NOVARTIS

Gilenya®

Composition

Active substance: Fingolimod.

Excipients: Mannitol, Magnesium stearate, Titanium dioxide, Gelatin.
Pharmaceutical form and quantity of active substance per unit
Capsules containing 0.5 mg fingolimod (as hydrochloride).

Indications / Potential uses

Gilenya is indicated for the treatment of patients with relapsing-remitting multiple sclerosis (MS) to reduce the frequency of relapses and delay the progression of disability.

Dosage / Administration

General patient populations
Dosage
The recommended dose of Gilenya is one 0.5 mg capsule once daily, taken orally with or without food.
If a dose is missed treatment should be continued with the next dose as planned.
Patients can switch directly from interferon beta or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related adverse effects, e.g. neutropenia.
Caution is advised when switching patients from natalizumab and other immunosuppressants to Gilenya (see "**Warnings and precautions: Prior treatment with immunosuppressants**").

Monitoring following first dose of Gilenya
A 12-lead ECG must be carried out in all patients before the start of treatment and at the end of the 6-hour monitoring period. Pulse and blood pressure in all patients should be measured at hourly intervals for signs of bradycardia and atrioventricular conduction disturbances for at least 6 hours after ingestion of the first dose. Provisions must be made for emergency cardiological treatment. Continuous real-time ECG monitoring is recommended for the first six hours after the first dose of Gilenya.
Certain patients require cardiac monitoring continuing beyond the first 6 hours after the start of treatment (also see "**Monitoring following first dose of Gilenya – Summary table**" in this section and "**Warnings and precautions**"). In addition, it is the responsibility of the attending physician to decide to what extent monitoring of vital parameters/ECG will also be necessary after subsequent doses (see "**Warnings and precautions**").
The following table summarizes the cardiac monitoring measures following the first dose of Gilenya (also see "**Warnings and precautions**").

Table 1: Monitoring following first dose of Gilenya – Summary table

All patients	
should be monitored for 6 hours for symptoms of bradycardia and atrioventricular conduction disturbances as follows: • Hourly pulse and blood pressure measurement • 12-lead ECG before the start of treatment and after the 6-hour monitoring period • Provisions for emergency cardiological treatment • Continuous (real-time) ECG monitoring is recommended	
Patients with abnormalities in the first 6 hours following the first dose	
In the event of symptomatic bradyarrhythmia	the patient must continue to be monitored following the 6-hour monitoring period until symptoms have fully resolved.
If heart rate reaches the lowest value 6 hours following the first dose	cardiac monitoring must be continued until the heart rate has recovered, and for a minimum of 2 hours.
If one of the following findings are present in the ECG 6 hours following the first dose: • Heart rate < 45 beats per minute • Persistent new second-degree AV block or higher-degree AV block • QTc interval ≥500 msec If the following ECG finding is present at any point in time during the monitoring phase following the first dose: • New-onset third-degree AV block	cardiac monitoring must be continued at least overnight.
If pharmacological treatment of bradyarrhythmia-related symptoms is required after the first dose, the patient should be monitored overnight in a medical facility. The first-dose monitoring strategy should be repeated for administration of the second dose.	
Patients with pre-existing cardiac disease	
In certain patient populations, Gilenya may be considered only if the expected benefit outweighs the potential risks.	
In predisposed patients with: • Known ischaemic heart disease (including angina pectoris) • Congestive heart failure • Cerebrovascular disease • Uncontrolled hypertension • Severe untreated sleep apnoea As well as patients with a history of the following illnesses: • Myocardial infarction • Cardiac arrest • Recurrent syncope • Symptomatic bradycardia	the following should be carried out before starting treatment: • A cardiologist should be consulted • Suitable cardiac monitoring (at least overnight) should be determined
Patients on heart rate-lowering medication	
In patients on: • Beta-blockers • Calcium channel blockers (with a heart rate-lowering effect such as verapamil, diltiazem, ivabradine) • Other substances which may decrease heart rate (e.g. digoxin, acetylcholinesterase inhibitors [AChEI], pilocarpine)	the following should be carried out before starting treatment: A cardiologist should be consulted • To examine the possibility of switching to a drug that does not slow heart rate or delay AV conduction- or • If the patient cannot be switched to different medication, suitable cardiac monitoring (incl. continuous ECG) should be carried out at least overnight.
Patients with QT interval prolongation	
In patients with: • significant QTc prolongation (QTc >470 msec in women, QTc >450 msec in men) before starting treatment • additional risk factors for the occurrence of QT prolongation (e.g. hypokalaemia, hypomagnesaemia or congenital long QT syndrome)	the following should be carried out before starting treatment: • A cardiologist should be consulted and • Suitable cardiac monitoring (incl. continuous ECG monitoring at least overnight in a medical facility) should be determined.

Special patient populations
Renal impairment
No clinical data are available on safety and efficacy in patients with renal impairment.

Hepatic impairment
Although no adjustments in the dose of Gilenya are needed in patients with mild hepatic impairment (Child-Pugh class A) caution should be exercised when treating these patients (see "**Warnings and precautions**, **Hepatic function**" and "**Pharmacokinetics**"). Gilenya should not be administered to patients with moderate (Child-Pugh class B) or severe (Child-Pugh class C) hepatic impairment (see "**Contraindications**").

Children and adolescents
Gilenya is not indicated for use in children and adolescents (see "**Pharmacokinetics**" and "**Contraindications**").

Elderly patients
Clinical data for multiple sclerosis patients over 55 years of age are very limited.

Ethnicity
No Gilenya dose adjustments are needed based on ethnic origin (see "**Pharmacokinetics**").
Gender
No Gilenya dose adjustments are needed based on gender (see "**Pharmacokinetics**").

Contraindications

- Patients with myocardial infarction, unstable angina pectoris, stroke/TIA, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure in the previous six months.
- Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia and class III anti-arrhythmic drugs should not be treated with Gilenya (see "**Warnings and precautions**", "**Interactions**").-
- Patients with second-degree Mobitz type II AV block or third-degree AV block, or sick sinus syndrome, if they do not wear a pacemaker.
- Patients with a baseline QTc interval from 500 msec (see "**Warnings and precautions**").
- Patients with moderate or severe hepatic impairment / liver cirrhosis (corresponding to Child-Pugh class B and C) or acute or chronic active hepatitis B infection should not be treated with Gilenya.
- Patients with macular oedema.
- Children and adolescents should not be treated with Gilenya.
- Gilenya is contraindicated during pregnancy and lactation.

Warnings and precautions

Bradyarrhythmia
Initiation of Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays (see "**Adverse effects**" and "**Pharmacodynamics**"). After the first dose, heart rate starts to decline within 1 hour, with the lowest value being reached within the first 6 hours or, in some patients, within 24 hours. For this reason all patients should be monitored for symptoms of bradycardia for at least the first 6 hours after the first dose of Gilenya. Subsequently, heart rate returns to baseline within one month of chronic treatment (see "**Heart rate and heart rhythm**" subsection under "**Pharmacodynamics**"). In patients receiving 0.5 mg Gilenya, this decrease in heart rate averages 8 beats per minute (bpm). There have been rare reports of heart rates below 40 bpm (see "**Adverse effects**"). Patients who experienced bradycardia were generally asymptomatic but some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue, palpitations and chest pain, which usually resolved within the first 24 hours of treatment. If necessary, bradycardia can be treated with parenteral administration of atropine or isoprenaline.
Initiation of Gilenya treatment has been associated with atrioventricular (AV) conduction delays, usually first-degree AV block (prolonged PR interval in the electrocardiogram). Fewer than 0.5% of patients receiving 0.5 mg Gilenya developed second-degree atrioventricular block, usually Mobitz type I (Wenckebach). The conduction abnormalities were typically transient, asymptomatic, did not normally require treatment and resolved within the first 24 hours of treatment. Isolated cases of transient, spontaneously resolving complete AV block have been reported during post-marketing use of Gilenya (see "**Adverse effects**" and "**Pharmacodynamics**").
First-dose cardiac monitoring measures (also see "**Summary table**" under "**Dosage / Administration**")
In all patients, a 12-lead ECG should be carried out before the first dose and at the end of the 6-hour monitoring period. On initiation of Gilenya treatment, all patients should be monitored for a period of 6 hours, with hourly pulse and blood pressure measurements, for symptoms of bradycardia. In addition, continuous (real-time) ECG monitoring is recommended during the first six hours.
Should symptomatic bradyarrhythmia occur after the first dose, suitable measures must be taken and the patient must continue to be monitored following the 6-hour monitoring period until symptoms have fully resolved.
If a patient requires pharmacological treatment during the monitoring period following the first dose, he or she should be monitored overnight in a medical facility and the first-dose monitoring strategy should be repeated after the second dose of Gilenya.
If, at the end of the six-hour monitoring period following the first dose, the heart rate reaches the lowest value following administration (suggesting that the maximum pharmacodynamic effect on the heart is not yet manifest), monitoring should be continued until the heart rate has recovered, and for a minimum of 2 hours.
In addition, continued cardiac monitoring, at least overnight, is required if one of the following criteria is present:

- New-onset third-degree AV block at any point in time during the monitoring phase following treatment initiation
- 6 hours after treatment initiation, the presence of:
- Heart rate < 45 beats per minute
- Persistent new second-degree AV block or higher-degree AV block
- QTc interval ≥ 500 msec

In certain patient populations, Gilenya may be considered only if the expected benefit outweighs the potential risks. Bradycardia may be poorly tolerated in patients with known ischaemic heart disease (including angina pectoris), history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, history of recurrent syncope and/or symptomatic bradycardia, uncontrolled hypertension or severe untreated sleep apnoea. If treatment with Gilenya is being considered, advice from a cardiologist should be sought prior to initiation of treatment to determine suitable cardiac monitoring (at least overnight) (see "**Interactions**").
Experience with Gilenya is limited in patients receiving concurrent therapy with 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, acetylcholinesterase inhibitors [AChEI], pilocarpine). Since the initiation of Gilenya treatment is also associated with slowing of the heart rate (see "**Bradyarrhythmia**"), concomitant use of these substances during initiation of Gilenya treatment may lead to severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with Gilenya should generally not be initiated in patients who are concurrently treated with such substances. If treatment with Gilenya is being considered, advice from a cardiologist should be sought regarding the possibility of switching to drugs that do not slow heart rate or delay AV conduction, and to determine the most suitable monitoring measures for treatment initiation. Patients whose medication cannot be switched should be monitored using continuous ECG monitoring at least overnight (see "**Interactions**").
If Gilenya therapy is discontinued for more than 2 weeks after the first month of treatment, the effects on heart rate and atrioventricular conduction may recur on reintroduction of treatment. The same precautionary measures as for the first dose therefore apply. Within the first 2 weeks of treatment, the same precautionary measures as for the first dose are recommended after interruption of treatment for one day or more; during weeks 3 and 4 of treatment, the same precautionary measures as for the first dose are recommended after interruption of treatment for more than 7 days.

QT prolongation
QT interval prolongation has been reported in some patients exposed to Gilenya (individual patients with QTcF prolongation between 30 and 60 msec; no QTcF prolongation >60 msec and no individual results >500 msec). Patients at risk of QTc prolongation were not included in clinical studies. The clinical relevance of these findings is unclear.
Since initiation of Gilenya treatment results in decreased heart rate and a prolongation of the QT interval, Gilenya is contraindicated in patients with a baseline QTc interval from 500 msec (see "**Contraindications**"). If treatment with Gilenya is being considered in the following patient groups, advice from a cardiologist should be sought to determine suitable cardiac monitoring (incl. continuous ECG monitoring at least overnight in a medical facility):

- Patients with significant QTc prolongation (QTc >470 msec in women, QTc >450 msec in men) before starting treatment.
- Patients with additional risk factors for the occurrence of QT prolongation (e.g. hypokalaemia, hypomagnesaemia or congenital long QT syndrome) (see "**Pharmacodynamics**" and "**Interactions**").

Continued cardiac monitoring is necessary at least overnight in patients with a QTc interval ≥500 msec at the end of the 6-hour monitoring phase following treatment initiation (see "**Dosage / Administration**").
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, among other things, cases of torsade de pointes in patients with bradycardia. Since initiation of Gilenya treatment results in decreased heart rate, Gilenya must not be used concomitantly with such drugs (see "**Contraindications**").

Infections
A core pharmacodynamic effect of Gilenya is a dose-dependent reduction in the peripheral lymphocyte count to 20-30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues (see "**Pharmacokinetics**").
The immune system effects of Gilenya (see "**Pharmacokinetics**") may increase the risk of infections (see "**Adverse effects**"). Treatment with Gilenya should not be initiated in patients with acute or chronic active infections (see "**Contraindications**"). Appropriate diagnostic and therapeutic measures must therefore be employed immediately in patients who develop signs of infection during treatment, particularly if infection with herpes virus is suspected. Because the elimination of fingolimod after discontinuation of treatment may take up to two months, monitoring for infection must be continued throughout this period (see subsection below: "**Withdrawal of therapy**"). Anti-neoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects.
Patients receiving Gilenya should be instructed to report symptoms of infection to their physician. Suspension of treatment with Gilenya should be considered if a patient develops a serious infection, and a benefit-risk assessment should be undertaken prior to re-initiation of therapy.

Vaccination
The efficacy of vaccination may be limited during, and for up to two months after, treatment with Gilenya (see subsection below: "**Withdrawal of therapy**"). The use of live attenuated vaccines must be avoided.
As should 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. Treatment with Gilenya should not be initiated until one month after vaccination in order to ensure the full efficacy of the vaccination.

Macular oedema
Macular oedema with or without visual symptoms has been reported in 0.4% of patients treated with 0.5 mg Gilenya (see "**Adverse effects**"), and occurring predominantly in the first 3-4 months of treatment. An ophthalmological examination – with an assessment of the ocular fundus, including the macula – must be carried out prior to, and 3–4 months after, initiation of Gilenya treatment. The patient's eyesight should be checked every 6 months by the attending neurologist. If patients report visual disturbances at any time while on Gilenya therapy, evaluation of the fundus, including the macula, should be carried out. Regular ophthalmological examinations should be carried out during treatment with Gilenya in patients with diabetes mellitus or a history of uveitis and in patients with a history of macular oedema (see "**Contraindications**").

Hepatic function
Liver values should be determined prior to the start of treatment with Gilenya and 1, 3 and 6 months after initiating treatment. Liver values should be tested periodically during the further course of treatment, even in the absence of clinical symptoms.
Close monitoring should be undertaken if transaminase levels are shown to rise by more than 5 times the upper limit of normal (ULN). Gilenya should be withdrawn if there is repeated proof of transaminase levels rising by more than 5 times the ULN, and should not be reinstituted until the values have returned to normal.
Ingestion of other potentially hepatotoxic medicinal products/substances (including alcoholic drinks) should be avoided. Patients with liver cirrhosis and hepatic impairment (Child-Pugh class B and C) should not be treated with Gilenya. In addition, no treatment should be given to patients with acute or chronic active hepatitis B infection due to the risk of exacerbation of the viral hepatic disease (also see "**Contraindications**").
Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained vomiting or jaundice, should have liver enzymes checked immediately. Gilenya should be discontinued if significant hepatic injury is confirmed (see "**Liver transaminases**"). Resumption of treatment depends both on whether any other cause of liver disease could be ascertained, and on the benefit of resuming treatment as opposed to the risk of recurrence of hepatic dysfunction.

Pulmonary function
A dose-dependent reduction in FEV_1 and in the values for the diffusing capacity of the lung for carbon monoxide (DLCO) was already observed in the first month after the start of treatment with Gilenya. These reduced values remained stable thereafter. After 24 months of treatment, the reduction in predicted FEV_1 – as a percentage of the baseline value – was 3.1% for 0.5 mg fingolimod and 2.0% for placebo. For DLCO, the reductions from baseline after 24 months of treatment were 3.8% for 0.5 mg fingolimod and 2.7% for placebo. The changes in FEV_1 seem reversible following discontinuation of treatment. Data on the reversibility of DLCO changes following withdrawal of treatment are limited. In controlled clinical studies in MS patients dyspnoea occurred in 5% of those given 0.5 mg fingolimod and 4% of those given placebo. Some patients terminated treatment with Gilenya due to unexplained dyspnoea in the (uncontrolled) extension studies. Gilenya has not been studied in MS patients with impaired pulmonary function. Patients presenting with symptoms suggestive of a pulmonary disorder must be examined by a specialist (with testing to include spirometry and determination of DLCO).

Cutaneous neoplasms
Patients at risk of cutaneous malignant neoplasms should undergo dermatological examinations prior to the start of treatment with Gilenya, and regularly during the further course of treatment.

Changes in the lymphocyte count
Based on the mechanism of action, 0.5 mg Gilenya reversibly reduces the lymphocyte count by 70% of the steady-state value. Blood counts should be carried out regularly.

Prior treatment with immunosuppressants
When switching patients from interferon beta or glatiramer acetate to Gilenya, no washout phase is necessary provided that the immune effects (i.e. cytopenia) of these therapies have resolved.
Due to the long half-life of natalizumab, concomitant exposure and thus concomitant immune effects may occur if Gilenya treatment is initiated 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 immunosuppressants (e.g. mitoxantrone), the duration and mechanism of action of the particular substance must be considered when initiating Gilenya treatment in order to avoid additive immunosuppressive effects.

Withdrawal of therapy
If a decision is made to stop treatment with Gilenya, it must be borne in mind 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 1-2 months of stopping therapy (see "**Pharmacokinetics**"). Starting other therapies during this period will result in concomitant exposure to fingolimod. Use of immunosuppressants shortly after discontinuation of Gilenya may lead to an additive effect on the immune system, and caution is therefore required.

General note
The data are still insufficient for an assessment of the efficacy and side effects of treatment with Gilenya for periods longer than 24 months.

Interactions

Pharmacodynamic interactions
Anti-neoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects (see "**Warnings and precautions**"). Therefore, the appropriate waiting periods should also be observed when switching patients from long-acting therapies with immune-system effects, such as natalizumab or mitoxantrone (see "**Warnings and precautions: Prior treatment with immunosuppressants**"). In multiple sclerosis clinical trials, concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection.
When fingolimod is used concomitantly with atenolol, there is an additional 15% reduction in the heart rate following initiation of treatment with fingolimod, an effect not seen with diltiazem.
Treatment with Gilenya should 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, acetylcholinesterase inhibitors [AChEI], pilocarpine) because of the potential additive effect on heart rate. If treatment with Gilenya is being considered, advice from a cardiologist should be sought at treatment initiation regarding the possibility of switching to drugs that do not slow heart rate. Patients whose medication cannot be switched should be monitored using continuous ECG monitoring at least overnight (see "**Warnings and precautions**" and "**Dosage / Administration**"). Gilenya is contraindicated in patients taking class Ia or class III anti-arrhythmic drugs (see "**Contraindications**").
The efficacy of vaccination may be limited during, and for up to two months after, treatment with Gilenya. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided (see "**Adverse effects**").

Pharmacokinetic interactions
In humans, fingolimod is primarily metabolized via CYP4F2 and possibly other CYP4F isoenzymes. *In vitro* studies in hepatocytes showed that CYP3A4 may contribute to the metabolism of fingolimod if CYP3A4 is strongly induced.

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 their own metabolism and/or the metabolism of co-medications

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2 and ABCB1 (Pgp) 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 (Pgp) by fingolimod is expected at therapeutic concentrations. *In vitro* experiments showed no evidence of CYP induction by fingolimod phosphate.

Transporters
Fingolimod and fingolimod phosphate are not expected to inhibit the uptake of co-medications and/or biological active substances transported by OATP1B1, OATP1B3 or NTCP. Similarly, they are not expected to inhibit the efflux of co-medications and/or biological active substances transported by the breast cancer resistant protein (MXR), the bile salt export pump (BSEP), multidrug resistance-associated protein 2 (MRP2) and MDR1-mediated transport at therapeutic concentrations.

Oral contraceptives
The co-administration of 0.5 mg fingolimod daily with oral contraceptives (ethinylestradiol and levonorgestrel) did not cause any change in exposure to the oral contraceptives. Fingolimod and fingolimod phosphate exposure were consistent with the values measured in previous studies. No interaction studies have been performed with oral contraceptives containing other progestagens; however, fingolimod is not expected to affect exposure to these substances.

Ciclosporin
The pharmacokinetics of single-dose fingolimod were not altered during co-administration with ciclosporin at steady-state, nor were ciclosporin steady-state pharmacokinetics altered by single-dose, or multi-dose (28 days) fingolimod administration. These data indicate that fingolimod neither reduces nor increases 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
Co-administration of 200 mg ketoconazole twice daily at steady state and a single 5 mg dose of fingolimod led to an increase (1.7-fold) in the AUC of fingolimod and fingolimod phosphate, indicating that potent inhibitors of CYP4F have an effect on fingolimod pharmacokinetics.

Isoprenaline, atropine, atenolol and diltiazem
No differences were found when single doses of fingolimod and fingolimod phosphate were co-administered with isoprenaline or atropine. Likewise, the single-dose pharmacokinetics of fingolimod and fingolimod phosphate and the steady-state pharmacokinetics of atenolol and diltiazem were unchanged by co-administration of atenolol or diltiazem with fingolimod.

Population pharmacokinetics analysis of potential drug-drug interactions
A population pharmacokinetics evaluation, performed in multiple sclerosis patients, did not provide evidence of a significant effect of fluoxetine and paroxetine (potent CYP2D6 inhibitors) on fingolimod or fingolimod phosphate concentrations. Administration of carbamazepine reduces levels of fingolimod phosphate by less than 30%. 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, corticosteroids and oral contraceptives.

Laboratory tests
Since fingolimod reduces blood lymphocyte counts via redistribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be used 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 the reduction in the number of circulating lymphocytes.

Pregnancy and Lactation

Pregnancy
Gilenya is contraindicated during pregnancy.
Animal studies have shown reproductive toxicity including fetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect (see "**Preclinical data**"). Furthermore, the receptor affected by fingolimod (sphingosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. It is not currently known whether cardiovascular malformations occur in humans. There are very limited data on the use of fingolimod in pregnant women. In clinical trials, 20 patients were being treated with fingolimod when pregnancy was ascertained, but the data are too limited to draw conclusions on the safety of Gilenya during pregnancy.

Labour and delivery: No data are available on the effects of fingolimod on labour and delivery.

Women of childbearing potential
Before initiation of Gilenya treatment, women of childbearing potential must be advised of the potential serious risk to the unborn child, and of the need for effective contraception during treatment with Gilenya. As it takes approximately 2 months for the compound to be eliminated from the body after stopping treatment (see "**Warnings and precautions**"), the risk to the fetus may persist and contraception must thus be used during this period.

Lactation
Fingolimod is excreted in the milk of treated animals during lactation. Because of the potential for serious adverse drug reactions in nursing infants exposed to fingolimod, women receiving Gilenya must not breast feed.
Gilenya is contraindicated in breastfeeding women.

Effects on ability to drive and use machines

Gilenya has little or no effect on the patient's ability to drive or use machines.

Adverse effects

The safety population in the two Phase III studies consisted of a total of 1703 patients with relapsing-remitting multiple sclerosis who were given 0.5 or 1.25 mg doses of Gilenya (see "**Clinical efficacy**"). Study 1 (FREEDOMS) was a 2-year placebo-controlled clinical study in 854 multiple sclerosis patients treated with fingolimod (placebo: 418 patients). In this study, the most serious adverse reactions in the group given the 0.5 mg recommended therapeutic dose were infections, macular oedema, as well as transient atrioventricular block and bradycardia on treatment initiation. The most frequent adverse reactions (incidence ≥10%) at the 0.5 mg dose were headache, influenza, diarrhoea, back pain, liver enzyme elevations and cough. The most common adverse event with an incidence greater than 1% and leading to withdrawal of treatment in patients given 0.5 mg Gilenya was an increase in serum transaminase levels (3.8%).
The adverse reactions 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 those in study 1, taking into account the differences in study duration.
Adverse reactions are listed according to MedDRA system organ class. Frequencies were defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Infections and infestations
Very common: Influenza viral infections (13%).
Common: Bronchitis, sinusitis, gastroenteritis, herpes viral infections, tinea infections.
Uncommon: Pneumonia*.

Blood and lymphatic system disorders
Common: Leucopenia, lymphopenia.

Psychiatric disorders
Common: Depression

Nervous system disorders
Very common: Headache (25%).
Common: Dizziness, paraesthesia, migraine.

Eye disorders
Common: Eye pain, blurred vision.
Uncommon: Macular oedema*‡.

Cardiac disorders
Common: Bradycardia, atrioventricular block.

Vascular disorders
Common: Hypertension.

Respiratory disorders
Very common: Cough (10%).
Common: Dyspnoea.

Gastrointestinal disorders
Very common: Diarrhoea (12%).

Skin and subcutaneous tissue disorders
Common: Eczema, alopecia, pruritus.

Musculoskeletal disorders
Very common: Back pain (12%).

General disorders
Common: Asthenia.

Investigations
Very common: Alanine transaminase (ALT) increased (10%).
Common: Gamma-glutamyl transferase (GGT) increased, liver enzymes increased, weight loss, blood triglycerides increased, liver function test abnormal.
* Plausible relationship to study drug.
‡Not reported in study 1 in connection with the 0.5 mg dose, however, cases occurred in another study at this dose. The frequency category is based on the incidence at the 0.5 mg dose in study 2.

Description of selected adverse drug reactions
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 patients treated with Gilenya.
Two serious cases of herpes infection with a fatal outcome occurred at the 1.25 mg dose; a case of herpes encephalitis in a patient in whom initiation of aciclovir 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 oedema
In clinical trials, macular oedema 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 studies 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 during a routine ophthalmological examination. The macular oedema generally improved or resolved spontaneously after drug discontinuation. The risk of recurrence following resumption of treatment has not been evaluated.
The incidence of macular oedema 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).

Bradyarrhythmia
Initiation of Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays (see "**Dosage / Administration**", "**Warnings and precautions**" and "**Pharmacodynamics**").
In multiple sclerosis clinical trials, the mean maximum decrease in heart rate was reached within 6 hours after the first dose, with declines in mean heart rate of 8 beats per minute with 0.5 mg Gilenya. The second dose may result in a slight further decrease. Heart rates below 40 beats per minute were rare in patients given 0.5 mg Gilenya. Heart rate returned to baseline within the first month of chronic dosing.
In clinical trials, first-degree AV block (prolonged PR interval in the electrocardiogram) occurred following treatment initiation in 4.7% of patients receiving 0.5 mg Gilenya, in 2.8% of patients receiving interferon beta-1a i.m., and in 1.5% of patients receiving placebo. Second-degree AV block was determined in less than 0.5% of patients treated with 0.5 mg Gilenya. In the post-marketing setting, isolated cases of transient, spontaneously resolving complete AV block have been reported during the 6-hour monitoring period following Gilenya administration. The conduction abnormalities observed both in clinical trials and post-marketing were typically transient, asymptomatic and resolved within 24 hours following treatment initiation. Although most patients did not require medical intervention, in clinical trials one patient on the 0.5 mg dose received isoprenaline for an asymptomatic second-degree Mobitz type I AV block.
In the post-marketing setting, isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These cases have been confounded by concomitant medications and/or pre-existing disease. The causal relationship of such events to Gilenya is uncertain.

Blood pressure
In multiple sclerosis clinical trials, 0.5 mg Gilenya was associated with a mild average increase of 1 mmHg in mean arterial pressure manifesting approximately 2 months after treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6.1% of patients on 0.5 mg Gilenya and in 3.8% of patients on placebo.

Liver transaminases
In multiple sclerosis clinical trials, 8.5% and 1.9% of patients treated with 0.5 mg Gilenya experienced asymptomatic elevation in serum levels of liver transaminases of ≥3 × ULN or ≥5 × ULN, respectively, in most cases within 6-9 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of Gilenya. In the few patients who continued on Gilenya therapy and who experienced liver transaminase elevations of ≥5 × ULN, i.e. 10 patients given 1.25 mg Gilenya and 2 patients given 0.5 mg Gilenya, it took approximately 5 months for the levels to return to normal.

Respiratory system
A dose-dependent reduction in values for FEV_1 and in the diffusing capacity of the lung for carbon monoxide (DLCO) has been observed during treatment with Gilenya (see "**Warnings and precautions**" and "**Pharmacokinetics**").

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 with 0.5 mg Gilenya in clinical trials and in the post-marketing setting. A causal relationship with Gilenya treatment is considered a possibility. Rare cases of ischaemic and haemorrhagic strokes have also been reported with 0.5 mg Gilenya in clinical trials and in the post-marketing setting, although a causal relationship has not been established.

Cutaneous neoplasms
In study 2, malignant melanoma and basal cell carcinoma each occurred in 3 patients using 0.5 mg fingolimod daily (interferon group: one basal cell carcinoma and one squamous cell carcinoma). In study 1, four patients each in the placebo and Gilenya (0.5 mg daily) groups developed cutaneous malignant neoplasms. Although there was no clear-cut accumulation of cases during treatment with Gilenya, patients at risk of cutaneous malignant neoplasms should undergo regular dermatological examinations prior to the start of treatment with Gilenya and during the course of treatment.

Lymphoma
Cases of lymphoma (cutaneous T-cell lymphoma or diffuse B-cell lymphoma) were reported in MS patients being treated with ≥0.5 mg fingolimod. Based on the small number of cases and short duration of exposure, the relationship to Gilenya remains unclear.

Overdose

Single doses up to 80 times the recommended dose (0.5 mg) were studied 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 and cause atrioventricular conduction delays. The decline in heart rate normally starts within one hour of the first dose, and generally reaches a maximum within 6 hours. Subsequently, heart rate usually returns to baseline within one month of chronic treatment (see "**Warnings and precautions**"). There have been reports of atrioventricular conduction delays with isolated reports of transient, spontaneously resolving complete AV block (see "**Warnings and precautions**" and "**Adverse effects**").
If an overdose with Gilenya occurs, it is important to also observe for symptoms of bradycardia and bradyarrhythmia. If the overdose occurs at the beginning of treatment, it is important to monitor patients with continuous (real-time) ECG monitoring and hourly pulse and blood pressure measurements for at least the first six hours. The same measures as for first-dose monitoring apply (see "**Table 1: Monitoring following first dose of Gilenya**" under "**Dosage / Administration**", and "**Warnings and precautions**").
Neither dialysis nor plasma exchange result in meaningful removal of fingolimod from the body.

Properties / Actions

ATC code: L04AA27

Mechanism of action
Fingolimod is a sphingosine-1-phosphate receptor modulator. The active substance 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 on lymphocytes, and readily crosses the blood brain barrier to bind to S1P receptors 1, 3 and 5 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.

Pharmacodynamics

Immune system
Effects on blood immune cell counts: Within 4-6 hours of the first 0.5 mg dose of fingolimod, 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. 18% 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, so these are the cells most affected by fingolimod. Approximately 15-20% of T lymphocytes have an effector memory phenotype, i.e. these cells are important for peripheral immune surveillance. Since this lymphocyte subset does not traffic through lymphoid organs, it is not affected by fingolimod. Peripheral lymphocyte counts increase within days of stopping fingolimod treatment, and normal counts are typically 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 heart rhythm
Fingolimod causes a transient reduction in heart rate and atrioventricular conduction at the start of treatment (see "**Adverse effects**"). The maximum decline in heart rate occurs 4-5 hours post dose, with 70% of the negative chronotropic effect achieved on the first day. With chronic treatment, heart rate usually returns to baseline values within one month.
Autonomic responses of the heart, including diurnal variations in heart rate and response to exercise, are not affected by fingolimod treatment.
With initiation of fingolimod treatment, there is an increase in premature atrial contractions, but there is no increase in the rate of atrial fibrillation/flutter, ventricular arrhythmias or ectopy. Treatment with fingolimod does not lower 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 msec. There is no dose or exposure-response relationship of fingolimod and QTcI prolongation. No consistent signal of an increased incidence of QTcI outliers, either absolute or as a change from baseline, is associated with fingolimod treatment. However, in study 1, QTcF prolongation between 30 and 60 msec occurred after the initial 0.5 mg dose of fingolimod in 6.6% of patients (placebo: 2.4%), and in 13.9% (placebo: 6.7%) of patients during the further course of treatment. The clinical relevance is unknown.

Pulmonary function
Fingolimod treatment with single or multiple doses of 0.5 or 1.25 mg for two weeks is not associated with an increase in airway resistance as measured by FEV_1 or FEF_{25-75}. However, single fingolimod doses >5 mg (10 times the recommended dose) were 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, oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Patients being treated with fingolimod have a normal response to inhaled beta-agonists.

Clinical efficacy

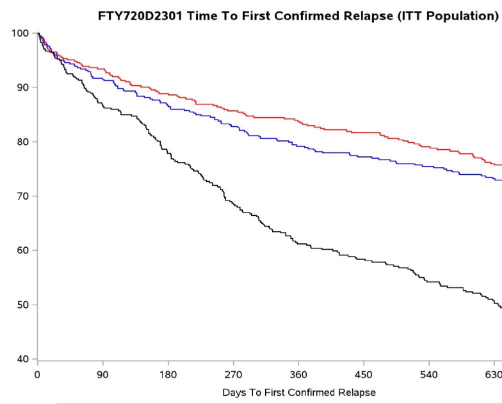
The efficacy of Gilenya has been demonstrated in two studies that evaluated once-daily doses of 0.5 mg and 1.25 mg Gilenya in patients with relapsing-remitting multiple sclerosis. Both studies included patients who had experienced at least 2 clinical relapses during the 2 years prior to randomization or at least 1 clinical relapse during 1 year prior to randomization, and had an expanded disability status scale (EDSS) score between 0 and 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 interferon-beta or glatiramer acetate for at least 3 months prior to the start of the study, and had not received natalizumab for at least 6 months prior to the start of the study. Neurological evaluations were performed at screening, every 3 months and at the time of a suspected relapse. In addition, MRI evaluations were performed at screening and at months 6, 12 and 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 0.5 mg Gilenya (n = 425), 1.25 mg Gilenya (n = 429), or placebo (n = 418) for up to 24 months. Median duration of treatment was 717 days on 0.5 mg Gilenya, 715 days on 1.25 mg Gilenya and 718.5 days on placebo.
The annualized relapse rate (ARR) was significantly lower in patients treated with Gilenya than in the placebo group. 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 (increase of at least 0.5 points 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 1.25 mg doses at any endpoint.

The results for this study are shown in Table 2 and Figure 1.
Table 2 Clinical results and MRI results in 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 (%)	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 / Month 12 / Month 24	0.0 (0.2) / 0.0 (0.2) / 0.0 (0.2) (p < 0.001* at each timepoint)	0.0 (0.3) / 0.0 (0.3) / 0.0 (0.2) (p < 0.001* at each timepoint)	0.0 (1.3) / 0.0 (1.1) / 0.0 (1.1)
Percent change in T2 lesion total volume	n=368	n=343	n=339
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 carried out in the intent-to-treat (ITT) population. MRI analyses used evaluable datasets.
* Indicates statistical significance vs. placebo at two-sided 0.05 level.
Determination of p-values: analysis of aggregate ARR by negative binomial regression adjusting for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS; analysis of percentage of patients remaining relapse-free by logistic regression adjusted for treatment, country, number of relapses in previous 2 years and baseline EDSS; analysis of time to 3-month/6-month disability progression by Cox's proportional hazards model adjusted for treatment, pooled country, baseline EDSS and age; analysis of new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment and pooled country; analysis of Gd-enhancing lesions by rank ANCOVA adjusted for treatment, pooled country and baseline number of Gd-enhancing lesions; analysis of % change in lesion and brain volume by rank ANCOVA adjusted for treatment, pooled country and corresponding baseline value.

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



Study D2302 (TRANSFORMS) was a 1-year randomized, double-blind, active-controlled (interferon beta-1a, 30 micrograms i.m., once weekly) Phase III study in patients with relapsing-remitting MS who had not received natalizumab for 6 months prior to the start of the study. Prior therapy with interferon beta or glatiramer acetate up to the time of randomization was permitted.

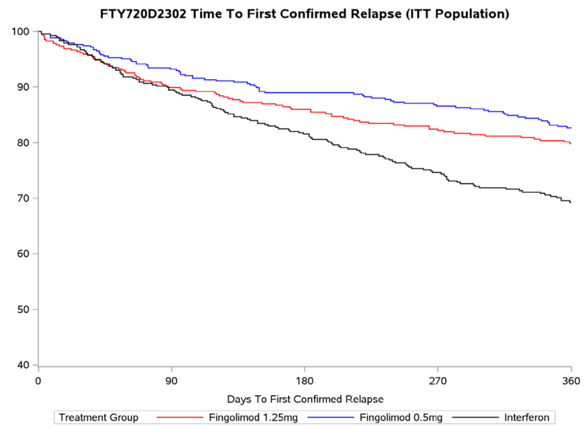
Neurological evaluations were performed at screening, every 3 months and at the time of a suspected relapse. MRI evaluations were performed at screening and at month 12. The primary endpoint was the annualized relapse rate.
Median age was 36 years, median disease duration was 5.9 years and median EDSS score at baseline was 2.0. Patients were randomized to receive 0.5 mg Gilenya (n=431), 1.25 mg Gilenya (n=426), or 30 µg interferon beta-1a i.m. once weekly (n=435) for up to 12 months. Median duration of treatment was 365 days on 0.5 mg Gilenya, 354 days on 1.25 mg Gilenya 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. There was no significant difference between the 0.5 mg and 1.25 mg doses of Gilenya. 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 (increase of at least 0.5 points for patients with baseline EDSS of 5.5), sustained for 3 months. The number of new or newly enlarging T2 lesions was significantly lower in patients treated with Gilenya than in patients who received interferon beta-1a. There was no significant difference in the time to 3-month confirmed disability progression between Gilenya and interferon beta-1a patients at 1 year. There were no significant differences between the 0.5 mg and 1.25 mg doses at any endpoint.

The results for this study are shown in Table 3 and Figure 2.
Table 3 Clinical results and MRI results in study 2

	Gilenya 0.5 mg	Gilenya 1.25 mg	Interferon beta-1a, 30 µg,
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 (%)	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 carried out in the intent-to-treat (ITT) population. MRI analyses used evaluable datasets.
* Indicates statistical significance vs. interferon beta-1a (i.m.) at two-sided 0.05 level.
Determination of p-values: analysis of aggregate ARR by negative binomial regression adjusting for treatment, country, number of relapses in previous 2 years and baseline EDSS; analysis of percentage of patients remaining relapse-free by logistic regression adjusted for treatment, country, number of relapses in previous 2 years and baseline EDSS; analysis of risk of disability progression by Cox's proportional hazards model adjusted for treatment, country, baseline EDSS and age; analysis of new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment, country, number of relapses in previous 2 years and baseline EDSS; analysis of Gd-enhancing lesions by rank ANCOVA adjusted for treatment, country and baseline number of Gd-enhancing lesions; analysis of % change in brain volume by Wilcoxon rank sum test.

Figure 2 Kaplan-Meier plot for time to first confirmed relapse up to month 12 –study D2302 (ITT population)



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

Pharmacokinetics

Absorption
Fingolimod absorption is slow (t_{max} of 12-16 hours) and extensive (≥85%, based on the amount of radioactivity excreted in the urine and the amount of metabolites excreted in the faeces, extrapolated to infinity). The apparent absolute oral bioavailability is high (93%).
Food intake does not alter C_{max} or exposure (AUC) of fingolimod. Gilenya may therefore be taken independently of meals (see "**Dosage / Administration**").
Steady-state blood concentrations are reached within 1 to 2 months of once-daily dosing and are approximately 10 times greater than after the first dose.

Distribution
Fingolimod is highly distributed in red blood cells, with a fraction in blood cells of 86%. Fingolimod phosphate has an uptake in blood cells of only <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 litres.

Metabolism
The biotransformation of fingolimod in humans occurs by three main pathways: reversible stereoselective phosphorylation to the pharmacologically active (S)-enantiomer of fingolimod phosphate; oxidative biotransformation mainly via the cytochrome P450 4F2 isoenzyme and possibly other CYP4F isoenzymes, and subsequent fatty acid-like degradation to inactive metabolites; and formation of pharmacologically inactive non-polar ceramide analogues of fingolimod.
Following single oral administration of $[^{14}C]$-fingolimod, the major fingolimod-related components in blood – as assessed by their contribution to the AUC relative to the total contribution of all radiolabelled components up to 816 hours post dose – 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 litres/hour, and the average apparent terminal half-life ($t_{1/2}$) is 6–9 days. Blood levels of fingolimod phosphate decline in parallel with those of fingolimod in the terminal phase, yielding similar half-lives for both substances.
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 the urine but are the major components in the faeces, with amounts representing less than 2.5% of the dose in each case. After 34 days, recovery of the administered dose is 89%.

Linearity
Fingolimod and fingolimod phosphate levels increase in an apparently dose-proportional manner after multiple, once-daily, 0.5 mg or 1.25 mg doses of fingolimod.

Pharmacokinetics in special patient populations
Patients with renal impairment
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.

Patients with hepatic impairment
The pharmacokinetics of a single dose (1 or 5 mg) of fingolimod in patients with mild, moderate and severe hepatic impairment showed no change in fingolimod C_{max} but an increase in AUC of 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.

Children and adolescents
The safety and efficacy of Gilenya have not been studied in children and adolescents below the age of 18. Gilenya is not indicated for use in paediatric patients.

Elderly patients
The mechanism for elimination, and results from population pharmacokinetic studies, suggest that dose adjustment would not be necessary in elderly patients. However, clinical experience in patients aged above 55 years is limited.

Ethnicity
The effects of ethnic origin on fingolimod and fingolimod phosphate pharmacokinetics are not clinically relevant.

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

Preclinical 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 bronchoalveolar junction) and heart (negative chronotropic effect, increase in blood pressure, perivascular changes and myocardial degeneration) in several species; in 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.

Mutagenicity and carcinogenicity
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.
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 approximately 50-fold margin based on human systemic exposure (AUC) at the 0.5 mg dose. 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 approximately 6-fold margin based on human systemic exposure (AUC) at a daily dose of 0.5 mg.

Reproductive toxicity
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 approximately 150-fold margin based on human systemic exposure (AUC) at the 0.5 mg dose.
Fingolimod was teratogenic in rats 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 the rate of post-implantation loss was observed at doses of 1 mg/kg and higher. A decrease in the number of viable fetuses was observed at doses of 3 mg/kg. Fingolimod was not teratogenic in rabbits, but increased embryofetal mortality was seen at doses of 1.5 mg/kg and higher, as well as fetal growth retardation and a decrease in the number of viable fetuses at doses of 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, behaviour and fertility were not affected by treatment with fingolimod. In a toxicity study in juvenile rats, no additional organ toxicity was observed compared to adult rats. Repeated stimulations with Keyhole Limpet Hemocyanin (KLH) showed a moderately decreased response during the treatment period, but functional immune reactions were fully restored at the end of an 8-week recovery period.
Fingolimod was excreted in the milk of treated animals during lactation. Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

Other information

Incompatibilities
Not applicable.

Shelf life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
Keep out of the reach of children.
Do not store above 30°C.
Store in the original pack in order to protect the contents from moisture.

Pack sizes

Country specific pack sizes.

Manufacturer

See folding box.

Information last revised

March 2013

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists