanium dioxide.

Teva-Fingolimod 0.5 mg Capsule: A hard gelatin capsule filled with white to off-white powder, with small agglomerates. White opaque body and yellow cap, both imprinted with "TEVA" over "7820" in black ink. Available in cartons of unit dose blisters of 30 capsules.

7 WARNINGS AND PRECAUTIONS

General

Varicella vaccination

There have been very rare fatal cases of varicella zoster virus (VZV) infections in patients taking fingolimod (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 Teva-Fingolimod treatment. It is recommended that patients without a health 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 Teva-Fingolimod therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended (if not contraindicated) prior to commencing treatment with Teva-Fingolimod. If vaccinated, treatment with Teva-Fingolimod should only be initiated 1 month after the patient has been vaccinated to allow full effect of vaccination to occur (see 7 WARNINGS AND PRECAUTIONS, Immune, Herpetic Infections**).**

Cardiovascular

Initiation of Teva-Fingolimod 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 Teva-Fingolimod (see 4.4 Administration, 4.5 Missed Dose, 7 WARNINGS AND PRECAUTIONS, Cardiovascular- Bradyarrhythmia; - PR Interval Prolongation and Atrioventricular [AV] Block;).Teva-Fingolimod is also associated with QTc interval prolongation (see 7 WARNINGS AND PRECAUTIONS, cardiovascular - QTc interval prolongation).

Bradyarrhythmia

Decreased heart rate

Initiation of fingolimod treatment results in a reversible decrease in heart rate. After the first 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 10.2 Pharmacodynamics – Heart rate and rhythm). Heart rates below 40 bpm in adults were rarely observed (see 8 ADVERSE REACTIONS). Patients who experienced bradycardia in controlled multiple sclerosis clinical trials were generally asymptomatic but some patients (0.5% receiving fingolimod 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 8.2 Clinical Trail Adverse Reactions, ECG Findings and Bradyarrhythmia; 9.2 Drug Interactions Overview, Pharmacodynamic Interactions, and 10.2 Pharmacodynamics, Heart rate and rhythm).

PR Interval Prolongation and Atrioventricular (AV) Block

Initiation of fingolimod 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 in adults, the incidence of first degree AV block on ECG at 6 h after the first dose was 4.7% of patients receiving fingolimod 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 fingolimod 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 fingolimod 0.5 mg and 2% of patients on placebo, while 2:1 AV block was reported in 1.7% of patients receiving fingolimod 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 fingolimod (see 8.2 Clinical Trail Adverse Reactions, ECG Findings and Bradyarrhythmia; 9.2 Drug Interactions Overview, Pharmacodynamic Interactions; 10.2 Pharmacodynamics, Heart rate and rhythm).

QTc Prolongation

Fingolimod is associated with QTc interval prolongation (see 8.2 Clinical Trail Adverse Reactions, ECG Findings; 9.2 Drug Interactions Overview, Pharmacodynamic Interactions; and 10.2 Pharmacodynamics, Thorough QT Study).

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.

Treatment initiation recommendations in patients with certain cardiovascular conditions

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 Teva-Fingolimod on heart rate and cardiac conduction, Teva-Fingolimod should not be used in patients with the following conditions.

- Since initiation of Teva-Fingolimod treatment results in decreased heart rate, and therefore a prolongation of the QT interval, Teva-Fingolimod should not be used in

patients with significant QT prolongation (QTc >470 msec in females or >450 msec in males) see 2 CONTRAINDICATIONS) or in patients with relevant risk factors for QT prolongation (e.g., hypokalemia, hypomagnesemia or congenital QT prolongation). Teva-Fingolimod should also not be used in patients with a history or presence of sino-atrial heart block, a history of recurrent syncope or symptomatic bradycardia, due to the risk of serious cardiac rhythm disturbances. In patients for whom Teva-Fingolimod is not contraindicated, 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.

- Teva-Fingolimod should not be used in patients with a history of cardiac arrest, uncontrolled hypertension or severe untreated sleep apnea because significant bradycardia may be poorly tolerated in these patients (see 2 CONTRAINDICATIONS). In patients for whom Teva-Fingolimod is not contraindicated, 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.

- Teva-Fingolimod 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 (see 2 CONTRAINDICATIONS).

- There is limited experience with Teva-Fingolimod 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. ivabradine, digoxin, cholinesterase inhibitors or pilocarpine). Since the initiation of Teva-Fingolimod treatment is also associated with bradycardia (see "Decreased Heart Rate"), concomitant use of these substances during Teva-Fingolimod initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, Teva-Fingolimod should not be initiated in patients who are concurrently treated with these substances. If treatment with Teva-Fingolimod 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 9 DRUG INTERACTIONS).

- Teva-Fingolimod 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 Teva-Fingolimod 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.

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

Blood Pressure Effects

In multiple sclerosis clinical trials, patients treated with fingolimod 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 fingolimod 0.5 mg and 511 multiple sclerosis patients on placebo, hypertension was reported as an adverse reaction in 5% of patients on fingolimod 0.5 mg and in 3% of patients on placebo. Blood pressure should be monitored during treatment with Teva-Fingolimod.

Endocrine and Metabolism

Total Cholesterol, LDL Cholesterol, and Triglycerides

Fingolimod treatment results in increased levels of total cholesterol, LDL cholesterol, and triglycerides (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and other Quantitative Data, Clinical Trial Findings, Cholesterol and Triglycerides). These observations should be taken into consideration when treating patients with pre-existing hyperlipidemia, atherosclerosis, or ischemic heart disease.

Hematologic

Isolated cases of autoimmune hemolytic anemia and thrombocytopenia, including with purpura, having a suspected relationship to fingolimod have been observed post-market. If a patient presents with symptoms of anemia or thrombocytopenia, confirm diagnosis with appropriate laboratory tests. If confirmed, promptly initiate appropriate medical intervention and consider discontinuation of fingolimod (see 8.5 Post-Market Adverse Reactions).

Hepatic/Biliary/Pancreatic

Liver function

Signs of liver injury, including markedly elevated serum hepatic enzymes, mostly alanine aminotransaminase (ALT), and elevated total bilirubin have been reported in multiple sclerosis patients treated with fingolimod. These have occurred shortly following initiation of treatment as well after prolonged use. Post market cases of clinically significant liver injury and acute liver

failure requiring liver transplant have also been reported. In clinical trials, a 3-fold the upper limit of normal (ULN) or greater elevation in ALT occurred in 8% of patients treated with fingolimod 0.5 mg, as compared to 2% of patients on placebo. Elevations 5-fold the ULN occurred in 2% of patients on fingolimod 0.5 mg and 1% of patients on placebo. In clinical trials, fingolimod 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 fingolimod (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and other Quantitative Data, Clinical Trial 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 Teva-Fingolimod.

During treatment with Teva-Fingolimod, patients should be monitored for signs and symptoms of hepatic injury, such as unexplained vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. Liver enzymes and bilirubin should be evaluated promptly in the presence of symptoms suggestive of liver injury; otherwise, at months 1, 3, 6, 9, 12 and at regular intervals thereafter on therapy, until 2 months after Teva-Fingolimod discontinuation. If liver transaminases rise above 3 times the ULN, more frequent monitoring should be instituted, including serum alkaline phosphatase (ALP) measurement. With repeated confirmation of liver transaminases above 5 times the ULN, or if the if the patient has ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range, treatment with Teva-Fingolimod should be interrupted. Treatment should not be resumed if a plausible alternative etiology for the signs and symptoms cannot be established, because these patients are at risk for severe drug-induced liver injury (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and other Quantitative Data, Clinical Trial Findings, Liver function).

Patients with pre-existing liver disease should be more closely monitored as they are at an increased risk of developing elevated liver enzymes during Teva-Fingolimod treatment. Teva-Fingolimod is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS, 10.3 Pharmacokinetics, Special Populations and Conditions).

Immune

Infections

A core pharmacodynamic effect of Teva-Fingolimod 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 Teva-Fingolimod may take up to 2 months, recovery of peripheral lymphocyte counts to baseline values is gradual (see 10.2 Pharmacodynamics). Teva-Fingolimod may therefore increase the risk of infections, including opportunistic infections (see 8 ADVERSE REACTIONS) during treatment

and for up to 2 months after discontinuation of treatment. Continue monitoring for infections and instruct patients to promptly report symptoms or signs suggestive of any infection during this period to facilitate early diagnosis and initiation of appropriate treatment.

Teva-Fingolimod 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 2 CONTRAINDICATIONS).

In the 24-month placebo controlled multiple sclerosis clinical trial, the overall rate of infections (72%) and serious infections (2%) with fingolimod 0.5 mg was similar to that of placebo. However, bronchitis and pneumonia were more common in fingolimod-treated patients (see 8 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 Teva-Fingolimod (see 7 WARNINGS AND PRECAUTIONS, Immune System Effects Following Discontinuation of Treatment). For patients who develop serious infections, suspending treatment with Teva-Fingolimod should be considered, and the benefits and risks of treatment should be re-assessed prior to re-initiation of treatment.

Herpetic Infections

Serious, life-threatening, and sometimes fatal, events of disseminated varicella zoster and herpes simplex infections, including cases of encephalitis, meningitis, meningoencephalitis and multiorgan failure, have occurred with fingolimod during controlled trials (1.25 mg and 0.5 mg) and in the post-marketing setting (0.5 mg).

Two patients died of herpetic infections during controlled trials, while being treated with a 1.25 mg dose of fingolimod (higher than the recommended dose). One death was due to a disseminated primary varicella zoster infection and the other to herpes simplex encephalitis. Very rare fatal cases of disseminated reactivation of varicella zoster virus have also been reported in the post-marketing experience in patients treated with the recommended dose of fingolimod (0.5 mg). In most of these fatal cases, patients had received prolonged (more than 5 days) concomitant corticosteroid therapy to treat suspected MS relapses (see 9.2 Drug Interactions Overview).

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 Teva-Fingolimod present with an atypical MS relapse or multiorgan failure. For cases of disseminated herpetic infections, antiviral therapy and discontinuation of Teva-Fingolimod treatment is recommended. Treatment of zoster should follow current relevant guidelines.

Progressive Multifocal Leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML), some of which have been fatal, have been reported in the post-marketing setting (see 8 ADVERSE REACTIONS). PML is an opportunistic infection caused by JC virus (JCV) that typically only occurs in patients who are immunocompromised, which may be fatal or result in severe disability. 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 estimated risk appears to increase with cumulative exposure of fingolimod over time. The incidence rate for PML appears to be higher for patients in Japan; the reasons are currently unknown.

Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, Teva-Fingolimod 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.

MRI findings suggestive of PML may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with MS medications associated with PML, including fingolimod. Many of these patients subsequently became symptomatic with PML. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Before initiating treatment with Teva-Fingolimod, a recent MRI should be available. During routine MRI (in accordance with national and local recommendations), physicians should pay attention to PML suggestive lesions. Lower PML-related mortality and morbidity have been reported following discontinuation of another MS medication associated with PML in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis. It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

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 8 ADVERSE REACTIONS). Some cases of cryptococcal meningitis have been fatal. 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.

Human papilloma virus

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with fingolimod in the post-marketing setting (see 8 ADVERSE REACTIONS). Due to the immunosuppressive properties of fingolimod, vaccination against HPV should be considered prior to treatment initiation with Teva-Fingolimod taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care.

Vaccination

- The use of live attenuated vaccines during Teva-Fingolimod treatment and for two months after discontinuing treatment is not recommended due to the risk of infection from the vaccine (see 7 WARNINGS AND PRECAUTIONS, Infections).

- Vaccination may be less effective during and for up to two months after discontinuing treatment with Teva-Fingolimod (see 7 WARNINGS AND PRECAUTIONS, Immune System Effects Following Discontinuation of Treatment; 10.2 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 Teva-Fingolimod. Initiation of Teva-Fingolimod therapy should be postponed for one month after vaccination to allow the full effect of vaccination to occur (see 7 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 Teva-Fingolimod.

Immune System Effects Following Discontinuation of Treatment

If a decision is made to stop treatment with Teva-Fingolimod, 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 10.2 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 Teva-Fingolimod.

Because of the continuing pharmacodynamic effects of fingolimod, starting other therapies during the 2 months following stopping Teva-Fingolimod warrants the same precautions as concomitant treatment with Teva-Fingolimod. Use of immunosuppressants soon after the discontinuation of Teva-Fingolimod may lead to an additive effect on the immune system and, therefore, caution should be applied (see 9 DRUG INTERACTIONS and 7 WARNINGS AND PRECAUTIONS, Return of disease activity (rebound) and severe increase in disability after fingolimod discontinuation).

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 9 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 Teva-Fingolimod 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

Teva-Fingolimod 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 Teva-Fingolimod. A careful case-by-case assessment regarding the timing of the initiation of Teva-Fingolimod treatment is recommended.

Alemtuzumab

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

Monitoring and Laboratory Tests

The following assessments should be done during treatment with Teva-Fingolimod.

- Monitor for signs and symptoms of infections regularly during treatment. Complete blood count should also be periodically monitored (see 7 WARNINGS AND PRECAUTIONS, Immune).
- Monitor for signs and symptoms of liver injury. See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic for detailed monitoring recommendations.
- Monitor for suspicious skin lesions regularly during treatment with Teva-Fingolimod, particularly in patients with risk factors for skin cancer (see 7 WARNINGS AND PRECAUTIONS, Neoplasm).
- 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 for macular edema and should have regular ophthalmic evaluations while receiving Teva-Fingolimod therapy (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).
- Monitor blood pressure regularly in all patients (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

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.

Lymphoma

Cases of lymphoma, mainly Non-Hodgkin's Lymphoma, including both T-cell and B-cell types and CNS lymphoma have been reported in clinical trials and in the post-marketing setting with fingolimod (see 8 ADVERSE REACTIONS). The cases reported were heterogeneous in nature. The incidence of lymphoma (B-cell and T-cell) cases was higher in clinical trials than expected in the general population. Cutaneous T-cell lymphoma (including mycosis fungoides) has been reported with fingolimod in the post-market setting (see 8 ADVERSE REACTIONS).

Basal cell carcinoma and other cutaneous neoplasms

Basal cell carcinoma (BCC) and other cutaneous neoplasms, including malignant melanoma, squamous cell carcinoma, Merkel cell carcinoma and Kaposi's sarcoma have been reported in patients receiving fingolimod (see 8 ADVERSE REACTIONS). Vigilance for cutaneous neoplasms is recommended in patients receiving Teva-Fingolimod. Health professionals and patients are

advised to monitor for suspicious skin lesions before initiating treatment and regularly during treatment with Teva-Fingolimod, particularly for patients with risk factors for skin cancer. If a suspicious skin lesion is observed, it should be promptly evaluated.

Since there is a potential risk of malignant skin growths, patients treated with Teva-Fingolimod should be cautioned against exposure to sunlight and ultraviolet light by wearing protective clothing and using a sunscreen with a high protection factor. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

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; status epilepticus has been reported in association with PRES. 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, Teva-Fingolimod should be discontinued.

Tumefactive lesions

Cases of tumefactive lesions associated with MS relapse have been reported in the post-marketing setting. In case of severe relapses, MRI should be performed to exclude tumefactive lesions. Discontinuation of Teva-Fingolimod should be considered by the physician on a case-by-case basis taking into account individual benefits and risks.

Return of disease activity (rebound) and severe increase in disability after fingolimod discontinuation

Severe increase in disability accompanied by multiple new lesions on MRI has been reported after discontinuation of fingolimod in the postmarketing setting. Patients in most of these reported cases did not return to the functional status they had before stopping fingolimod. The increase in disability generally occurred within 12 weeks after stopping fingolimod, but was reported up to and beyond 24 weeks after fingolimod discontinuation. Therefore, caution is indicated when stopping Teva-Fingolimod therapy. Monitor patients for development of high disease activity and severe increase in disability following discontinuation of Teva-Fingolimod and begin appropriate treatment as needed.

Seizures

Caution should be exercised when administering Teva-Fingolimod to patients with pre-existing seizure disorder. In the pivotal studies, cases of seizures were reported at a greater incidence

for fingolimod-treated patients compared to their respective control arms (see 8.2 Clinical Trials Adverse Reactions). It is not known whether these events were related to the effects of MS alone, to fingolimod, or to a combination of both.

Ophthalmologic

Macular Edema

Macular edema (see 8.2 Clinical Trials Adverse Reactions, Macular edema) with or without visual symptoms has been reported in 0.4% of patients treated with fingolimod 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 fingolimod 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 Teva-Fingolimod therapy, an evaluation of the fundus, including the macula, should be carried out.

It is recommended that Teva-Fingolimod 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 Teva-Fingolimod 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 8.2 Clinical Trials Adverse Reactions, Macular edema). Multiple sclerosis patients with concomitant diabetes mellitus were excluded from the clinical trials with fingolimod. In other clinical trials with fingolimod 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 fingolimod (diabetic and non-diabetic) compared to patients receiving control treatment.

In addition to an ophthalmic evaluation prior to initiating Teva-Fingolimod 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 Teva-Fingolimod therapy.

Psychiatric

Depression and Suicidal Ideation:

Depression and suicidal ideation are known to occur at an increased frequency in the MS population. A relationship between the occurrence of depression and/or suicidal ideation and the use of fingolimod in the MS population has not been established. Patients, families and caregivers of patients being treated with Teva-Fingolimod should be advised to monitor for the emergence of any symptoms of depression and/or suicidal ideation and report such symptoms immediately to a health professional, for prompt evaluation.

Reproductive Health: Female and Male Potential

Women of childbearing potential / Contraception: Teva-Fingolimod is contraindicated in women (including female adolescents) who are pregnant or of child bearing potential not using effective contraception (see 2 CONTRAINDICATIONS). Therefore, before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available and counselling should be provided regarding the serious risk to the fetus. Women of childbearing potential must use effective contraception during treatment and for 2 months after discontinuation of Teva-Fingolimod, since fingolimod takes approximately 2 months to eliminate from the body after treatment discontinuation (see 10.2 Pharmacodynamics, Immune system). If the woman becomes pregnant while taking this drug, the patient must be apprised of the risk to the fetus.

- **Fertility**

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

- **Teratogenic Risk**

Female reproductive toxicity

Based on human and animal data, Teva-Fingolimod is potentially teratogenic (see 2 CONTRAINDICATIONS, 7.1.1 Pregnant Women, 16 NON-CLINICAL TOXICOLOGY).

Male reproductive toxicity

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

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 fingolimod as early as 1 month after treatment initiation (see 8.2 Clinical Trials Adverse Reactions, Respiratory System). 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.

Advise patients that they should contact their physician if they experience new onset or worsening dyspnea. Spirometric evaluation of respiratory function and evaluation of DLCO should be performed during therapy with Teva-Fingolimod 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 fingolimod clinical trials.

Teva-Fingolimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis, moderate and severe asthma or chronic obstructive pulmonary disease (see 10.2 Pharmacodynamics, Pulmonary Function).

7.1 Special Populations

7.1.1 Pregnant Women

Teva-Fingolimod is contraindicated in women (including female adolescents) who are pregnant or of child bearing potential not using effective contraception (see 2 CONTRAINDICATIONS). There are no adequate and well-controlled studies in pregnant women.

Available human data (post-marketing data and pregnancy registry information) suggest that use of fingolimod is associated with an increased risk of overall major congenital malformation (approximately 5%) when administered during pregnancy in comparison with the prevalence observed in the general population (2-4%).

The pattern of malformation reported for fingolimod is similar to that observed in the general population, however, increased prevalence of the following specific major malformations were noted:

- Congenital heart disease such as atrial and ventricular septal defects, tetralogy of Fallot
- Renal abnormalities
- Musculoskeletal abnormalities

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

If a female becomes pregnant while taking Teva-Fingolimod, treatment must be discontinued.

Fingolimod must be discontinued 2 months before planning a pregnancy. Medical advice should be given regarding the risk of harmful effects on the fetus associated with treatment and medical follow-up examination should be performed (e.g. ultrasonography examination). Also, the possibility of severe exacerbation of disease should be considered in females discontinuing Teva-Fingolimod because of pregnancy or planned pregnancy, and patients should consult their physicians on potential alternatives (see 7 WARNINGS AND PRECAUTIONS, Return of disease activity (rebound) and severe increase in disability after fingolimod discontinuation and Immune System Effects Following Discontinuation of Treatment).

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 16 NON-CLINICAL TOXICOLOGY).

Pregnancy exposure registry: There is a registry that monitors pregnancy outcomes in women exposed to Teva-Fingolimod during pregnancy. If a patient becomes pregnant while taking Teva-Fingolimod, physicians are encouraged to report this event by calling Teva Canada Ltd. at 1-800-268-4127 ext. 3 or visiting druginfo@tevacanada.com.

7.1.2 Breast feeding

Teva-Fingolimod is excreted in the milk of animals treated during lactation. There are no data on the effects of fingolimod on the breastfed child or the effects of fingolimod 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 Teva-Fingolimod should not breast feed.

7.1.3 Pediatrics

Pediatrics patients (<18 years of age): Teva-Fingolimod is not indicated for use in pediatric patients.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Clinical studies of fingolimod 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 Fingolimod merits caution and may necessitate additional or more frequent monitoring in geriatric patients (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

A total of 1703 patients on 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 14 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 7 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 fingolimod 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 fingolimod 0.5 mg at ≥1% higher rate than for placebo.

Primary system organ class Preferred Term	Fingolimod 0.5mg N=425 (%)	Placebo N=418 (%)
Infections		
Influenza viral infections	55 (12.9)	41 (9.8)
Bronchitis	34 (8.0)	15 (3.6)
Sinusitis	28 (6.6)	19 (4.5)
Gastroenteritis	19 (4.5)	13 (3.1)
Pneumonia*	2 (0.5)	1 (0.2)
Herpes viral infections*	37 (8.7)	33 (7.9)
Tinea infections	16 (3.8)	6 (1.4)
Cardiac Disorders		
Bradycardia	15 (3.5)	4 (1.0)
Nervous system disorders		
Headache	107 (25.2)	96 (23.0)
Dizziness	31 (7.3)	23 (5.5)
Paresthesia	23 (5.4)	18 (4.3)
Migraine	20 (4.7)	6 (1.4)
Gastrointestinal disorders		
Diarrhea	50 (11.8)	31 (7.4)
General disorders and administration site conditions		
Asthenia	11 (2.6)	5 (1.2)
Musculoskeletal and connective tissue disorders		
Back pain	50 (11.8)	29 (6.9)
Skin and subcutaneous tissue disorders		
Eczema	14 (3.3)	8 (1.9)
Alopecia	15 (3.5)	10 (2.4)
Pruritus	11 (2.6)	5 (1.2)
Investigations		

Primary system organ class Preferred Term	Fingolimod 0.5mg N=425 (%)	Placebo N=418 (%)
Alanine transaminase (ALT) increased	43 (10.1)	16 (3.8)
Gamma-glutamyl transferase (GGT)	22 (5.2)	4 (1.0)
Hepatic enzyme increased	14 (3.3)	1 (0.2)
Weight decreased	20 (4.7)	14 (3.3)
Blood triglycerides increased	11 (2.6)	5 (1.2)
Liver function test abnormal	6 (1.4)	1 (0.2)
Respiratory, thoracic and mediastinal disorders		
Cough	43 (10.1)	34 (8.1)
Dyspnea	34 (8.0)	19 (4.5)
Psychiatric disorders		
Depression	33 (7.8)	28 (6.7)
Eye disorders		
Eye pain	11 (2.6)	6 (1.4)
Vision blurred	15 (3.5)	6 (1.4)
Vascular disorders		
Hypertension	27 (6.4)	16 (3.8)
Blood and lymphatic system disorders		
Leucopenia	12 (2.8)	1 (0.2)
Lymphopenia	15 (3.5)	2 (0.5)
* 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 fingolimod-treated patients (Table 1).

There have been very rare fatal cases of VZV infections in patients taking fingolimod (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 7 WARNINGS AND PRECAUTIONS, Herpetic Infections).

Macular Edema

In clinical trials, macular edema occurred in 0.4% of patients treated with the recommended fingolimod 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 fingolimod 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 7 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 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).

ECG Findings

Fingolimod was associated with PR interval prolongation, QTc interval prolongation, and decreased heart rate (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 9.2 Drug Interactions Overview, Pharmacodynamic Interactions; 10.2 Pharmacodynamics-Heart rate and rhythm, -Thorough QT Study).

Bradyarrhythmia

Initiation of Fingolimod treatment results in a reversible decrease in heart rate that may also be associated with AV conduction delays (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 9.2 Drug Interactions Overview, Pharmacodynamic Interactions; 10.2 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 fingolimod 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 fingolimod 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 fingolimod 0.5 mg.

Isolated reports of complete AV block during the 6 hour observation period and delayed onset cardiac events, including transient asystole and unexplained death within 24 hours of the first dose, have been reported during post-marketing experience (see 8.5 Post-Market Adverse Reactions). These events were confounded by concomitant and/or pre-existing disease, and the relationship to fingolimod cannot be excluded.

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

Fingolimod 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, fingolimod 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 fingolimod 0.5 mg group compared to a maximal mean decrease of 1.8 mmHg (4 hours post-dose) in the placebo group (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 10.2 Pharmacodynamics, Blood Pressure). Cases of syncope were also reported after the first dose of fingolimod in the post-marketing setting.

In multiple sclerosis clinical trials fingolimod 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 fingolimod 0.5 mg and 511 multiple sclerosis patients on placebo, hypertension was reported as an adverse reaction in 5% of patients on fingolimod 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 fingolimod in clinical trials and in the post-marketing setting. The relationship to fingolimod 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

There have been cases of cutaneous neoplasms and lymphoma reported in clinical studies and the post-marketing setting (see 7 WARNINGS AND PRECAUTIONS, Neoplasms).

Basal cell carcinoma and other cutaneous 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.

During Phase III placebo controlled clinical trials there was no difference in the frequency of melanoma in patients treated with fingolimod for up to 2 years, compared to patients receiving placebo. In open label clinical trials and in the post-marketing setting, melanoma has been reported in a small number of patients, who were treated with fingolimod, and who had no apparent risk factors, signs of melanoma at treatment initiation or concurrent medical conditions (see 7 WARNINGS AND PRECAUTIONS, Neoplasm).

Kaposi's sarcoma has been reported in clinical trials and in the post-marketing setting in patients treated with fingolimod who did not have risk factors commonly associated with Kaposi's sarcoma.

Lymphoma

Cases of lymphoma have been reported in clinical studies and the post-marketing setting. The reported lymphoma cases were heterogeneous in nature, mainly Non-Hodgkin's Lymphoma, including B-cell and T-cell lymphomas. Cases of cutaneous T-cell lymphoma (including mycosis fungoides) have been observed in the post-marketing setting.

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 fingolimod as early as 1 month after treatment initiation (see 7 WARNINGS AND PRECAUTIONS, Respiratory). At Month 24, the reduction from baseline in the percent of predicted values for FEV1 was 3.1% for fingolimod 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 fingolimod 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 fingolimod 0.5 mg and 4.5% of patients receiving placebo. Several patients discontinued fingolimod because of unexplained dyspnea during the extension (uncontrolled) studies.

Seizures

Cases of seizures, including status epilepticus, have been reported with the use of fingolimod in clinical trials and in the post-marketing setting. In clinical trials, the rate of seizures was 0.9% in fingolimod treated patients and 0.3% in placebo treated patients. It is unknown whether these events were related to the effects of multiple sclerosis alone, to fingolimod, or to a combination of both.

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%).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Liver function

Increased hepatic enzymes (mostly ALT elevation) have been reported in multiple sclerosis patients treated with fingolimod. In clinical trials, patients treated with fingolimod 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 fingolimod 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 fingolimod. Findings were similar, but less frequent for AST and GGT.

ALT levels returned to normal after discontinuation of fingolimod within approximately 2 months. In a small number of patients (2 patients on fingolimod 0.5 mg), who experienced liver transaminase elevations of ≥5x ULN and who continued on fingolimod therapy, the ALT levels returned to normal within approximately 5 months (see 7 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 fingolimod 0.5 mg from Week 2 to Month 24. The incidence of notable high cholesterol levels (>6.21 mmol/L) was 39.6% for fingolimod 0.5 mg and 31.9% for placebo. The incidence of notable high triglyceride levels (> 3.39 mmol/L) was 13.7% for fingolimod 0.5 mg and 7.5% for placebo.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported during post-marketing experience:

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.

Cardiac Disorders: Isolated reports of transient, spontaneously resolving complete AV block have been observed during the six-hour observation period with fingolimod. Isolated delayed-onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose of fingolimod. These cases have been confounded by concomitant medications and/or pre-existing disease, but the relationship to fingolimod 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. JCV causing Progressive Multifocal Leukoencephalopathy (PML), herpes simplex or varicella zoster virus which may lead to encephalitis, meningitis, meningoencephalitis and multiorgan failure, fungal (e.g. cryptococci causing cryptococcal meningitis), or bacterial (e.g. atypical mycobacterium) pathogens, have been reported, some of which have been fatal (see 7 WARNINGS AND PRECAUTIONS, Immune).

Cases of tuberculosis have been reported.

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with fingolimod in the post-marketing setting (see 7 WARNINGS AND PRECAUTIONS, Immune - Human papilloma virus).

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

Gastrointestinal disorders: nausea

Hematologic: thrombocytopenia (with or without purpura)

Hepatic and biliary: Liver injury

Investigations: Weight decreased

Musculoskeletal and connective tissue disorders: Myalgia, arthralgia

Nervous system disorders: Severe exacerbation of disease after fingolimod discontinuation, posterior reversible encephalopathy syndrome, seizures including status epilepticus (see 7 WARNINGS AND PRECAUTIONS).

Neoplasms, benign, malignant, and unspecified (incl cysts and polyps): melanoma, squamous cell carcinoma, Merkel cell carcinoma, Kaposi's sarcoma, B-cell lymphoma, T-cell lymphoma, CNS lymphoma, cutaneous T-cell lymphoma (including mycosis fungoides).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Class Ia or Class III anti-arrhythmic drugs See 9.2 Drug Interactions Overview, Pharmacodynamic interactions – QTc prolonging drugs

9.2 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 7 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 7 WARNINGS and PRECAUTIONS and 8

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: 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, fingolimod should not be used concomitantly with antiarrhythmics, beta-blockers, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem), or other substances that may decrease heart rate (e.g. ivabradine, digoxin, cholinesterase inhibitors, or pilocarpine). If treatment with fingolimod 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular**;** 10.2 Pharmacodynamics-Heart rate and rhythm).

QTc prolonging drugs: Fingolimod may result in QTc prolongation during the first month of treatment (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 10.2 Pharmacodynamics-Thorough QT Study). Fingolimod 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 fingolimod treatment results in both a decreased heart rate and a prolongation of QTc interval, the co-administration of fingolimod with Class Ia or Class III drugs is contraindicated (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular-Bradyarrhythmia).

The initiation of treatment with fingolimod 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-HT_3 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 fingolimod vaccination may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore also be avoided during fingolimod treatment and for up to 2 months after treatment with fingolimod (see 7 WARNINGS AND PRECAUTIONS, Immune -Vaccination). It is recommended that pediatric patients be brought up to date with all immunizations in agreement with current immunization guidelines, as clinically indicated, prior to initiating fingolimod therapy.

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 co-medications

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.

9.4 Drug-Drug Interactions

Table 2 - Established or Potential Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated.

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Oral contraceptive (ethinylestradiol and levonorgestrel)	CT	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	CT	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	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

		(28 days) fingolimod administration.	does not influence fingolimod disposition.
Ketoconazole	CT	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 fingolimod and systemic ketoconazole and patients should be closely monitored as the risk of adverse events may be increased.
Isoproterenol and atropine	CT	Single-dose fingolimod and fingolimod-phosphate exposure was not altered by co-administered isoproterenol, or atropine.	
Carbamazepine	C	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.
Atenolol and	CT	The co-administration	Due to potential

Diltiazem		of atenolol 50 mg/day at steady-state and a single dose of fingolimod 5 mg induced an additional 15% reduction of heart rate at fingolimod treatment initiation, an effect that was not observed with the co-administration of diltiazem 240 mg/day at steady-state.	additive effects on heart rate or cardiac conduction, fingolimod should not be used concomitantly with heart rate lowering drugs. If treatment with fingolimod is considered necessary, advice from a cardiologist should be sought regarding the switch to a non heart-rate lowering drug or for appropriate monitoring (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Legend: C = Case Study; CT = Clinical Trial

9.5 Drug-Food Interactions

Fingolimod may be taken with or without food (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics, Absorption).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test 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 Teva-Fingolimod.

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

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

Immune system

Effects on immune cell numbers in the blood. In a study in which 12 subjects were treated with 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 fingolimod 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 Fingolimod may take up to 2 months (see 10.3 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 fingolimod 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 fingolimod 0.5 mg. Similarly, IgG titers were decreased by 45% and 50%, in response to KLH and PPV, respectively, in subjects on fingolimod 0.5 mg daily compared to placebo. The responder rate for fingolimod 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 fingolimod 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).

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

Heart rate and rhythm

Fingolimod causes a reversible prolongation of PR interval and reduction in heart rate upon treatment initiation (see 8 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8.2 Clinical Trial 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.

10.3 Pharmacokinetics

Table 3-The pharmacokinetic parameters of fingolimod 0.5 mg after a single dose and at steady-state

		C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng.h/mL)
Fingolimod	Single dose	0.42	12	7.84
	Steady-state	3.66	12	76.1
Fingolimod-P	Single dose	0.45	6	6.1
	Steady-state	1.81	6	33.1

Values are mean, except Tmax (median)

Absorption

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 Fingolimod is taken with food. Fingolimod may be taken without regard to meals (see 4 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%)).

Elimination

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:** Teva-Fingolimod is not indicated for use in pediatric patients.

- **Geriatrics:** Clinical studies of fingolimod did not include sufficient numbers of patients aged 65 years and over to determine whether the safety and efficacy of fingolimod 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 Fingolimod merits caution and may necessitate additional or more frequent monitoring in geriatric patients.

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

- **Ethnic Origin:** 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.

Fingolimod is contraindicated in patients with severe hepatic impairment (Child-Pugh class C) (see 2 CONTRAINDICATIONS). Fingolimod 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 Teva-Fingolimod.

- **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 Teva-Fingolimod in patients with severe renal impairment.

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

11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C – 30°C. Protect from moisture.

Teva-Fingolimod must be kept out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

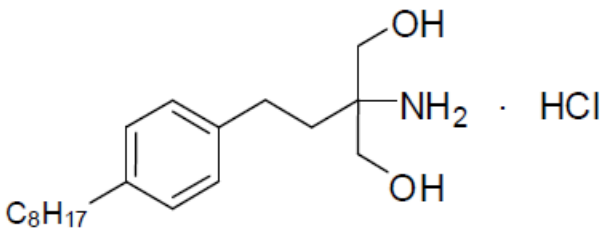
Common Name: Fingolimod hydrochloride

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 g / mol

Structural Formula:



Physicochemical properties: Fingolimod hydrochloride is white to off-white solid. It is freely soluble in water. The pH (of 1% aqueous solution at 22°C) is 4.0.

14. CLINICAL TRIALS

14.1 Clinical trials by Indication

Monotherapy for the treatment of adult patients with the relapsing-remitting form of multiple sclerosis (RRMS)

Table 4 –Summary of adult patient demographics for clinical trials in RRMS

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study D2301 (FREEDOMS)	Randomized, double-blind, placebo-controlled study	Fingolimod 0.5 mg or 1.25 mg, or placebo, once-daily (oral). 2-year study	Fingolimod 0.5 mg: n=425 Fingolimod 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	Fingolimod 0.5 mg or 1.25 mg, once- daily (oral), or Avonex 30 µg, once weekly (IM). 1-year study.	Fingolimod 0.5 mg: n=429 Fingolimod 1.25 mg: n=420 Avonex: n=431	36.2 (18-55 years)	Male: 32.7% Female: 67.3%

The efficacy of fingolimod has been demonstrated in two studies evaluating once daily doses of fingolimod 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.

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.

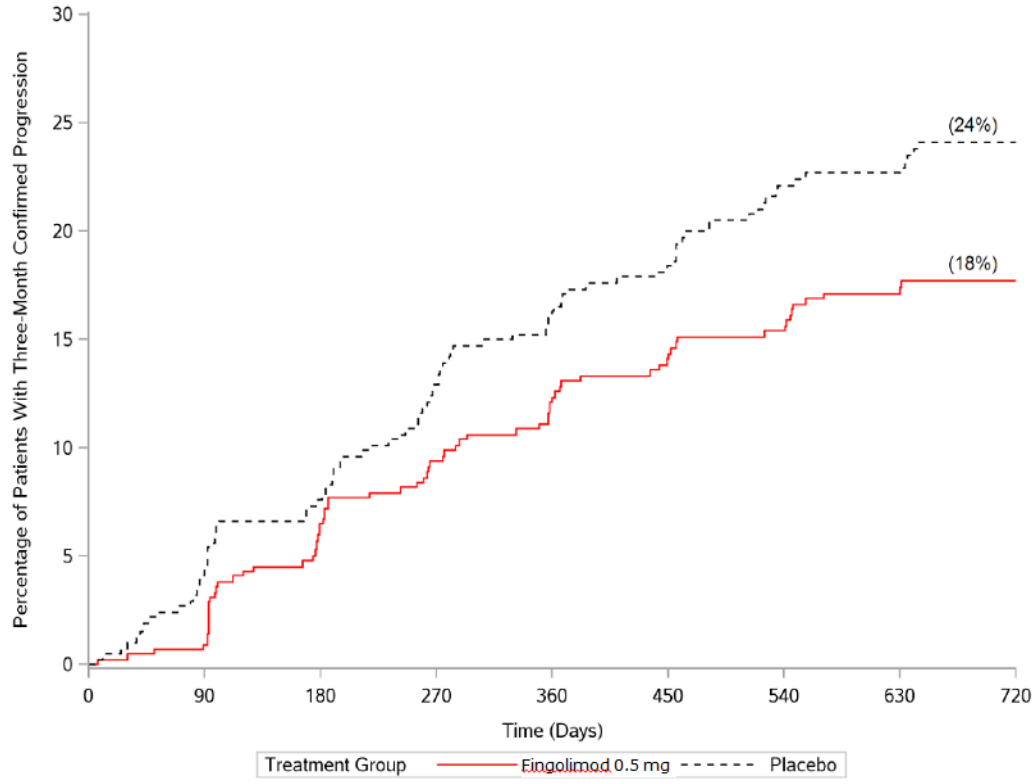
Table 5 – Results of study D2301 (FREEDOMS) in RRMS

	Fingolimod 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 $\geq$ 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, 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 fingolimod vs placebo.

The primary endpoint, the annualized relapse rate was significantly lower in patients treated with fingolimod than in patients who received placebo, with a relative reduction in relapse of 54% for patients treated with fingolimod 0.5 mg (see Table 5). 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 fingolimod treatment compared to placebo. The time to disability progression was significantly longer with fingolimod vs. placebo (see Table 5 and Figure 1).The 1.25 mg dose did not provide additional benefit over the 0.5 mg dose

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 fingolimod 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 fingolimod 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 fingolimod (-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.

Table 6 – Results of study D2302 (TRANSFORMS) in RRMS

	Fingolimod 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 ≥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.

The annualized relapse rate was significantly lower in patients treated with fingolimod than in patients who received interferon beta-1a, with a relative reduction in relapse of 52% for patients treated with fingolimod (see Table 6). 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 fingolimod than in patients who received interferon beta-1a. There was no significant difference in the time to 3-month confirmed disability progression between

fingolimod and interferon beta-1a-treated patients at 1 year (see Table 6). There were no significant differences between the 0.5 mg and the 1.25 mg doses on either endpoint.

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 fingolimod 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 fingolimod 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 fingolimod (-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.

14.3 Comparative Bioavailability Study

A randomized, blinded, 2-way crossover bioequivaleence study of Teva-Fingolimod 0.5 mg Capsules (Teva Pharmaceutical Industries Ltd.) and PrGilenya® 0.5 mg Capsules (Novartis Pharmaceuticals Canada Inc., Canada) administered as a single 1 x 0.5 mg dose was conducted in healthy male and female subjects (n=24) under fasting conditions. The results from the measured data are summarized in the table below.

Fingolimod 1 x 0.5 mg From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (pg·h/mL)	22389.56 22517.21 (10.8)	22642.09 22800.01 (12.1)	98.9%	95.7 - 102.1%
C_{max} (pg/mL)	399.31 402.48 (12.9)	409.70 412.58 (12.4)	97.5%	94.4 – 100.6%
T_{max} § (h)	17.4 (57.1)	18.5 (61.2)		

* Teva-Fingolimod 0.5 mg Capsules (Teva Pharmaceutical Industries Ltd.)
† PrGilenya® 0.5 mg Capsules (Novartis Pharmaceuticals Canada Inc., Canada) were purchased in Canada
§ Expressed as the arithmetic mean (CV%)
Due to the long elimination half-life of fingolimod, AUC_I and $T_{1/2}$ could not be accurately calculated from the data obtained in this study.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16. NON-CLINICAL TOXICOLOGY

Detailed Pharmacology

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

General 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.

Carcinogenicity: 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.

Genotoxicity: 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.

Reproductive and Developmental Toxicology: 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.

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

17 SUPPORTING PRODUCT MONOGRAPH

1. GILENYA® (Capsules, 0.25 mg and 0.5 mg), Submission Control No.; 249522, Product Monograph, Novartis Pharmaceuticals Canada Inc., (July 26, 2021).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Teva-Fingolimod

Fingolimod Capsules

Read this carefully before you start taking **Teva-Fingolimod** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Teva-Fingolimod**.

What is Teva-Fingolimod used for?

Teva-Fingolimod is used to treat:

- Adult patients with the relapsing and remitting form of multiple sclerosis (MS). Teva-Fingolimod 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.

How does Teva-Fingolimod?

Teva-Fingolimod 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 progression of physical problems that happen due to MS (disability progression).

Teva-Fingolimod changes how the body's immune system works by decreasing the ability of lymphocytes, a type of white blood cell, 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.

What are the ingredients in Teva-Fingolimod?

Medicinal ingredient: fingolimod (as fingolimod hydrochloride)

Non-medicinal ingredients: gelatin, iron oxide yellow, pregelatinized starch, sodium lauryl sulphate and titanium dioxide.

Teva-Fingolimod comes in the following dosage forms:

Hard gelatin capsules: 0.5 mg

Do not use Teva-Fingolimod if:

- you are allergic (hypersensitive) to fingolimod or to any of the other ingredients in Teva-Fingolimod (see **What are the ingredients in Teva-Fingolimod?**).
- 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 (TB).
- you have an active cancer (except for a type of skin cancer called basal cell carcinoma).
- you have severe liver disease.

- you have had a heart attack, angina (chest pain), stroke or warning of a stroke, or certain types of heart failure in the last 6 months.
- you have certain types of irregular or abnormal heartbeat (arrhythmia), or your electrocardiogram (ECG) shows prolonged QT interval before starting Teva-Fingolimod.
- you are taking or have recently taken medicine for irregular heartbeat such as quinidine, disopyramide, amiodarone or sotalol (due to a possible added effect on irregular heartbeat).
- you are pregnant, think you might be pregnant or plan to get pregnant.
- you are of childbearing age and are not using effective methods of birth control
- you are of childbearing age, until it is confirmed with a pregnancy test that you are not pregnant. This is done just before you begin treatment with Teva-Fingolimod.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Teva-Fingolimod. Talk about any health conditions or problems you may have, including if:

- you have heart problems, such as high blood pressure, or severe untreated sleep apnea
- you have a 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 Teva-Fingolimod 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 Teva-Fingolimod.
- you have never had chickenpox or have not been vaccinated for chickenpox.
- you have had infections such as hepatitis or tuberculosis (TB).
- 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.
- you have liver problems.
- you have low or high blood pressure.
- you have high cholesterol or triglyceride levels.
- you have kidney problems.
- you have breathing problems.
- you are breast feeding.
- you are 65 years of age or older. You may have a higher risk of side effects.

Other warnings you should know about:

Chickenpox: 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 Teva-Fingolimod. There have been very rare fatal cases of chickenpox infection reported in patients treated with Teva-Fingolimod, who also received a relatively long course of corticosteroid therapy. If you are not protected against chickenpox, your healthcare professional may recommend that you receive the chickenpox vaccine 1 month before starting treatment with Teva-Fingolimod.

Human Papilloma Virus (HPV): Your healthcare professional will tell you if you need to have a vaccination against Human Papilloma Virus (HPV) before starting treatment. If you are a female, your healthcare professional will recommend HPV screening. HPV infection, including papilloma (finger-like growths on the skin and mucous membranes), dysplasia (abnormal cells on the cervix found by PAP smear in women), warts and HPV-related cancer, has been reported in patients treated with Teva-Fingolimod.

Blood Tests and Monitoring: Before you start taking Teva-Fingolimod and periodically during treatment, your healthcare professional will do tests to help monitor side-effects. These will include: blood tests (to check your white blood cell counts and the health of your liver, see Liver Problems below), eye exams (to monitor for macular

edema, see Eye Problems below), checks of your heart rhythm and blood pressure, and possibly lung function.

Because fingolimod has side effects on the heart (see **Heart Problems** below), you will be required to have an electrocardiogram (ECG) to check the health of your heart before you start fingolimod (or after taking the first dose of 0.5 mg when your child switches from the 0.25 mg capsule daily dose). Your healthcare professional will ask you to stay in the clinic or office for at least 6 hours after taking the first dose of fingolimod 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 healthcare facility. The same observation process may apply if you are starting treatment again after a break from fingolimod therapy.

Heart Problems: Teva-Fingolimod causes the heart rate to slow down, especially during the first month of treatment. Teva-Fingolimod 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 to happen in patients with risk factors, such as heart disease, or when Teva-Fingolimod is taken with certain medicines. Patients aged 65 years and older are also at a 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 Teva-Fingolimod. This might also happen if you have a slow heart rate or if you are taking medicines which slow the heartbeat.
- If you have any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, while you are taking Teva-Fingolimod, get immediate medical help.

Liver Problems: Teva-Fingolimod may cause liver damage. Your healthcare professional should do blood tests to check your liver before you start taking Teva-Fingolimod and periodically during treatment and for two months after you have stopped taking Teva-Fingolimod. Tell your healthcare professional **right away** if you have any of the following symptoms of liver problems:

- nausea
- vomiting
- stomach pain
- tiredness
- loss of appetite
- your skin or the whites of your eyes turn yellow
- dark urine

Infections: Teva-Fingolimod may lower your body's ability to fight infections. This means you may get infections more easily while you are taking Teva-Fingolimod, and for up to 2 months after you stop taking it. If you have an infection before you start taking Teva-Fingolimod, tell your healthcare professional. Any infection that you already have may get worse. Infections could be serious and sometimes life-threatening.

- Before you start taking Teva-Fingolimod, your healthcare professional will make sure you have enough white blood cells in your blood.
- While you are taking Teva-Fingolimod, if you think you have an infection, have a fever, feel like you have the flu, or have a headache with a stiff neck, sensitivity to light, nausea, confusion and/or seizures (fits), tell your healthcare professional right away. These may be the symptoms of inflammation in your brain (encephalitis) or of the membranes covering your membranes (meningitis) caused by a serious fungal (Cryptococcus) or viral (herpes simplex or chickenpox) infection).
- 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 healthcare professional as soon as possible. These may be the symptoms of a rare brain disorder caused by infection called progressive multifocal leukoencephalopathy (PML). Your healthcare professional might do an MRI scan to check for this condition. Your healthcare professional will decide whether you need to stop taking Teva-Fingolimod.

- The use of other medications and treatments that suppress or change how the immune system works is not recommended during treatment with Teva-Fingolimod because they can further increase the risk of infections.

Eye Problems: A problem with your vision, called macular edema, can occur during treatment with Teva-Fingolimod. 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 Teva-Fingolimod. Your healthcare professional will test your vision 3 to 4 months after you start taking Teva-Fingolimod, or anytime 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 healthcare professional should test your vision before you start taking Teva-Fingolimod.

Seizures: Some patients have had seizures (fits) while taking Teva-Fingolimod. It is not known whether the seizures were related to the effects of their MS, Teva-Fingolimod, or to a combination of both. If you have a seizure while taking Teva-Fingolimod, get immediate medical help.

Depression and Suicidal Thoughts: Patients with MS can have depression and suicidal thoughts. Patients, families and caregivers of patients being treated with Teva-Fingolimod should watch for these symptoms. Tell your healthcare professional right away if any of these symptoms occur.

Cancer Risk: The effects of Teva-Fingolimod 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 Teva-Fingolimod.

- If you already have moles or open sores before starting treatment with Teva-Fingolimod, watch 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 healthcare professional about.
- A type of skin cancer called basal cell carcinoma (BCC) and other types of skin cancer such as malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma have been reported in MS patients treated with Teva-Fingolimod. While you are taking Teva-Fingolimod you should check your skin regularly for unusual changes. Symptoms of BCC may include skin nodules (e.g. shiny pearly nodules) and patches or open sores that do not heal within weeks. Symptoms of other skin cancers may include abnormal growth or changes of skin, such as unusual moles, that may change in color, shape or size over time. Your healthcare professional will do regular skin examinations during your treatment with Teva-Fingolimod.
- Long-term exposure to the sun and a weak immune system can affect the risk of developing Merkel cell carcinoma. You should limit your exposure to the sun and UV rays by: wearing appropriate protective clothing and regularly applying sunscreen with a high degree of UV protection.

Return of MS Symptoms: After Teva-Fingolimod treatment is stopped, symptoms of MS can return and may become worse compared to before or during treatment. Tell your healthcare professional if you have worsening of MS symptoms after stopping Teva-Fingolimod.

Brain Lesions: A condition with unusually large brain lesions associated with MS relapse has been rarely reported in patients treated with Teva-Fingolimod. This condition is called tumefactive lesions. In case of severe relapse, your healthcare professional will consider performing an MRI scan to check for this condition and will decide whether you need to stop taking Teva-Fingolimod.

Blood Disorders: Teva-Fingolimod may cause the following blood conditions:

- Destruction of red blood cells (autoimmune hemolytic anemia): weakness, looking pale, feeling tired.
- Low levels of platelets (thrombocytopenia): easy bruising, bleeding from a cut that is hard to stop, heavier menstrual periods than normal, bleeding from your gums or nose, small, scattered spots on your skin that are red, pink, or purple.

If these symptoms occur, tell your healthcare professional right away.

Pregnancy: Do **not** take Teva-Fingolimod if you are pregnant. Teva-Fingolimod can harm your unborn baby. If you are a female who could become pregnant or are a female planning to become pregnant, before you start treatment with Teva-Fingolimod your healthcare professional will:

- tell you about the risk to an unborn baby.
- ask you to do a pregnancy test to make sure you are not pregnant.
- talk to you about your birth control options. You must use effective birth control while you are taking Teva-Fingolimod and for two months after you stop taking it.

If you do become pregnant while taking Teva-Fingolimod tell your healthcare professional right away. You and your healthcare professional will decide what is best for you and your baby. If you become pregnant while taking Teva-Fingolimod, you can call Teva Canada Ltd. at 1-800-268-4127 ext. 3

Breastfeeding: You should not breastfeed while you are taking Teva-Fingolimod. Teva-Fingolimod can pass into breast milk and there is a risk of serious side effects for your baby.

Driving and using machines: After the first dose of Teva-Fingolimod, you will need to be monitored in a medical setting for at least 6 hours to have your heart rate and blood pressure checked. Your ability to drive and use machines may be affected during and potentially after this period. Do not drive or operate machinery until you know how you respond to Teva-Fingolimod.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do **not** take Teva-Fingolimod if you are taking, or have recently taken, medicines for an irregular heartbeat such as:

- quinidine
- disopyramide
- amiodarone
- sotalol

The following may interact with Teva-Fingolimod:

- Medicines for heart problems or high blood pressure.
- Medicines that slow down the heartbeat such as atenolol or metoprolol (called beta-blockers), verapamil, or diltiazem (called calcium channel blockers) or ivabradine or digoxin.
- Medicines to treat fungal infections, such as ketoconazole.
- Antibiotics, used to treat bacterial infections, such as erythromycin.
- Medicines used to treat HIV infection.
- Medicines used to treat asthma.
- Medicines that suppress or change 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. Teva-Fingolimod should not be started while you are on these medications. If you are switching to Teva-Fingolimod from another MS treatment, your healthcare professional may want to wait for several months to reduce the possible added effect on the immune system and potential for increased risk of serious infections.
- Vaccines. If you need to receive a vaccine, talk to your healthcare professional first. While you are taking Teva-Fingolimod and for up to 2 months after stopping treatment some vaccines containing live virus (live attenuated vaccines) may cause the infection that the vaccination should prevent. Other vaccines may not work well enough to protect you.

How to take Teva-Fingolimod:

- Always take Teva-Fingolimod exactly as your healthcare professional has told you.
- Do not stop taking Teva-Fingolimod or change your dose without talking to your healthcare professional.
- Take Teva-Fingolimod once a day, at the same time each day with half a glass of water. Teva-Fingolimod can be taken with or without food.
- Teva-Fingolimod 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.

Usual dose:

Adults: One 0.5 mg capsule per day.

Overdose:

If you think you, or a person you are caring for, have taken too much Teva-Fingolimod, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, 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, skip that dose and take the next dose as planned. Do not take a double dose to make up for a forgotten dose.

If you missed a dose on one day during the first 2 weeks, or if you stop taking Teva-Fingolimod for more than 7 days during weeks 3 and 4 of treatment, tell your healthcare professional right away. Your healthcare professional may decide to monitor you at the time you take the next dose.

If you start Teva-Fingolimod again after stopping for 2 weeks or more, you will need to start taking Teva-Fingolimod again in a medical setting. Do not restart Teva-Fingolimod after stopping it for more than two weeks without talking to your healthcare professional.

What are possible side effects from using Teva-Fingolimod?

These are not all the possible side effects you may have when taking Teva-Fingolimod. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Flu virus infection
- Headache
- Diarrhea
- Back pain
- Cough
- Sinusitis (sinus infection)
- 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
- Nausea
- Muscle pain
- Joint pain

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Bronchitis: cough with phlegm, chest pain, fever		✓	
Gastroenteritis: vomiting, nausea, diarrhea, fever		✓	
Shingles (herpes zoster infection): blisters, burning, itching or pain of the skin, (typically on the upper body or the face), fever, followed by numbness, itching or red patches with severe pain		✓	
Bradycardia (slow heartbeat): feeling dizzy, tired, awareness of own heartbeat, low blood pressure (dizziness, fainting, light-headedness, especially when you got from lying or		✓	
Skin Cancer: shiny pearly nodules, moles, patches or open sores that changes in size, shape or colour or do not heal, red or brown blotches or tumours usually on the skin of the legs		✓	
Low Levels of White blood cells: Symptoms of infection (fever, sore throat, mouth ulcers, flu-like feeling)		✓	
UNCOMMON			
Pneumonia: fever, cough, difficulty breathing		✓	
Macular Edema: shadows or blind spot in the center of the vision, blurred vision, problems seeing colors or fine details		✓	
Liver Problems: nausea, vomiting, loss of appetite, swelling and/or pain in the abdomen, feeling tired, itching, yellowing of the skin or eyes, dark urine)		✓	
Shortness of breath		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Seizures (fits) (more frequent in children and adolescents than in adults)			✓
Thrombocytopenia (low levels of platelets): easy bruising, bleeding from a cut that is hard to stop, heavier menstrual periods than normal, bleeding from your gums or nose, small, scattered spots on your skin that are red, pink, or purple		✓	
RARE			
Stroke: weakness and/or loss of feeling of limbs or face, difficulty speaking, clumsiness, vision loss			✓
Peripheral Artery Disease (poor circulation in the limbs): cold, painful, discolored limb, fingers or toes			✓
Posterior Reversible Encephalopathy Syndrome (PRES): sudden severe headache, nausea, vomiting, confusion, drowsiness, personality change, paralysis, abnormal speech, seizures (fits), vision changes			✓
Lymphoma (cancer of the lymphatic system): painless swelling of lymph node, swollen tonsils, fever, chills, night sweats, feeling tired, itching, unexplained weight loss, loss of appetite, persistent coughing/ difficulty breathing or not being able to breathe, headache		✓	
VERY RARE			
Heart Problems: dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, seizures (fits)			✓
FREQUENCY NOT KNOWN			
Encephalitis and/or meningitis (inflammation of your brain/of the membranes covering your brain, which may be caused by Cryptococcus, a type of fungus, or the herpes simplex or chickenpox viruses): headache with a stiff neck, sensitivity to light, nausea, confusion, seizures (fits)		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Progressive Multifocal Leukoencephalopathy (PML) (a rare brain infection): weakness on one side of your body, problems thinking, vision changes		✓	
Human Papilloma Virus (HPV) Infection: papilloma, (finger-like growths on the skin and mucous membranes), dysplasia (abnormal cells on the cervix found by PAP smear in women), warts, can lead to HPV-related cancer		✓	
Allergic Reactions: rash or itchy hives, swelling of lips, tongue or face, difficulty swallowing or breathing			✓
Autoimmune Hemolytic Anemia (destruction of red blood cells): weakness, looking pale, feeling tired.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not use Teva-Fingolimod after the expiry date shown on the box.
Store at room temperature (15°C-30°C).
Store in the original package, protect from moisture.
Keep out of the reach and sight of children.

If you want more information about Teva-Fingolimod:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9.

Last revised: April 20, 2022