1 Trade name

GILENYA 0.5 mg, hard capsules

2 Description and composition

Pharmaceutical form

Hard capsules

Active substance

Each capsule contains 0.5 mg fingolimod (as hydrochloride)

Fingolimod hydrochloride is a synthetic analogue of sphingosine. The chemical designation is 2-amino-2[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride. Its molecular formula is C19H33NO2-HCl and it has a molecular weight of 343.93.

Fingolimod hydrochloride is a white to almost white crystalline powder which is freely soluble in water.

Active Moiety

Fingolimod

Excipients

Mannitol, Magnesium stearate, Titanium dioxide, Gelatin, Yellow iron oxide, Printing ink (black, yellow).

3 Indications

Gilenya is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

4 Dosage and administration

General target population

The recommended dose of Gilenya is one 0.5 mg capsule taken orally once daily, which can be taken with or without food. If a dose is missed treatment should be continued with the next dose as planned.

Patients can switch directly from beta interferon or glatiramer acetate to Gilenya providing there are no signs of relevant treatment-related abnormalities e.g. neutropenia. Caution is advised when switching patients from natalizumab to Gilenya (see Section 6 Warnings and Precautions: Prior treatment with immunosuppressants).

First Dose Monitoring

Initiation of Gilenya treatment results in a decrease in heart rate (see 6 Warnings and Precautions and 11 Clinical Pharmacology). After the first dose of Gilenya, the heart rate decrease starts within an hour and the Day 1 nadir generally occurs within approximately 6 hours, although the nadir can be observed up to 24 hours after the first dose in some patients.

The first dose of Gilenya should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. In order to assess patient response to the first dose of fingolimod, observe all patients for 6 hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Obtain in all patients an electrocardiogram prior to dosing, and at the end of the observation period.

Additional observation should be instituted until the finding has resolved in the following situations:

- If the heart rate 6 hours post-dose is <45 bpm
- Or if the heart rate 6 hours post-dose is at the lowest value post-dose (suggesting that the maximum pharmacodynamic effect on the heart may not have occurred)
- Or if the ECG 6-hours post-dose shows new onset second degree or higher AV block

Should post-dose symptomatic bradycardia occur, initiate appropriate management, begin continuous ECG monitoring, and continue observation until the symptoms have resolved.

Should a patient require pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated after the second dose of Gilenya.

Patients with some pre-existing conditions (e.g., ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, history of symptomatic bradycardia, history of recurrent syncope, uncontrolled hypertension, severe untreated sleep apnea, AV block, sino-atrial heart block) may poorly tolerate the Gilenya-induced bradycardia, or experience serious rhythm disturbances after the first dose of Gilenya. Prior to treatment with Gilenya, these patients should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation, and, if treated with Gilenya, should be monitored overnight with continuous ECG in a medical facility after the first dose. Gilenya is contraindicated in patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure) (see 5 Contraindications).

Since initiation of Gilenya treatment results in decreased heart rate and may prolong the QT interval, patients with a prolonged QT interval (>450 msec males, >470 msec females) before dosing or during 6 hour observation, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome), or on concurrent therapy with QT prolonging drugs with a known risk of Torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin): advice from a cardiologist should be sought and the patients should be monitored overnight with continuous ECG in a medical facility (see 8 Interactions).

Experience with Gilenya is limited in patients receiving concurrent therapy with drugs that slow heart rate (e.g., beta blockers, heart-rate lowering calcium channel blockers such as diltiazem or verapamil, or digoxin). Because the initiation of Gilenya treatment is also associated with slowing of the heart rate, concomitant use of these drugs during Gilenya initiation may be associated with severe bradycardia or heart block. The possibility to switch to non-heart-rate lowering drugs should be evaluated by the physician prescribing the heart-rate lowering drug before initiating Gilenya. In patients who cannot switch, overnight continuous ECG monitoring after the first dose is recommended (see 8 Interactions).

Clinical data indicate effects of Gilenya on heart rate are maximal after the first dose although milder effects on heart rate may persist for, on average, 2-4 weeks after initiation of therapy at which time heart rate generally returns to baseline. Physicians should continue to be alert to patient reports of cardiac symptoms.

Re-initiation of Therapy Following Discontinuation

If Gilenya therapy is discontinued for more than 14 days, after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of Gilenya treatment and the same precautions (first dose monitoring) as for initial dosing should apply. Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of one day or more, during week 3 and 4 of treatment first dose procedures are recommended after treatment interruption of more than 7 days.

Dosing in special populations

Renal impairment

No Gilenya dose adjustments are needed (see section 11 Clinical pharmacology).

Hepatic impairment

No Gilenya dose adjustments are needed in patients with mild or moderate hepatic impairment. Gilenya should be used with caution in patients with severe hepatic impairment (Child-Pugh class C) (see section 11 Clinical pharmacology).

Pediatrics patients

Gilenya is not indicated for use in pediatric patients (see section 11 Clinical Pharmacology).

Geriatrics patients

Gilenya should be used with caution in patients aged 65 years and over (see section 11 Clinical pharmacology).

Ethnicity

No Gilenya dose adjustments based on ethnic origin are needed (see section 11 Clinical pharmacology).

Gender

No Gilenya dose adjustments are needed based on gender (see section 11 Clinical pharmacology).

Diabetic patients

Gilenya should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular edema (see section 7 Warnings and precautions).

5 Contraindications

Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization or Class III/IV heart failure)

History or presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless patient has a functioning pacemaker

Baseline QTc interval ≥500 ms

Treatment with Class Ia or Class III anti-arrhythmic drugs

6 Warnings and precautions

Infections

A core pharmacodynamic effect of Gilenya is a dose dependent reduction of peripheral lymphocyte count to 20 - 30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues (see section 11 Clinical pharmacology).

The immune system effects (see section 11 Clinical Pharmacology) of Gilenya may increase the risk of infections (see section 7 Adverse drug reactions). Effective diagnostic and therapeutic strategies should therefore be employed in patients with symptoms of infection while on therapy. Because the elimination of fingolimod after discontinuation may take up to two months, vigilance for infection should be continued throughout this period (see below subsection: Stopping Gilenya therapy).

Anti-neoplastic, immunosuppressive or immune modulating therapies should be co-administered with caution due to the risk of additive immune system effects (see section 8 Interactions).

Patients receiving Gilenya should be instructed to report symptoms of infections to their physician. Suspension of dosing with Gilenya should be considered if a patient develops a serious infection and consideration of benefit-risk should be undertaken prior to re-initiation of therapy.

As could be considered for any immune modulating drug, before initiating Gilenya therapy, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with Gilenya, following which initiation of treatment with Gilenya should be postponed for 1 month to allow full effect of vaccination to occur.

Vaccination

Vaccination may be less effective during and for up to two months after treatment with Gilenya (see below subsection: Stopping Gilenya therapy). The use of live attenuated vaccines should be avoided.

Macular Edema

Macular edema (see section 7 Adverse drug reactions) with or without visual symptoms has been reported in 0.4% of patients treated with Gilenya 0.5 mg, occurring predominantly in the first 3-4 months of therapy. An ophthalmologic evaluation is therefore recommended at 3-4 months after treatment initiation. If patients report visual disturbances at any time while on Gilenya therapy, evaluation of the fundus, including the macula, should be carried out.

Patients with history of uveitis and patients with diabetes mellitus are at increased risk of macular edema (see section 7 Adverse drug reactions). Gilenya has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. It is recommended that multiple sclerosis patients with diabetes mellitus or a history of uveitis undergo an ophthalmologic evaluation prior to initiating Gilenya therapy and have follow-up evaluations while receiving Gilenya therapy.

Continuation of Gilenya in patients with macular edema has not been evaluated. A decision on whether or not Gilenya therapy should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Bradyarrhythmia and Atrioventricular Blocks

Because of a risk for bradyarrhythmia and atrioventricular (AV) blocks, patients should be monitored during Gilenya treatment initiation (see 4 Dosage and Administration).

Reduction in heart rate

After the first dose of Gilenya, the heart rate decrease starts within an hour. On Day 1, the maximal decline in heart rate generally occurs within 6 hours and recovers, although not to baseline levels, by 8-10 hours post dose. Because of physiological diurnal variation, there is a second period of heart rate decrease within 24 hours after the first dose. In some patients,

heart rate decrease during the second period is more pronounced than the decrease observed in the first 6 hours. Heart rates below 40 beats per minute were rarely observed. Adverse reactions of symptomatic bradycardia following the first dose were reported in 0.5% of patients receiving Gilenya 0.5 mg, but in no patient on placebo. Patients who experienced bradycardia were generally asymptomatic, but some patients experienced hypotension, dizziness, fatigue, palpitations, and chest pain that usually resolved within the first 24 hours on treatment.

Following the second dose, a further decrease in heart rate may occur when compared to the heart rate prior to the second dose, but this change is of a smaller magnitude than that observed following the first dose. With continued dosing, the heart rate returns to baseline within one month of chronic treatment.

Atrioventricular blocks

Initiation of Gilenya treatment has been associated with atrio-ventricular conduction delays, usually as first-degree atrio-ventricular blocks (prolonged PR interval on electrocardiogram). Second-degree atrio-ventricular blocks, usually Mobitz type I (Wenckebach) have been observed in less than 0.5% of patients receiving Gilenya 0.5 mg in clinical trials. The conduction abnormalities typically were transient, asymptomatic, usually did not require treatment and resolved within the first 24-hours on treatment (see section 7 Adverse drug reactions).

Post-marketing experience

In the post-marketing setting, third degree AV block and AV block with junctional escape have been observed during the first-dose six-hour observation period with Gilenya. Isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These events were confounded by concomitant medications and/or pre-existing disease, and the relationship to Gilenya is uncertain. Cases of syncope were also reported after the first dose of Gilenya.

Gilenya has not been studied in patients with arrhythmias requiring treatment with Class Ia (e.g. quinidine, procainamide) or Class III anti-arrhythmic drugs (e.g., amiodarone, sotalol). Class Ia and Class III anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. Since initiation of Gilenya treatment results in decreased heart rate, Gilenya should not be used concomitantly with these drugs.

Liver function

During clinical trials, 3-fold or greater elevation in liver transaminases occurred in 8.5% of patients treated with Gilenya 0.5 mg and drug was discontinued if the elevation exceeded 5-fold increase. Recurrence of liver transaminase elevations occurred upon re-challenge in some patients, supporting a relationship to the drug. Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have liver enzymes checked and Gilenya should be discontinued if significant liver injury is confirmed (see section 7 Adverse drug reactions, liver transaminases subsection). Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function tests (LFTs) when taking Gilenya, caution in the use of Gilenya should be exercised in patients with a history of significant liver disease.

Prior treatment with immunosuppressants

When switching patients from beta interferon or glatiramer acetate to Gilenya, a washout is not necessary, assuming any immune effects (i.e. cytopenia) of such therapies have resolved.

Due to the long half-life of natalizumab, concomitant exposure, and thus concomitant immune effects, could occur if Gilenya is started within the first 2 to 3 months following discontinuation of natalizumab. Therefore careful case-by-case assessment regarding the timing of the initiation of Gilenya treatment is recommended when switching patients from natalizumab to Gilenya.

When switching from other immunosuppressive medications, the duration and mode of action of such substances must be considered when initiating Gilenya to avoid additive immune suppressive effects.

Stopping therapy

If a decision is made to stop treatment with Gilenya, the physician needs 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 normal range within 1-2 months of stopping therapy (see section 11 Clinical pharmacology). Starting other therapies during this interval will result in a concomitant exposure to fingolimod. Use of immunosuppressants soon after the discontinuation of Gilenya may lead to an additive effect on the immune system and therefore caution should be applied.

7 Adverse drug reactions

A total of 1703 patients on Gilenya (0.5 or 1.25 mg dose) constituted the safety population in the two Phase III studies in patients with relapsing remitting multiple sclerosis (see section 12 Clinical studies). Study #1 (FREEDOMS) was a 2-year placebo-controlled clinical study in 854 multiple sclerosis patients treated with fingolimod (placebo: 418). In this study the most serious adverse reactions (ADRs) for the 0.5 mg recommended therapeutic dose were infections, macular edema and transient atrio-ventricular blocks on treatment initiation. The most frequent ADRs (incidence ≥10%) at the 0.5 mg dose were headache, influenza, diarrhea, back pain, liver enzyme elevations and cough. The most frequent adverse event reported for Gilenya 0.5 mg at an incidence greater than 1% leading to treatment interruption included serum transaminase elevations (3.8%).

The ADRs in Study #2 (TRANSFORMS), a 1-year controlled study using interferon beta-1a as comparator in 849 patients with multiple sclerosis treated with fingolimod), were generally similar to Study 1, taking into account the differences in study duration.

ADRs are listed according to MedDRA system organ class. Frequencies were defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 7-1 ADRs occurring in ≥1% of patients in Study 1, and reported for Gilenya 0.5 mg at ≥1% higher rate than for placebo

Primary system organ class Preferred Term	Placebo N=418 %	Fingolimod 0.5mg N=425 %	Fingolimod 1.25mg N=429 %	Frequency range for the 0.5 mg dose
Infections				
Influenza viral infections	41 (9.8)	55 (12.9)	40 (9.3)	very common
Bronchitis	15 (3.6)	34 (8.0)	39 (9.1)	common
Sinusitis	19 (4.5)	28 (6.6)	27 (6.3)	common
Gastroenteritis	13 (3.1)	19 (4.5)	18 (4.2)	common
Pneumonia*	1 (0.2)	2 (0.5)	7 (1.6)	uncommon
Herpes viral infections*	33 (7.9)	37 (8.7)	25 (5.8)	common
Tinea infections	6 (1.4)	16 (3.8)	6 (1.4)	common
Cardiac Disorders				
Bradycardia	4 (1.0)	15 (3.5)	10 (2.3)	common
Nervous system disorders				
Headache	96 (23.0)	107 (25.2)	114 (26.6)	very common
Dizziness	23 (5.5)	31 (7.3)	30 (7.0)	common
Paresthesia	18 (4.3)	23 (5.4)	17 (4.0)	common
Migraine	6 (1.4)	20 (4.7)	15 (3.5)	common
Gastrointestinal disorders				
Diarrhea	31 (7.4)	50 (11.8)	40 (9.3)	very common
General disorders and administration site conditions				
Asthenia	5 (1.2)	11 (2.6)	9 (2.1)	common
Musculoskeletal and connective tissue disorders				
Back pain	29 (6.9)	50 (11.8)	45 (10.5)	very common
Skin and subcutaneous tissue disorders				
Eczema	8 (1.9)	14 (3.3)	15 (3.5)	common
Alopecia	10 (2.4)	15 (3.5)	9 (2.1)	common
Pruritus	5 (1.2)	11 (2.6)	4 (0.9)	common
Investigations				
Alanine transaminase (ALT) increased	16 (3.8)	43 (10.1)	50 (11.7)	very common
Gamma-glutamyl transferase (GGT) increased	4 (1.0)	22 (5.2)	32 (7.5)	common
Hepatic enzyme increased	1 (0.2)	14 (3.3)	22 (5.1)	common
Weight decreased	14 (3.3)	20 (4.7)	15 (3.5)	common
Blood triglycerides increased	5 (1.2)	11 (2.6)	8 (1.9)	common
Liver function test abnormal	1 (0.2)	6 (1.4)	7 (1.6)	common
Respiratory, thoracic and mediastinal disorders				
Cough	34 (8.1)	43 (10.1)	37 (8.6)	very common
Dyspnea	19 (4.5)	34 (8.0)	28 (6.5)	common
Psychiatric disorders				
Depression	28 (6.7)	33 (7.8)	26 (6.1)	common
Eye disorders				
Eye pain	6 (1.4)	11 (2.6)	8 (1.9)	common
Vision blurred	6 (1.4)	15 (3.5)	8 (1.9)	common
Macular edema	0 (0.0)	0 (0.0)	7 (1.6)	uncommon*†
Vascular disorders				
Hypertension	16 (3.8)	27 (6.4)	28 (6.5)	common

Primary system organ class Preferred Term	Placebo N=418 %	Fingolimod 0.5mg N=425 %	Fingolimod 1.25mg N=429 %	Frequency range for the 0.5 mg dose
Blood and lymphatic system disorders				
Leucopenia	1 (0.2)	12 (2.8)	27 (6.3)	common
Lymphopenia	2 (0.5)	15 (3.5)	23 (5.4)	common

*** Plausible relationship to study drug**

†Not reported in Study 1 at the 0.5 mg dose; however cases were reported in other studies at that dose. Frequency category is based on the incidence at the 0.5 mg dose in Study 2

Infections

In multiple sclerosis clinical trials, the overall rate of infections (72%) and serious infections (2%) at the 0.5 mg dose was similar to placebo. However, lower respiratory tract infections, bronchitis and pneumonia, were more common in Gilenya treated patients.

Two serious cases of disseminated herpes infection which were fatal have occurred on the 1.25 mg dose; a case of herpes encephalitis in a patient in whom initiation of acyclovir therapy was delayed by one week and a case of a primary disseminated varicella zoster infection in a patient not previously exposed to varicella receiving concomitant high-dose steroid therapy for a multiple sclerosis relapse.

Macular Edema

In clinical trials, macular edema occurred in 0.4% of patients treated with the recommended Gilenya dose of 0.5 mg and in 1.1% of patients treated with the higher 1.25 mg dose.

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 ophthalmologic examination. The macular edema generally improved or resolved spontaneously after drug discontinuation. The risk of recurrence after re-challenge has not been evaluated.

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

Gilenya has not been tested in multiple sclerosis patients with diabetes mellitus. In renal transplant clinical studies where patients with diabetes mellitus were included, therapy with Gilenya 2.5 mg and 5 mg resulted in a 2-fold increase in the incidence of macular edema. Multiple sclerosis patients with diabetes mellitus are therefore expected to be at a higher risk for macular edema (see section 6 Warnings and precautions).

Bradyarrhythmia

Initiation of Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrio-ventricular conduction delays (see section 6 Warnings and precautions).

In multiple sclerosis clinical trials the mean maximal decrease in heart rate after the first dose intake was seen 4 - 5 hours post-dose, with declines in mean heart rate, as measured by pulse, of 8 beats per minute for Gilenya 0.5 mg. The second dose may result in a slight further decrease. Heart rates below 40 beats per minute were rarely observed in patients on Gilenya 0.5 mg. Heart rate returned to baseline within 1 month of chronic dosing.

In the multiple sclerosis clinical program first-degree atrio-ventricular block (prolonged PR interval on electrocardiogram) was detected following drug initiation in 4.7% of patients on Gilenya 0.5 mg, in 2.8% of patients on intramuscular interferon beta-1a IM and in 1.5% of patients on placebo. Second degree atrio-ventricular block were detected in less than 0.5 % patients on Gilenya 0.5 mg.

The conduction abnormalities observed both in clinical trials and post-marketing were typically transient, asymptomatic and resolved within 24 hours on treatment. Although most patients did not require medical intervention, in clinical trials, in rare cases, they required treatment with atropine or isoproterenol.

Blood pressure

In multiple sclerosis clinical trials Gilenya 0.5 mg was associated with a mild increase of approximately 1 mmHg on average in mean arterial pressure manifesting after approximately 1 month of treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6.1% of patients on Gilenya 0.5 mg and in 3.8 % of patients on placebo.

Liver transaminases

In multiple sclerosis clinical trials, 8.5% and 1.9% of patients treated with Gilenya 0.5mg experienced asymptomatic elevation in serum levels of hepatic transaminases ≥3x ULN and ≥5x ULN, respectively, compared with corresponding figures in the placebo group of 1.7% and 1.0% respectively. The majority of elevations occurred within 6-9 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of Gilenya. In the few patients who experienced liver transaminase elevations ≥5x ULN and who continued on Gilenya therapy, the elevations returned to normal within approximately 5 months.

Respiratory System

Minor dose-dependent reductions in forced expiratory volume in 1 second (FEV_1) and in the diffusing capacity of the lung for carbon monoxide (DLCO) values were observed with fingolimod treatment starting at month 1 and remaining stable thereafter. At month 24, the reduction from baseline values in percent of predicted FEV_1 was 3.1% for fingolimod 0.5 mg and 2.0% for placebo, a difference that resolved after treatment discontinuation. For DLCO the reductions at month 24 were 3.8% for fingolimod 0.5 mg and 2.7% for placebo.

Vascular events

In phase III clinical trials rare cases of peripheral arterial occlusive disease occurred in patients treated with Gilenya at higher doses (1.25 or 5.0 mg). Rare cases of posterior reversible encephalopathy syndrome have been reported at 0.5 mg dose in clinical trials and in the post-marketing setting. Rare cases of ischemic and hemorrhagic strokes have also been reported at 0.5 mg dose in clinical trials and in the post-marketing setting although a causal relationship has not been established.

Lymphomas

Cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma) were reported in premarketing clinical trials in MS patients receiving Gilenya at, or above, the recommended dose of 0.5 mg. Based on the small number of reported cases and short duration of exposure, the relationship to Gilenya remains uncertain.

8 Interactions

Pharmacodynamic interactions

Anti-neoplastic, immunosuppressive or immune modulating therapies should be co-administered with caution 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 or mitoxantrone (see section 6 Warnings and precautions: Prior treatment with

immunosuppressants). In multiple sclerosis clinical trials the concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection.

When fingolimod is used with atenolol, there is an additional 15% reduction of heart rate upon fingolimod initiation, an effect not seen with diltiazem. Treatment with Gilenya should generally not be initiated in patients receiving beta blockers, heart rate lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin) because of the potential additive effects on heart rate. If treatment with Gilenya is considered, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products or appropriate monitoring for treatment initiation (should last overnight) (see section 6 Warnings and precautions).

QT prolonging drugs: Gilenya has not been studied in patients treated with drugs that prolong the QT interval. Drugs that prolong the QT interval have been associated with cases of torsades de pointes in patients with bradycardia. Since initiation of Gilenya treatment results in decreased heart rate and may prolong the QT interval, patients on QT prolonging drugs with a known risk of Torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility (see 4 Dosage and Administration and 6 Warnings and Precautions).

During and for up to two months after treatment with Gilenya vaccination may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided (see section 7 Adverse drug reactions).

Pharmacokinetic interactions

Fingolimod is primarily metabolized *via* human CYP4F2 with significant contribution also observed for CYP2D6*1, 2E1, 3A4, and 4F12. The involvement of multiple CYP isoenzymes in the oxidation of fingolimod suggests that the metabolism of fingolimod will not be subject to substantial inhibition in the presence of a single specific CYP inhibitor.

Potential of fingolimod and fingolimod-phosphate to inhibit the metabolism of co-medications.

In vitro inhibition studies in 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 CYP450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11. Therefore, fingolimod and fingolimod-phosphate are unlikely to reduce the clearance of drugs that are mainly cleared through metabolism by the major cytochrome P450 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) 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 CYP450 enzymes and ABCB1 with respect to the vehicle control therefore no clinically relevant induction of the tested CYP450 enzymes or ABCB1 (P-gp) by fingolimod are expected at therapeutic concentrations.

Transporters

Fingolimod as well as fingolimod-phosphate are not expected to inhibit the uptake of co-medications and/or biologics transported by OATP1B1, OATP1B3 or NTCP. Similarly, they are not expected to inhibit the efflux of co-medications and/or biologics transported by the breast cancer resistant protein (MXR), the bile salt export pump (BSEP), the multidrug

resistance-associated protein 2 (MRP2) and MDR1-mediated transport at therapeutic concentrations.

Oral contraceptives

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

Cyclosporine

The pharmacokinetics of single-dose fingolimod were not altered during co-administration with cyclosporine at steady-state, nor was cyclosporine steady-state pharmacokinetics altered by single-dose, or multi-dose (28 days) fingolimod administration. These data indicate that fingolimod is unlikely to reduce the clearance of drugs mainly cleared by CYP3A4 and show that the potent inhibition of transporters PgP, MRP2 and OATP-C does not influence fingolimod disposition.

Ketoconazole

The co-administration of ketoconazole 200 mg twice daily at steady-state and a single dose of fingolimod 5 mg led to a modest increase in the AUC of fingolimod and fingolimod-phosphate (1.7-fold increase), indicating that potent inhibitors of CYP3A and CYP4F have a weak effect on fingolimod pharmacokinetics.

Isoproterenol, atropine, atenolol, and diltiazem

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

Population pharmacokinetics analysis of potential drug-drug interactions

A population pharmacokinetics evaluation, performed in multiple sclerosis patients, did not provide evidence for a significant effect of fluoxetine and paroxetine (strong CYP2D6 inhibitors) and carbamazepine (potent enzyme inducer) on fingolimod or fingolimod-phosphate concentrations. In addition, the following, commonly prescribed substances had no clinically relevant effect (≤20%) on fingolimod or fingolimod-phosphate concentrations: baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin, corticosteriods and oral contraceptives.

Laboratory tests

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

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

9 Pregnancy and breast-feeding

Pregnancy

The use of Gilenya in women who are or may become pregnant should only be considered if the potential benefit justifies the potential risk to fetus (see below subsection Women of childbearing potential).

Animal studies have shown reproductive toxicity including fetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect (see section 13 Non-clinical safety data). Furthermore, the receptor affected by fingolimod (sphingosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. At the present time it is not known whether cardiovascular malformations will be found in humans. There are very limited data from the use of fingolimod in pregnant women. In clinical trials, 20 pregnancies were reported in patients exposed to fingolimod at the time of diagnosis of pregnancy, but data are too limited to draw conclusions on safety of Gilenya in pregnancy.

Labour and delivery

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

Breast-feeding

Fingolimod is excreted in milk of treated animals during lactation. Because of the potential for serious adverse drug reactions in nursing infants from fingolimod, women receiving Gilenya should not breast feed.

Women of childbearing potential

Before initiation of Gilenya treatment, women of childbearing potential should be counselled on the potential for serious risk to the fetus and the need for effective contraception during treatment with Gilenya. Since it will take approximately 2 months to eliminate the compound from the body upon stopping treatment (see section 6 Warnings and precautions) risk potential to the fetus may persist and contraception should be pursued during that period.

Fertility

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

Male reproductive toxicity

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

10 Overdosage

Single doses up to 80-fold the recommended dose (0.5 mg) were well tolerated in healthy volunteers. 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 Section 6 Warnings and precautions and section 7 Adverse drug reactions).

In case of GILENYA overdosage, observe patients overnight with continuous ECG monitoring in a medical facility, and obtain regular measurements of blood pressure (see section 4 Dosage and administration and section 6 Warnings and precautions).

Neither dialysis nor plasma exchange would result in meaningful removal of fingolimod from the body.

11 Clinical pharmacology

ATC code: L04AA27

Mechanism of action

Fingolimod is a sphingosine-1-phosphate receptor modulator. Fingolimod is metabolized by sphingosine kinase to the active metabolite fingolimod-phosphate. Fingolimod-phosphate, binds at low nanomolar concentrations to sphingosine-1-phosphate (S1P) receptors 1, 3, and 4 located on lymphocytes, and readily crosses the blood brain barrier to bind to S1P receptors 1, 3, and 5 located on neural cells in the central nervous system. By acting as a functional antagonist of S1PR on lymphocytes, fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. This redistribution reduces the infiltration of pathogenic lymphocyte cells into the central nervous system where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and *in vitro* experiments indicate that fingolimod may also exert beneficial effects in multiple sclerosis via interaction with S1P receptors on neural cells.

Pharmacodynamic Properties

Immune system

Effects on immune cell numbers in the blood. Within 4-6 hours after the first dose of fingolimod 0.5 mg, the lymphocyte count decreases to approximately 75% of baseline. With continued daily dosing, the lymphocyte count continues to decrease over a two week period, reaching a nadir count of approximately 500 cells/µL or approximately 30% of baseline. Eighteen percent of patients reached a nadir of < 200 cells/µL on at least one occasion. Low lymphocyte counts are maintained with chronic daily dosing. The majority of T and B lymphocytes regularly traffic through lymphoid organs and these are the cells mainly affected by fingolimod. Approximately 15-20% of T lymphocytes have an effector memory phenotype, cells that are important for peripheral immune surveillance. Since this lymphocyte subset typically does not traffic to lymphoid organs it is not affected by fingolimod. Peripheral lymphocyte count increases are evident within days of stopping fingolimod treatment and typically normal counts are reached within one to two months. Chronic fingolimod dosing leads to a mild decrease in the neutrophil count to approximately 80% of baseline. Monocytes are unaffected by fingolimod.

Heart rate and rhythm

Fingolimod causes a transient reduction in heart rate and atrio-ventricular conduction at treatment initiation (see section 7 Adverse drug reactions). The maximal decline of 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 one 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 or 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, isoprenaline or salmeterol.

Potential to prolong the QT interval

In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTcI, with the upper bound of the 90% CI ≤13.0 ms. There is no dose or exposure - response relationship of fingolimod and QTcI prolongation. There is no consistent signal of increased incidence of QTcI outliers, either absolute or change from baseline, associated with fingolimod treatment. In the multiple sclerosis studies, there was no clinically relevant prolongation of QT interval.

Pulmonary function

Fingolimod treatment with single or multiple doses of 0.5 and 1.25 mg for two weeks is not associated with a detectable increase in airway resistance as measured by FEV_1 and forced expiratory flow during expiration of 25 to 75% of the forced vital capacity (FEF_{25-75}). However, single fingolimod doses ≥5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance. Fingolimod treatment with multiple doses of 0.5, 1.25, or 5 mg is not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Subjects on fingolimod treatment have a normal bronchodilator response to inhaled β-agonists.

Pharmacokinetic Properties

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 high (93%).

Food intake does not alter C_{max} or exposure (AUC) of fingolimod or fingolimod-phosphate. Therefore Gilenya may be taken without regard to meals (see section 4 Dosage and administration).

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

Distribution

Fingolimod highly 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 mainly via the cytochrome P450 4F2 isoenzyme 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 radiolabeled components, are fingolimod itself (23.3%), fingolimod-phosphate

(10.3%), and inactive metabolites (M3 carboxylic acid metabolite (8.3%), M29 ceramide metabolite (8.9%) and M30 ceramide metabolite (7.3%)).

Elimination

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

After an 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%.

Linearity

Fingolimod and fingolimod-phosphate concentrations increase in an apparent dose proportional manner after multiple once daily doses of fingolimod 0.5 mg or 1.25 mg.

Special Populations

Renal Dysfunction

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. No Gilenya dose adjustments are needed in patients with renal impairment.

Hepatic Dysfunction

The pharmacokinetics of single-dose fingolimod (1 or 5 mg), when assessed in subjects with mild, moderate and severe hepatic impairments, 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. Fingolimod-phosphate was measured in severe hepatic impairment only, and $C_{max,}$ and AUC were increased by 22% and 29%, respectively. Although hepatic impairment elicited changes in the disposition of fingolimod and fingolimod-phosphate, the magnitude of these changes suggests that the fingolimod dose does not need to be adjusted in mild or moderate hepatic impaired patients. Fingolimod should be used with caution in patients with severe hepatic impairment (Child-Pugh class C).

Pediatrics

Safety and efficacy of Gilenya in pediatric patients below the age of 18 have not been studied. Gilenya is not indicated for use in pediatric patients.

Geriatrics

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

Ethnicity

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

Gender

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

12 Clinical studies

The efficacy of Gilenya has been demonstrated in two studies which evaluated once daily doses of Gilenya 0.5 mg and 1.25 mg in patients with relapsing remitting multiple sclerosis. Both studies included patients who had experienced at least 2 clinical relapses during the 2 years prior to randomization or at least 1 clinical relapse during the 1 year prior to randomization, and had an Expanded Disability Status Scale (EDSS) between 0 to 5.5.

Study #1 (FREEDOMS) 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 time of suspected relapse. MRI evaluations were performed at Screening, month 6, month 12 and month 24. The primary endpoint was the annualized relapse rate.

Median age was 37 years, median disease duration was 6.7 years and median EDSS score at baseline was 2.0. Patients were randomized to receive Gilenya 0.5 mg (n=425) or Gilenya 1.25 mg (n=429), or placebo (n=418) for up to 24 months. Median time on study drug was 717 days on 0.5 mg, 715 days on 1.25 mg and 718.5 days on placebo.

The annualized relapse rate was significantly lower in patients treated with Gilenya than in patients who received placebo. The key secondary endpoint was the time to 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for patients with baseline EDSS of 5.5) sustained for 3 months. Time to onset of 3-month confirmed disability progression was significantly delayed with Gilenya treatment compared to placebo. There were no significant differences between the 0.5 mg and the 1.25 mg doses on either endpoint.

The results for this study are shown in Table 12-1 and Figures 12-1 and 12-2.

Table 12-1 Clinical and MRI results of Study 1

	Gilenya 0.5 mg	**Gilenya 1.25 mg**	**Placebo**
Clinical Endpoints	N=425	N=429	N=418
Annualized relapse rate (primary endpoint)	0.18 (p<0.001*)	0.16 (p<0.001*)	0.40
Relative reduction (percentage)	54	60	
Percent of patients remaining relapse-free at 24 months	70.4 (p<0.001*)	74.7 (p<0.001*)	45.6
Risk of disability progression			
Hazard ratio (95% CI) (3-month confirmed)	0.70 (0.52, 0.96) (p=0.024*)	0.68 (0.50, 0.93) (p=0.017*)	
Hazard ratio (95% CI) (6-month confirmed)	*0.63 (0.44, 0.90) (p=0.012*)*	*0.60 (0.41, 0.86) (p=0.006*)*	
MRI Endpoints			
Number of new or newly enlarging T2 lesions	n=370	n=337	n=339
Median (mean) number over 24 months	0.0 (2.5) (p<0.001*)	0.0 (2.5) (p<0.001*)	5.0 (9.8)
Number of Gd-enhancing lesions	n=369 (Month 24)	n=343 (Month 24)	n=332 (Month 24)
Median (mean) number at			
Month 6	0.0 (0.2)	0.0 (0.3)	0.0 (1.3)
Month 12	0.0 (0.2)	0.0 (0.3)	0.0 (1.1)
Month 24	0.0 (0.2) (p<0.001* at each timepoint)	0.0 (0.2) (p<0.001* at each timepoint)	0.0 (1.1)
Percent change in T2 lesion total volume	n=368	n= 343	n=339

	Gilenya 0.5 mg	Gilenya 1.25 mg	Placebo
Median (mean) % change over 24 months	-1.7 (10.6) (p<0.001*)	-3.1 (1.6) (p<0.001*)	8.6 (33.8)
Change in T1 hypointense lesion volume	n=346	n=317	n=305
Median (mean) % change over 24 months	0.0 (8.8) (p=0.012*)	-0.2 (12.2) (p=0.015*)	1.6 (50.7.)
Percent change in brain volume	n=357	n=334	n=331
Median (mean) % change over 24 months	-0.7 (-0.8) (p<0.001*)	-0.7 (-0.9) (p<0.001*)	-1.0 (-1.3)

All analyses of clinical endpoints were intent-to treat. MRI analyses used evaluable dataset.
*** Indicates statistical significance vs. placebo at two-sided 0.05 level.**

Determination of p-values: aggregate ARR by negative binomial regression adjusting for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS; percent of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapse in previous 2 years, and baseline EDSS; time to 3-month/6-month confirmed disability progression by Cox's proportional hazards model adjusted for treatment, pooled country, baseline EDSS, and age; new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment and pooled country; Gd-enhancing lesions by rank ANCOVA adjusted for treatment, pooled country, and baseline number of Gd-enhancing lesions; and % change in lesion and brain volume by rank ANCOVA adjusted for treatment, pooled country, and corresponding baseline value.

Figure 12-1 Kaplan-Meier plot for time to first confirmed relapse up to Month 24– Study D2301 (ITT population)

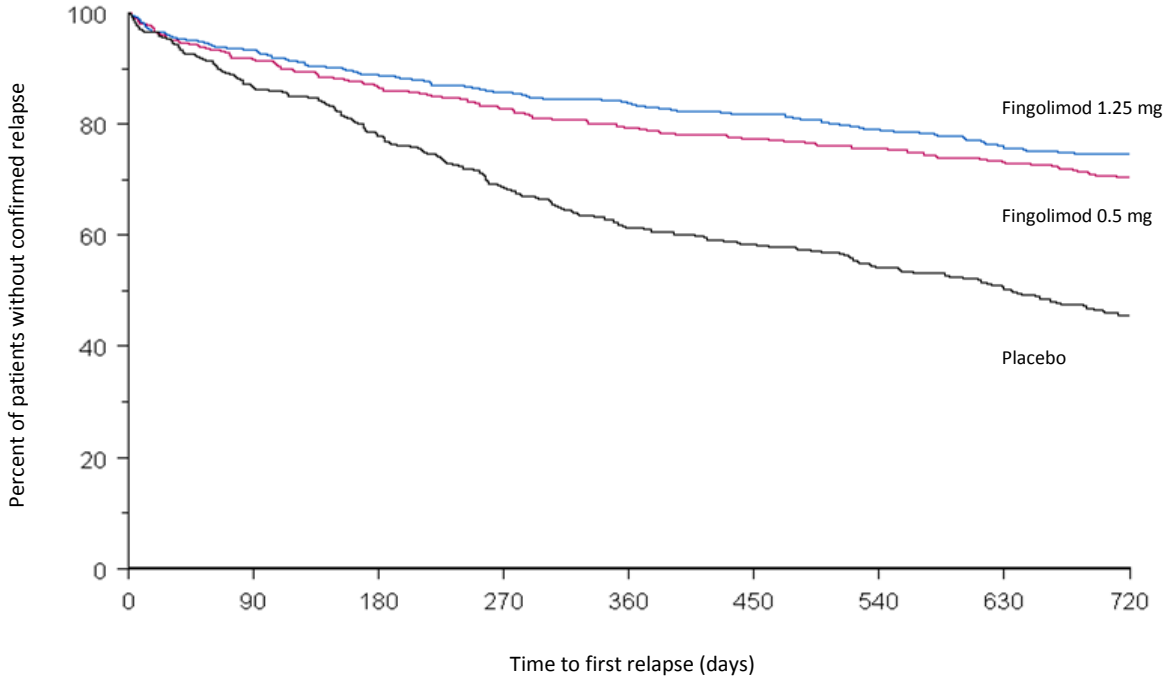
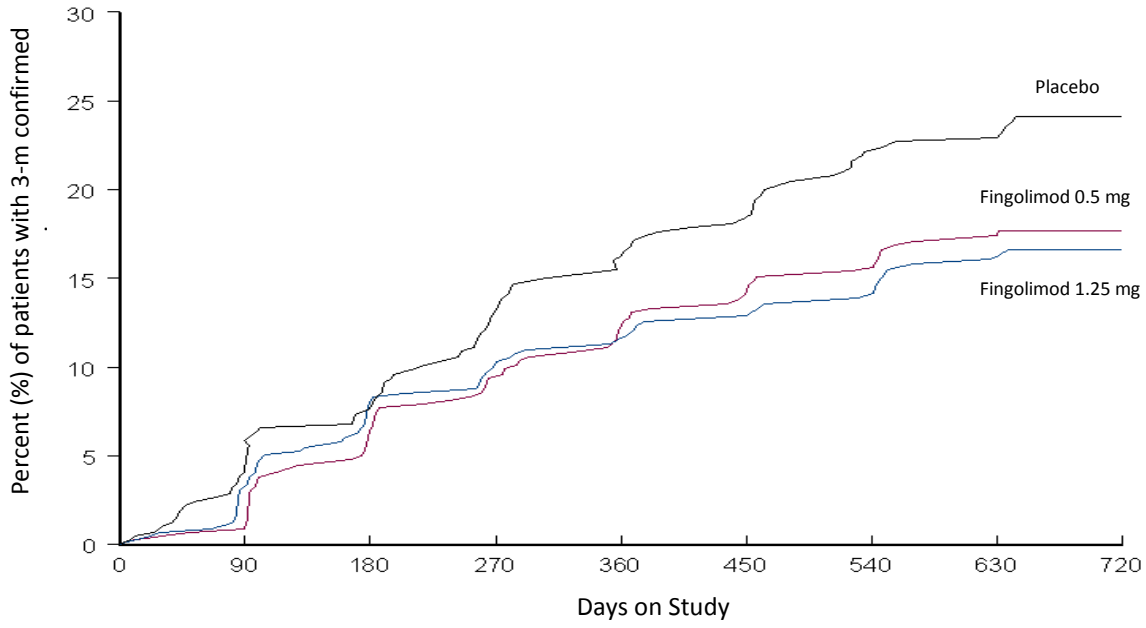


Figure 12-2 Cumulative plot of time to 3-month confirmed disability progression – Study D2301 (ITT population)



Study D2302 (TRANSFORMS) was a 1-year randomized, double-blind, double-dummy, active (interferon beta-1a, 30 micrograms, intramuscular, once weekly)-controlled Phase III study in patients with RRMS who had not received any natalizumab in the previous 6 months. Prior therapy with interferon-beta or glatiramer acetate up to the time of randomization was permitted.

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

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

The annualized relapse rate was significantly lower in patients treated with Gilenya than in patients who received interferon beta-1a IM. There was no significant difference between the Gilenya 0.5 mg and the 1.25 mg doses. The key secondary endpoints were number of new or newly enlarging T2 lesions and time to onset of 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for those with baseline EDSS of 5.5) sustained for 3 months. The number of new or newly enlarging T2 lesions was significantly lower in patients treated with Gilenya than in patients who received interferon beta-1a IM. There was no significant difference in the time to 3-month confirmed disability progression between Gilenya and interferon beta-1a IM-treated patients at 1 year. There were no significant differences between the 0.5 mg and the 1.25 mg doses on either endpoint.

The results for this study are shown in Table 12-2 and Figure 12-3.

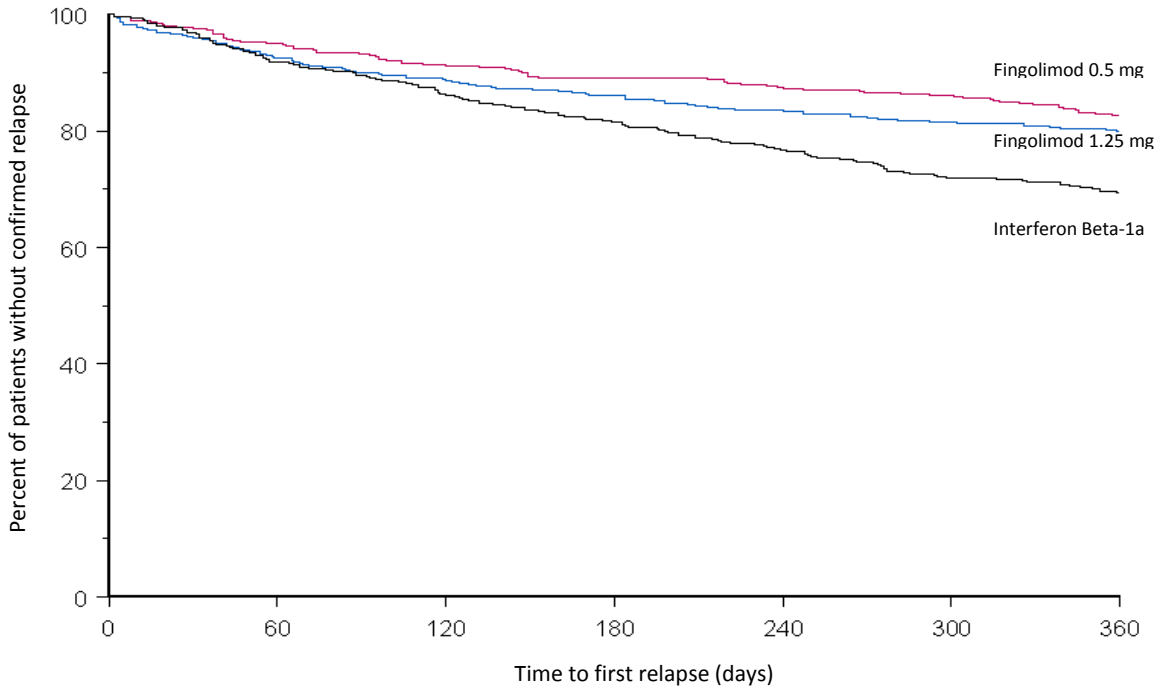
Table 12-2 Clinical and MRI results of Study 2

	Gilenya 0.5 mg	Gilenya 1.25 mg	Interferon beta-1a IM, 30 mcg,
Clinical Endpoints	N=429	N=420	N=431
Annualized relapse rate (primary endpoint)	0.16 (p<0.001*)	0.20 (p<0.001*)	0.33
Relative reduction (percent)	52	38	
Percent of patients remaining relapse-free at 12 months	82.5 (p<0.001*)	80.5 (p<0.001*)	70.1
Risk of disability progression			
Hazard ratio (95% CI) (3-month confirmed)	0.71 (0.42, 1.21) (p=0.209)	0.85 (0.51, 1.42) (p=0.543)	
MRI Endpoints			
Number of new or newly enlarging T2 lesions	n=380	n=356	n=365
Median (mean) number over 12 months	0.0 (1.7) (p=0.004*)	1.0 (1.5) (p<0.001*)	1.0 (2.6)
Number of Gd-enhancing lesions	n=374	n=352	n=354
Median (mean) number at 12 months	0.0 (0.2) (p<0.001*)	0.0 (0.1) (p<0.001*)	0.0 (0.5)
Percent change in brain volume	n=368	n=345	n=359
Median (mean) % change over 12 months	-0.2 (-0.3) (p<0.001*)	-0.2 (-0.3) (p<0.001*)	-0.4 (-0.5)

All analyses of clinical endpoints were intent-to treat. MRI analyses used evaluable dataset.
*** Indicates statistical significance vs. Interferon beta-1a IM at two-sided 0.05 level.**

Determination of p-values: aggregate ARR by negative binomial regression adjusting for treatment, country, number of relapses in previous 2 years and baseline EDSS; percent of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapse in previous 2 years, and baseline EDSS; risk of disability progression by Cox's proportional hazards model adjusted for treatment, country, baseline EDSS, and age; new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment, country, number of relapses in previous 2 years and baseline EDSS; Gd-enhancing lesions by rank ANCOVA adjusted for treatment, country, and baseline number of Gd-enhancing lesions; and % change in brain volume by Wilcoxon rank sum test.

Figure 12-3 Kaplan-Meier plot for time to first confirmed relapse up to Month 12 – Study D2302 (ITT population)



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.

13 Non-clinical safety data

The preclinical safety profile of fingolimod was assessed in mice, rats, dogs and monkeys. The major target organs were the lymphoid system (lymphopenia and lymphoid atrophy), lungs (increased weight, smooth muscle hypertrophy at the bronchio-alveolar junction), and heart (negative chronotropic effect, increase in blood pressure, perivascular changes and myocardial degeneration) in several species; blood vessels (vasculopathy) in rats only; and pituitary, forestomach, liver, adrenals, gastrointestinal tract and nervous system at high doses only (often associated with signs of general toxicity) in several species.

No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of fingolimod up to the maximally tolerated dose of 2.5 mg/kg, representing an approximate 50-fold margin based on the human systemic exposure (AUC) at the 0.5 mg dose. However, 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 the human systemic exposure (AUC) at a daily dose of 0.5 mg.

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

Fingolimod had no effect on sperm count/ 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 the human systemic exposure (AUC) at a daily dose of 0.5 mg.

Fingolimod was teratogenic in the rat when given at doses of 0.1 mg/kg or higher. The most common fetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. An increase in post-implantation loss was observed in rats at 1 mg/kg and higher and a decrease in viable fetuses at 3 mg/kg. Fingolimod was not teratogenic in the rabbit, where an increased embryo-fetal mortality was seen at doses of 1.5 mg/kg and higher, 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 that did not cause maternal toxicity. However, F1 body weights, development, behavior, and fertility were not affected by treatment with fingolimod. In a toxicity study in juvenile rats, no additional target organs of toxicity were observed compared to adult rats. Repeated stimulations with Keyhole Limpet Hemocyanin (KLH) showed a moderately decreased response during the treatment period, but fully functional immune reactions at the end of an 8 week recovery period.

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

14 Pharmaceutical information

Incompatibilities

Not applicable

Special Precautions for storage

Do not store above 30°C; store in the original package in order to protect from moisture

Packaging: DPX blister packs.

Gilenya must be kept out of the reach and sight of children.

Instructions for use and handling

No special requirements

Special precautions for disposal

No special requirements

Manufacturer:

Novartis Pharma Stein AG, Stein, Switzerland

For: Novartis Pharma AG, Basel, Switzerland

Registration Holder:

Novartis Pharma Services AG, 36 Shacham St., Petach-Tikva