1 PRODUCT NAME

GILENYA® 0.5 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 mg fingolimod (as hydrochloride).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

GILENYA 0.5 mg: white to almost white powder in white opaque body and bright yellow opaque cap gelatin capsules, size 3, radial imprint with black ink "FTY 0.5 mg" on cap and two radial bands imprinted on body with yellow ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

GILENYA is indicated as a disease modifying therapy for the treatment of patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

4.2 Dose and method of administration

Posology

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.

On initiation of GILENYA treatment, after the first dose, it is recommended that all patients be observed, with hourly pulse and blood pressure measurement, for a period of 6 hours for signs and symptoms of bradycardia. All patients should have an electrocardiogram performed prior to dosing and at the end of the 6-hour monitoring period (see section 4.4 special warnings and precautions, Bradyarrhythmia).

For recommendations related to switching patients from other disease modifying therapies to GILENYA (see section 4.4 special warnings and precautions: Prior treatment with immunosuppressants).

Special populations

Children

GILENYA is not indicated for use in paediatric patients. (See section 5 PHARMACOLOGICAL PROPERTIES).

The Elderly (≥ 65 years)

GILENYA should be used with caution in patients aged 65 years and over
(see section 5 PHARMACOLOGICAL PROPERTIES).

Patients with Renal Impairment

No GILENYA dose adjustments are needed in patients with renal impairment (see section 5 PHARMACOLOGICAL PROPERTIES).

Patients with 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 5 PHARMACOLOGICAL PROPERTIES).

Ethnicity

No GILENYA dose adjustments are needed based on ethnic origin (see section 5 PHARMACOLOGICAL PROPERTIES).

Gender

No GILENYA dose adjustments are needed based on gender (see section 5 PHARMACOLOGICAL PROPERTIES).

Diabetic Patients

GILENYA should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular oedema (see section 4.4 Special warnings and precautions for use).

4.3 Contraindications

- Patients who in the last 6 months had myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure.
- Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs (see section 4.4 Special warnings and precautions for use).
- Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not have a pacemaker (see section 4.4 Special warnings and precautions for use).
- Patients with a baseline QTc interval ≥500 msec (see section 4.4 Special warnings and precautions for use).

GILENYA should not be administered to patients with known hypersensitivity to fingolimod or any of the excipients.

4.4 Special warnings and precautions for use

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 5 PHARMACOLOGICAL PROPERTIES).

The immune system effects (see section 5 PHARMACOLOGICAL PROPERTIES) of GILENYA may increase the risk of infections, including opportunistic infections (see section 4.8 Undesirable effects). Before initiating treatment with GILENYA, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available.

Initiation of treatment with GILENYA should be delayed in patients with severe active infection until resolution. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Because elimination of fingolimod after discontinuation of GILENYA may take up to two months, vigilance for infection should be continued throughout this period (see section 4.4 Special warnings and precautions for use - Stopping GILENYA therapy).

Anti-neoplastic, immune modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution due to the risk of additive immune system effects (see section 4.5 Interaction with other medicines). Specific decisions as to the dosage and duration of treatment with corticosteroids should be based on clinical judgment. Co-administration of a short course of corticosteroids (up to 5 days as per study protocols) did not increase the overall rate of infection in patients treated with fingolimod in the Phase III clinical trials, compared to placebo. Based on these data, short courses of corticosteroids (up to 5 days) can be used in combination with GILENYA (see section 4.8 Undesirable effects and section 4.5 Interaction with other medicines).

Patients receiving GILENYA should be instructed to report symptoms of infections to their physician. Suspension of treatment 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.

Progressive Multifocal Leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in the post-marketing setting, including those who had not previously taken or were not concomitantly taking either immunosuppressive or immunomodulatory medications (see section 4.8 Undesirable effects). PML is an opportunistic infection caused by JC virus that typically only occurs in patients who are immunocompromised, and that can lead to severe disability or death. Cases of PML have occurred after approximately 2-3 years of treatment. Although the estimated risk appears to increase with cumulative exposure over time, an exact relationship with the duration of treatment is unknown. The incidence rate for PML appears to be higher for patients in Japan; the reasons are currently unknown. Additional PML cases have occurred in patients who had been treated previously with natalizumab, which has a known association with PML. During routine MRI (in accordance with national and local recommendations, physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, Gilenya treatment should be suspended until PML has been excluded. MRI findings suggestive of PML may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with MS medications associated with PML, including Gilenya. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

Cases of cryptococcal meningitis have been reported in the post-marketing setting after approximately 2-3 years of treatment, although an exact relationship with the duration of treatment is unknown (see section 4.8 Undesirable effects). Cryptococcal meningitis may be fatal. For this reason patients with symptoms and signs consistent with cryptococcal meningitis should undergo prompt diagnostic evaluation. If cryptococcal meningitis is diagnosed, appropriate treatment should be initiated.

Patients need to be assessed for their immunity to varicella (chickenpox) prior to GILENYA treatment. It is recommended that patients without a health care professional confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo antibody testing to varicella zoster virus (VZV) before initiating GILENYA therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with GILENYA (see section 4.8 Undesirable effects). Initiation of treatment with GILENYA should be postponed for 1 month to allow full effect of vaccination to occur.

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with Gilenya in the post-marketing setting (see section 4.8

Undesirable effects). Due to the immunosuppressive properties of fingolimod, vaccination against HPV should be considered prior to treatment initiation with Gilenya taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care.

Vaccination

Vaccination may be less effective during and for up to two months after stopping treatment with GILENYA (see section 4.4 Special warnings and precautions for use - Stopping GILENYA therapy). The use of live attenuated vaccines should be avoided (see section 4.5 Interaction with other medicines).

Macular Oedema

Macular oedema (see section 4.8 Undesirable effects) with or without visual symptoms has been reported in 0.5% of patients treated with GILENYA 0.5 mg, occurring predominantly in the first 3-4 months of therapy. An ophthalmologic evaluation is therefore recommended 3-4 months after treatment initiation. If patients report visual disturbances at any time while on GILENYA therapy, an evaluation of the fundus, including the macula, should be carried out.

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular oedema (see section 4.8 Undesirable effects). 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 ophthalmic evaluation prior to initiating GILENYA therapy and have follow-up evaluations while receiving GILENYA therapy.

Continuation of GILENYA in patients with macular oedema 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

Initiation of GILENYA treatment results in a transient decrease in heart rate. After the first dose, the heart rate decrease starts within an hour and the Day 1 decline is maximal within 6 hours.

With continued dosing, heart rate returns to baseline within one month of chronic treatment (see section 5 PHARMACOLOGICAL PROPERTIES - Heart rate and rhythm). In patients receiving GILENYA 0.5 mg this decrease in heart rate, as measured by pulse, averages approximately 8 beats per minute (bpm). Heart rates below 40 bpm were rarely observed (see section 4.8 Undesirable effects). Patients who experienced bradycardia were generally asymptomatic but some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue, and/or palpitations, which resolved within the first 24 hours of treatment.

Initiation of GILENYA treatment has been associated with atrioventricular conduction delays, usually first-degree atrioventricular blocks (prolonged PR interval on electrocardiogram). Second-degree atrioventricular blocks, usually Mobitz type I (Wenckebach) have been observed in less than 0.2% 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. Isolated cases of transient, spontaneously resolving complete AV block have been reported during post-marketing use of GILENYA (see section 4.8 Undesirable effects).

Therefore on initiation of GILENYA treatment, it is recommended that all patients be observed, with hourly pulse and blood pressure measurements, for a period of 6 hours for signs and symptoms of bradycardia. All patients should have an electrocardiogram performed prior to dosing and at the end of the 6-hour monitoring period. Should post-dose bradyarrhythmia-related symptoms occur, appropriate management should be initiated as necessary and the patient should be observed until the symptoms have resolved. Should a patient require pharmacologic intervention during the first dose observation, overnight monitoring in a medical facility should be instituted and the first dose monitoring strategy should be repeated after the second dose of GILENYA.

Additional observation until the finding has resolved is also required:

- if the heart rate at 6 hours post-dose is <45 bpm or is the lowest value post-dose (suggesting that the maximum pharmacodynamic effect on the heart is not yet manifest) or
- If the ECG at 6 hours after the first dose shows new onset second degree or higher AV block.
- If the ECG at 6 hours after the first dose shows a QTc interval ≥ 500 msec patients should be monitored overnight.

Due to the risk of serious cardiac rhythm disturbances, GILENYA should not be used in patients with sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope. Since initiation of GILENYA treatment results in decreased heart rate and therefore a prolongation of the QT interval, GILENYA should not be used in patients with significant QT prolongation (QTc >470 msec (females) or >450 msec (males) (see also section 4.3 Contraindications). GILENYA is best avoided in patients with relevant risk factors for QT prolongation, for example, hypokalaemia, hypomagnesaemia or congenital QT prolongation. Since significant bradycardia may be poorly tolerated in patients with a history of cardiac arrest, uncontrolled hypertension or severe untreated sleep apnoea, GILENYA should not be used in these patients (see also section 4.3 Contraindications). In patients for whom Gilenya is not contraindicated, if treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy, which should last overnight.

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 (see section 4.3 Contraindications).

Experience with GILENYA is limited in patients receiving concurrent therapy with beta blockers, heart-rate lowering calcium channel blockers (such as verapamil or diltiazem), or other substances that may decrease heart rate (e.g. digoxin or ivabradine). Since the initiation of GILENYA treatment is also associated with slowing of the heart rate (see "Bradyarrhythmia"), concomitant use of these substances during GILENYA initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with GILENYA should generally not be initiated in patients who are concurrently treated with these substances. If treatment with GILENYA is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation (should last overnight) (see section 4.5 Interaction with other medicines).

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 GILENYA treatment and the same precautions as for the first dose should apply. Within the first 2 weeks of treatment, first dose procedures are recommended after an interruption of one day or more. During weeks 3 and 4 of treatment first dose procedures are recommended after a treatment interruption of more than 7 days.

Liver Function

Increased hepatic enzymes, mostly alanine aminotransaminase (ALT) elevation, have been reported in multiple sclerosis patients treated with GILENYA. In clinical trials, a 3-fold or greater elevation in ALT occurred in 8.0% of patients treated with GILENYA 0.5 mg and the drug was discontinued if the elevation exceeded a 5 fold increase. Recurrence of ALT elevations occurred upon re-challenge in some patients, supporting a relationship to the drug.

Clinically significant liver injury has occurred in patients treated with Gilenya in the post-marketing setting (see section 4.8 Undesirable effects). Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, have occurred as early as ten days after the first dose and have also been reported after prolonged use. Cases of acute liver failure requiring liver transplant have been reported.

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with GILENYA and should be monitored periodically while on treatment and until two months after Gilenya discontinuation.

Patients should be monitored for signs and symptoms of hepatic injury. Liver transaminase and bilirubin levels should be measured promptly in patients who report symptoms that may indicate liver injury, such as unexplained nausea, vomiting, abdominal pain, right upper abdominal discomfort, new or worsening fatigue, anorexia, or jaundice and/or dark urine during treatment. In this clinical context, if the patient is found to have an alanine aminotransferase (ALT) greater than three times the reference range and serum total bilirubin greater than two times the reference range, treatment with Gilenya should be interrupted. Treatment should not be resumed unless a plausible alternative aetiology for the signs and symptoms of liver injury can be established.

Although there are no data to establish that patients with pre-existing liver disease are at increased risk to develop elevated liver function test (LFT) values when taking GILENYA, caution should be exercised when using GILENYA in patients with a history of significant liver disease.

Posterior reversible encephalopathy syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported at 0.5 mg dose in clinical trials and in the post-marketing setting (see section 4.8 Undesirable effects). Symptoms reported included sudden onset of severe headache, nausea, vomiting, altered mental status, visual disturbances and seizure. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral haemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, GILENYA should be discontinued.

Prior treatment with immunosuppressive and immunomodulating therapies

When switching from other disease modifying therapies, the elimination half-life and mode of action of the other therapy must be considered in order to avoid additive immune suppressive effects, whilst at the same time, minimizing the risk of disease reactivation. Before initiating treatment with Gilenya, a recent CBC (i.e. after discontinuation of prior therapy) should be available to ensure any immune effects of such therapies (e.g. cytopenia) have resolved.

Beta interferon, glatiramer acetate or dimethyl fumarate

Gilenya can generally be started immediately after discontinuation of beta interferon, glatiramer acetate or dimethyl fumarate.

Natalizumab or teriflunomide

Due to the long elimination half-life of natalizumab or teriflunomide, caution regarding potential additive immune effects is required when switching patients from these therapies to GILENYA. A careful case-by-case assessment regarding the timing of the initiation of GILENYA treatment is recommended.

Elimination of natalizumab usually takes up to 2-3 months following discontinuation.

Teriflunomide is also eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take several months to up to 2-years. An accelerated elimination procedure is described in the teriflunomide product information.

Alemtuzumab

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

Malignancies

Cutaneous Malignancies

Basal cell carcinoma (BCC) and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma, have been reported in patients receiving GILENYA (see section 4.8 Undesirable effects). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Since there is a potential risk of malignant skin growths, patients treated with GILENYA should be cautioned against exposure to sunlight without protection.

Lymphomas

There have been cases of lymphoma in clinical studies and the post-marketing setting. The cases reported were heterogeneous in nature, mainly Non-Hodgkin's Lymphoma, including B-cell and T-cell lymphomas. Cases of cutaneous T cell lymphoma (mycosis fungoides) have been observed (see section 4.8 Undesirable effects).

Return of disease activity (rebound) after GILENYA discontinuation

Cases of severe exacerbation of disease have been reported after stopping GILENYA in the post-marketing setting. This was generally observed within 12 weeks after stopping GILENYA, but was also reported up to and beyond 24 weeks after GILENYA discontinuation. Therefore, caution is indicated when stopping GILENYA therapy. If discontinuation of GILENYA is deemed necessary, patients should be monitored for relevant signs and symptoms and appropriate treatment should be initiated as required.

Tumefactive lesions

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

Stopping GILENYA 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 the normal range within 1-2 months of stopping therapy (see section 5 PHARMACOLOGICAL PROPERTIES). 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.

See also section above: Return of disease activity (rebound) after GILENYA discontinuation.

Pregnancy, fetal risk, and contraception

Due to the potential for a serious risk to the fetus, the pregnancy status of females of reproductive potential should be verified prior to starting treatment with GILENYA. Medical advice should be given regarding the risk of harmful effects on the fetus associated with treatment.

While on treatment with GILENYA, females should not become pregnant and effective contraception is recommended during treatment and for 2 months after stopping treatment. If a female becomes pregnant while taking GILENYA, discontinuation of GILENYA should be considered, taking into account the individual benefit risk assessment for both the mother and the fetus. (See section 4.6 Use in Pregnancy and section 4.4 Return of disease activity (rebound) after GILENYA discontinuation.)

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions:

Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution due to the risk of additive immune system effects. Specific decisions as to the dosage and duration of concomitant treatment with corticosteroids should be based on clinical judgment. Co-administration of a short course of corticosteroids (up to 5 days as per study protocols) did not increase the overall rate of infection in patients treated with fingolimod in the Phase III clinical trials, compared to placebo (see section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects).

Caution should also be applied when switching patients from long-acting therapies with immune effects such as natalizumab, teriflunomide, or mitoxantrone (see section 4.4 Special warnings and precautions for use - Prior treatment with immunosuppressive or immune-modulating therapies).

When fingolimod is used with atenolol, there is an additional 15% reduction in heart rate upon fingolimod initiation, 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 or diltiazem), or other substances which may decrease heart rate (e.g. digoxin or ivabradine) 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 4.4 Special warnings and precautions for use - Bradyarrhythmia).

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 4.8 Undesirable effects and section 4.4 Special warnings and precautions for use).

Pharmacokinetic interactions:

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

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

In vitro inhibition studies using pooled human liver microsomes and specific metabolic probe substrates demonstrated that fingolimod and fingolimod-phosphate have little or no capacity to inhibit the activity of CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11 (fingolimod only). Therefore, fingolimod and fingolimod-phosphate are unlikely to reduce the clearance of drugs that are mainly cleared through metabolism by the major CYP isoenzymes.

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

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2, and ABCB1 (P-glycoprotein) (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 CYP enzymes and ABCB1 with respect to the vehicle control. Therefore no clinically relevant induction of the tested CYP450 enzymes or MDR1 by fingolimod is expected at therapeutic concentrations. In vitro experiments did not provide an indication of CYP induction by fingolimod-phosphate.

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

Based on in vitro data, fingolimod as well as fingolimod-phosphate are not expected to inhibit the uptake of co-medications and/or biologics transported by the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1, OATP1B3) or the sodium taurocholate co-transporting polypeptide (NTCP). Similarly, they are not expected to inhibit the efflux of co-medications and/or biologics transported by the breast cancer resistance protein (BCRP), the bile salt export pump (BSEP), the multidrug resistance-associated protein 2 (MRP2) or P-gp 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 progestogens, however an effect of fingolimod on their exposure is not expected.

Cyclosporine:

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

Ketoconazole:

The co-administration of oral 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) by inhibition of CYP4F2.

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.

Carbamazepine

The co-administration of carbamazepine 600 mg twice daily at steady-state and a single dose of fingolimod 2 mg had a weak effect on the AUC of fingolimod and fingolimod-phosphate, decreasing both by approximately 40 %. The clinical relevance of this decrease is unknown.

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) 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, corticosteroids 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.

4.6 Fertility, pregnancy and lactation

Effects on 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 foetal toxicity.

Use in Pregnancy (Category D)

The use of GILENYA in women who are or may become pregnant should only be considered if the potential benefit justifies the potential risk to the foetus (see section 4.4 Special warnings and precautions for use - Women of childbearing potential).

Available human data (post-marketing data and pregnancy registry information) suggest that use of GILENYA is associated with an increased prevalence of major congenital malformation in comparison to the general population.

While on treatment, females should not become pregnant and effective contraception is recommended. If a female becomes pregnant while taking GILENYA, discontinuation of GILENYA should be considered, taking into account the individual benefit risk assessment for both the mother and the fetus.

Medical advice should be given regarding the risk of harmful effects on the fetus associated with treatment and medical follow-up examination should be performed (e.g. ultrasonography examination). Also, the possibility of severe exacerbation of disease should be considered in females discontinuing GILENYA because of pregnancy or planned pregnancy, and patients should consult their physicians on potential alternatives (see section 4.4 Special warnings and precautions for use - Women of childbearing potential).

In a prospective observational Gilenya Pregnancy Registry (GPR) (2011 - 2024), the rate of major birth defects among 166 live births, stillbirths or termination of pregnancy due to fetal anomaly from women who were exposed to fingolimod during pregnancy was 7.2% (95% CI: 3.8-12.3). The most frequent major congenital malformations were congenital heart defects, renal/urinary malformations and limb/musculoskeletal malformations. Important study limitations include no adjustment for confounders, no re-adjudication in case of spontaneous resolution, lack of an internal comparator cohort and small sample size.

Additionally, in the fingolimod prospective pharmacovigilance data, including data from the PRIM program (PRegnancy outcomes Intensive Monitoring), the rate of major birth defects among 700 live births, stillbirths or termination of pregnancy due to fetal anomaly from women who were exposed to fingolimod during pregnancy was 3.57% (95% CI: 2.32-5.23). The most frequent major congenital malformations were congenital heart defects, nervous system abnormalities and renal/urinary malformations. Important program limitations include possible under reporting of pregnancy exposure, a high number of cases being lost to follow-up, no adjustment for confounders, and lack of an internal comparator cohort.

The prevalence of major congenital malformation in the general population is 2 to 4%.

The pattern of malformation reported for GILENYA is similar to that observed in the general population.

There is no evidence of clustering of specific birth defects with GILENYA.

Animal studies have shown reproductive toxicity including foetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect. 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 the safety of GILENYA in pregnancy

Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

Fingolimod was teratogenic in the rat when given at doses of 0.1 mg/kg or higher. The most common foetal 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 foetuses at 3 mg/kg. Fingolimod was not teratogenic in the rabbit, where an increased embryo-foetal mortality was seen at doses of 1.5 mg/kg and higher, and a decrease in viable foetuses as well as foetal 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, behaviour, 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.

Women of Childbearing Potential

Pregnancy testing

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with GILENYA.

Contraception

Before initiation of GILENYA treatment, females of childbearing potential should be counselled on the potential for a serious risk to the foetus and the need for effective contraception during treatment with GILENYA and for 2 months after stopping treatment. Since it takes approximately 2 months to eliminate the compound from the body after stopping treatment (see section 4.4 Special warnings and precautions for use - Stopping GILENYA Therapy) the potential to the foetus may persist and contraception should be pursued during this period.

If GILENYA is discontinued because of pregnancy or planned pregnancy, see section 4.4 Special Warnings and precautions for use - Return of disease activity (rebound) after GILENYA discontinuation and Stopping therapy. For females planning to become pregnant, GILENYA should be stopped 2 months before conception.

Labour and Delivery

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

Use in Lactation

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

4.7 Effects on ability to drive and use machines

Gilenya has no or negligible influence on the ability to drive and use machines.

However, dizziness or drowsiness may occasionally occur when initiating therapy with Gilenya. On initiation of Gilenya treatment it is recommended that patients be observed for a period of 6 hours (see section 4.4, Bradyarrhythmia).

4.8 Undesirable effects

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://pophealth.my.site.com/carmreportnz/s/

The safety population of GILENYA is derived from two Phase III placebo-controlled clinical trials and one Phase III active-controlled clinical trial in patients with relapsing remitting multiple sclerosis. It includes a total of 2431 patients on GILENYA (0.5 or 1.25 mg dose) Study D2301 (FREEDOMS) was a 2-year placebo-controlled clinical study in 854 multiple sclerosis patients treated with fingolimod (placebo: 418). Study D2309 (FREEDOMS II) was a 2-year placebo-controlled clinical study in 728 multiple sclerosis patients treated with fingolimod (placebo: 355). In the pooled data from these two studies the most serious adverse drug reactions (ADRs) for the 0.5 mg recommended therapeutic dose were infections, macular oedema and transient atrioventricular blocks on treatment initiation. The most frequent ADRs (incidence ≥10%) at the 0.5 mg dose were headache, hepatic enzyme increased, diarrhoea, cough, influenza, sinusitis, and back pain. The most frequent adverse event reported for GILENYA 0.5 mg at an incidence greater than 1% leading to treatment interruption was ALT elevations (2.2 %).

The ADRs for fingolimod in Study D2302 (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 the placebo-controlled studies, taking into account the differences in study duration.

Table 1 presents the frequency of ADRs reported in the pooled analysis of the placebo-controlled studies FREEDOMS and FREEDOMS II. ADRs are listed according to MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Tabulated summary of adverse drug reactions

Adverse drug reactions	**Placebo N=773 (%)**	**Fingolimod 0.5 mg N=783 (%)**	**Frequency for 0.5 mg dose**
Infections and infestations			
Influenza	65 (8.4)	89 (11.4)	very common
Sinusitis	64 (8.3)	85 (10.9)	very common
Bronchitis	35 (4.5)	64 (8.2)	common
Herpes zoster	7 (0.9)	16 (2.0)	common
Tinea versicolour	3 (0.4)	14 (1.8)	common
Pneumonia*	1 (0.1)	7 (0.9)	uncommon
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basel cell carcinoma	5 (0.6)	14 (1.8)	common
Melanoma	2 (0.3)	1 (0.1)	uncommon**
Kaposi’s sarcoma	0	0	Very rare**
Blood and lymphatic system disorders			
Lymphopenia	2 (0.3)	53 (6.8)	common
Leucopenia	1 (0.1)	17 (2.2)	common
Thrombocytopenia	0 (0.0)	5 (0.3)	uncommon***
Nervous system disorders			
Headache	175 (22.6)	192 (24.5)	very common
Dizziness	65 (8.4)	69 (8.8)	common
Migraine	28 (3.6)	45 (5.7)	common
Seizure	7 (0.9)	2 (0.3)	uncommon
Posterior reversible encephalopathy syndrome (PRES)	0 (0.0)	0 (0.0)	rare*
Eye disorders			
Vision blurred	19 (2.5)	33 (4.2)	common
Macular oedema	3 (0.4)	4 (0.5)	uncommon
Cardiac Disorders			

Adverse drug reactions	Placebo N=773 (%)	Fingolimod 0.5 mg N=783 (%)	Frequency for 0.5 mg dose
Bradycardia	7 (0.9)	20 (2.6)	common
Vascular disorders			
Hypertension	28 (3.6)	63 (8.0)	common
Respiratory, thoracic and mediastinal disorders			
Cough	87 (11.3)	96 (12.3)	very common
Dyspnoea	54 (7.0)	71 (9.1)	common
Gastrointestinal disorders			
Diarrhoea	74 (9.6)	99 (12.6)	very common
Skin and subcutaneous tissue disorders			
Eczema	15 (1.9)	21 (2.7)	common
Pruritus	17 (2.2)	21 (2.7)	common
Musculoskeletal and connective tissue disorders			
Back pain	69 (8.9)	78 (10.0)	very common
General disorders and administration site conditions			
Asthenia	6 (0.8)	15 (1.9)	common
Investigations			
Hepatic enzyme increased	32 (4.1)	119 (15.2)	very common
(ALT, GGT, AST increased)			
Blood triglycerides increased	7 (0.9)	16 (2.0)	common

** Not reported in Study FREEDOMS, FREEDOMS II and TRANSFORMS. The frequency category was based on an estimated exposure of approximately 10,000 patients to fingolimod in all clinical trials*
***The frequency category and risk assessment were based on an estimated exposure of more than 24,000 patients to fingolimod 0.5 mg in all clinical trials*
**** n=1709, based on retrospective review of the pivotal clinical studies*

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Gilenya via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Blood and lymphatic system disorders
Autoimmune haemolytic anaemia
Immune system disorders
Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation
Nervous system disorders
Severe exacerbation of disease after discontinuation (see section 4.4 Special warnings and precautions for use)
Gastrointestinal disorders
Nausea
Hepatobiliary disorders
Liver injury
Musculoskeletal and connective tissue disorders
Myalgia, arthralgia
Investigations
Weight decreased

Description of selected adverse drug reactions

Infections

In multiple sclerosis clinical trials, the overall rate of infections (65.1 %) at the 0.5 mg dose was similar to placebo. However, bronchitis, herpes zoster, and pneumonia, were more common in GILENYA treated patients. Serious infections occurred at a rate of 1.6% in the fingolimod 0.5 mg group versus 1.4% in the placebo group.

Co-administration of a short course of corticosteroids (up to 5 days as per study protocols) did not increase the overall rate of infection in patients treated with fingolimod in the Phase III clinical trials, compared to placebo (see section 4.4 Special warnings and precautions for use and INTERACTIONS).

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with GILENYA in the post-marketing setting (see section 4.4 Special warnings and precautions for use).

In the post-marketing setting cases of infections with opportunistic pathogens, such as viral (e.g. JCV causing PML, herpes simplex or varicella zoster virus which may lead to meningitis/encephalitis), fungal (e.g. cryptococci causing cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported, some of which have been fatal (see section 4.4 Special warnings and precautions for use).

Macular Oedema

In clinical trials, macular oedema occurred in 0.5% 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 ophthalmic examination. The macular oedema generally improved or resolved spontaneously after drug discontinuation. The risk of recurrence after re-challenge has not been evaluated.

Macular oedema 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 oedema. Multiple sclerosis patients with diabetes mellitus are therefore expected to be at a higher risk for macular oedema (see section 4.4 Special warnings and precautions for use).

Bradyarrhythmia

Initiation of GILENYA treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays (see section 4.4 Special warnings and precautions for use).

In multiple sclerosis clinical trials the mean maximum decrease in heart rate after the first dose intake was seen 4 - 5 hours post-dose, with a decline in the 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 atrioventricular 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 and in 1.6% of patients on placebo. Second-degree atrioventricular block was detected in less than 0.2 % patients on GILENYA 0.5 mg.

In the post-marketing setting, isolated reports of transient, spontaneously resolving complete AV block have been observed during the six hour observation period following the first dose of GILENYA. The patients recovered spontaneously.

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 one patient on the 0.5 mg dose received isoprenaline for an asymptomatic second degree Mobitz I atrioventricular 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 relationship of such events to GILENYA is uncertain.

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 6.5% of patients on GILENYA 0.5 mg and in 3.3 % of patients on placebo.

Liver Transaminases

Increased hepatic enzymes (mostly ALT elevation) have been reported in multiple sclerosis patients treated with GILENYA. In clinical trials, 8.0% and 1.8% of patients treated with GILENYA 0.5mg experienced an asymptomatic elevation in serum levels of ALT ≥ 3 x ULN and ≥ 5 x ULN, respectively , compared with corresponding figures in the placebo group of 1.9% and 0.9 % respectively. The majority of elevations occurred within 6-9 months. ALT levels returned to normal within approximately 2 months after discontinuation of GILENYA. In the few patients who experienced ALT e elevations of ≥5 x ULN and who continued on GILENYA therapy, the ALT levels returned to normal within approximately 5 months (see section 4.4 Special warnings and precautions for use – Liver function).

Respiratory System

Minor dose-dependent reductions in FEV_1 and 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 2.7 % for fingolimod 0.5 mg and 1.2 % for placebo, a difference that resolved after treatment discontinuation. For DLCO the reductions at Month 24 were 3.3% for fingolimod 0.5 mg and 2.7% for placebo.

Seizures

Cases of seizures, including status epilepticus, have been reported with the use of Gilenya in clinical trials and in the post-marketing setting. It is unknown whether these events were related to the effects of multiple sclerosis alone, to Gilenya, or to a combination of both.

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 ischemic and haemorrhagic strokes have also been reported at the 0.5 mg dose in clinical trials and in the post-marketing setting although a causal relationship has not been established.

Lymphomas

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

4.9 Overdose

Single doses up to 80-fold the recommended dose (0.5mg) were well tolerated in healthy volunteers. At 40mg, 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 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects).

If the overdose constitutes first exposure to GILENYA it is important to observe for signs and symptoms of bradycardia, which could include overnight monitoring. Regular measurements of pulse rate and blood pressure are required and electrocardiograms should be performed (see DOSAGE AND ADMINISTRATION and section 4.4 Special warnings and precautions for use).

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, sphingosine-1-phosphate (S1P) receptor modulators, ATC code: L04AE01

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 (CNS). 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 lymphocytes, including pro-inflammatory Th17 cells, into the CNS 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. Fingolimod penetrates the CNS, in both humans and animals, and has been shown to reduce astrogliosis, demyelination and neuronal loss. Further, fingolimod treatment increases the levels of brain derived neurotropic factor (BDNF) in the cortex, hippocampus and striatum of the brain to support neuronal survival and improve motor functions.

Pharmacodynamic effects

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 atrioventricular conduction upon treatment initiation (see section 4.4 Special warnings and precautions for use - Bradyarrhythmia and section 4.8 Undesirable effects). The maximum decline in heart rate is seen in the first 6 hours post-dose, with 70% of the negative chronotropic effect achieved on the first day. Heart rate progressively returns to baseline values within 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, 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 boundary of the 90 % CI ≤ 13.0 msec. 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 the 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 forced expiratory volume in 1 second (FEV1) and forced expiratory flow during expiration of 25 to 75 % of the forced vital capacity (FEF25-75). 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

Clinical efficacy and safety

The efficacy of GILENYA has been demonstrated in two studies that 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 randomisation, and had an Expanded Disability Status Scale (EDSS) between 0 to 5.5. A third study targeting the same patient population was completed after registration of GILENYA.

Study D2301 (FREEDOMS)

Study D2301 (FREEDOMS) was a 2-year randomised, 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 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 (ARR).

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), 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 annualised 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 3 and Figures 1 and 2.

Table 3 Clinical and MRI results of FREEDOMS Study (D2301)

	GILENYA 0.5 mg **N=425**	**GILENYA 1.25 mg** **N=429**	**Placebo** **N=418**
Clinical endpoints			
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 Month 12 Month 24	 0.0 (0.2) 0.0 (0.2) 0.0 (0.2) (p<0.001* at each time point)	 0.0 (0.3) 0.0 (0.3) 0.0 (0.2) (p<0.001* at each time point)	 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)

	GILENYA 0.5 mg **N=425**	**GILENYA 1.25 mg** **N=429**	**Placebo** **N=418**
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 the 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; percentage 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 1 Kaplan-Meier plot for time to first confirmed relapse up to Month 24 – FREEDOMS Study (D2301) (ITT population)

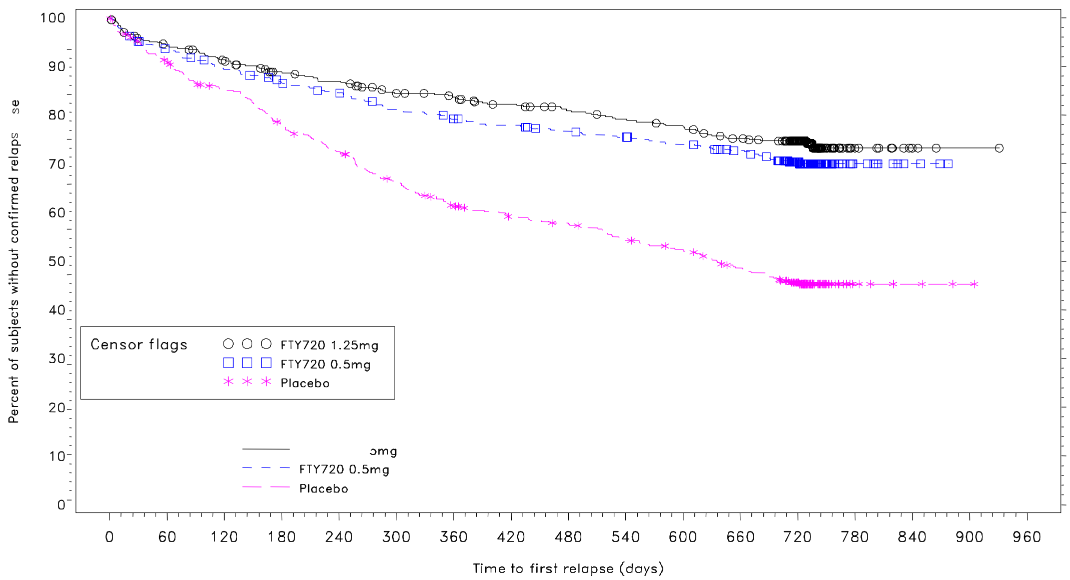
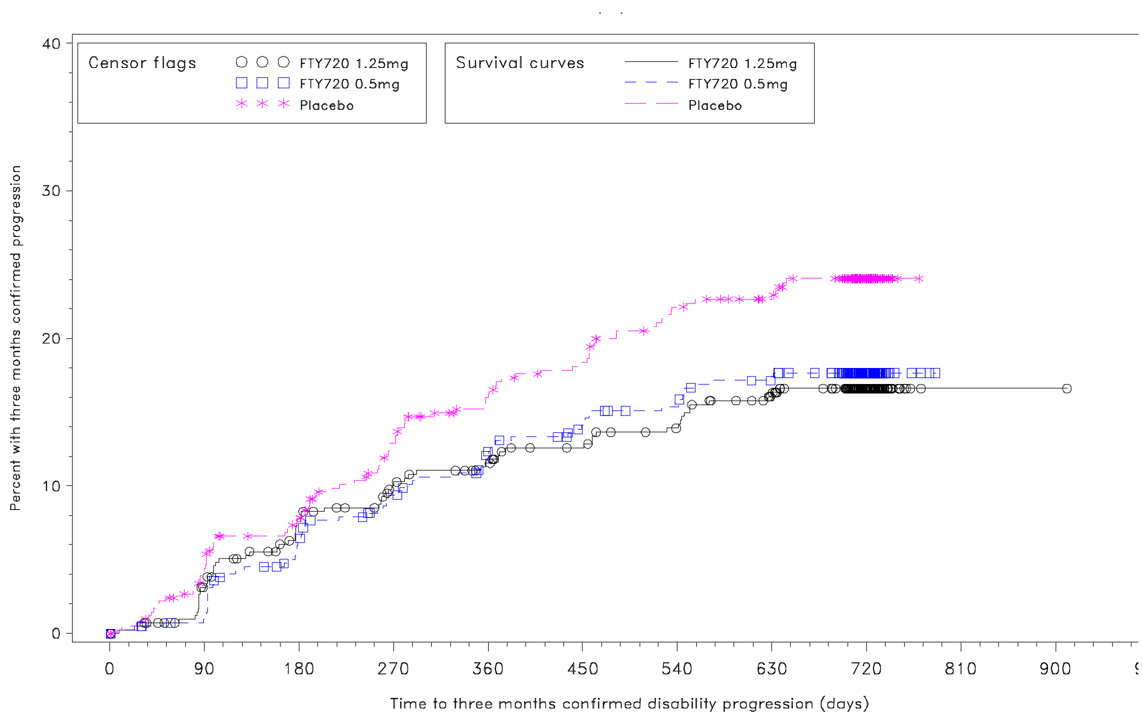


Figure 2 Cumulative plot of time to 3-month confirmed disability progression – FREEDOMS Study (D2301) (ITT population)



Patients who completed Study FREEDOMS (D2301) had the option to enter a dose-blinded extension study D2301E1. 920 patients from the core study entered the extension and were all treated with fingolimod (n=331 continued on 0.5 mg, 289 continued on 1.25 mg, 155 switched from placebo to 0.5 mg and 145 switched from placebo to 1.25 mg). 811 of these patients (88.2 %) had at least 18 months follow-up in the extension phase. The maximum cumulative duration of exposure to fingolimod 0.5 mg (core + extension study) was 1,782 days.

At Month 24 of the extension study, patients who received placebo in the core study had reductions in ARR of 55% after switching to fingolimod 0.5 mg (ARR ratio 0.45,95% CI 0.32 to 0.62, p<0.001). The ARR for patients who were treated with fingolimod 0.5 mg in the core study remained low during the extension study (ARR of 0.10 in the extension study).

Study D2309 (FREEDOMS II)

Study D2309 (FREEDOMS II) had a design similar to that of Study D2301 (FREEDOMS): it 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 (ARR).

Median age was 40.5 years, median disease duration was 8.9 years and median EDSS score at baseline was 2.5. Patients were randomized to receive GILENYA 0.5 mg (n=358) or GILENYA 1.25 mg (n=370), or placebo (n=355) for up to 24 months.

Median time on study drug was 719 days on 0.5 mg and 719 days on placebo. Patients randomized to the fingolimod 1.25 mg dose arm were switched in a blinded manner to receive fingolimod 0.5 mg when results of Study 2301 became available and confirmed a better benefit/risk profile of the lower dose. The dose was switched in 113 patients (30.5%) in this dose arm, median time on fingolimod 1.25 mg in this arm was 496.1 days and 209.8 days on fingolimod 0.5 mg.

The annualised relapse rate was significantly lower in patients treated with GILENYA than in patients who received placebo. The first key secondary endpoint was change from baseline in brain volume. Loss of brain volume was significantly less with GILENYA treatment compared to placebo. The other 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. The risk of disability progression for GILENYA and placebo groups was not statistically different.

There were no significant differences between the 0.5 mg and the 1.25 mg doses on any of the endpoints.

The results for this study are shown in Table 4 and Figure 3.

Table 4 Clinical and MRI results of FREEDOMS II Study (D2309)

	GILENYA 0.5 mg N=358	GILENYA 1.25 mg N=370	Placebo N=355
Clinical endpoints			
Annualized relapse rate (primary endpoint)	0.21 (p<0.001*)	0.20 (p<0.001*)	0.40
Relative reduction (percentage)	48	50	
Percent of patients remaining relapse-free at 24 months	71.5 (p<0.001*)	73.2 (p<0.001*)	52.7
Risk of disability progression†			
Hazard ratio (95% CI) (3-month confirmed)	0.83 (0.61, 1.12) (p=0.227)	0.72 (0.53, 0.99) (p=0.041*)	
Hazard ratio (95% CI) (6-month confirmed)	0.72 (0.48, 1.07) (p=0.113)	0.72 (0.48, 1.08) (p=0.101)	
MRI endpoints			
Percent change in brain volume	n=266	n=247	n=249
Median (mean) % change over 24 months	-0.7 (-0.9) (p<0.001*)	-0.6 (-0.9) (p<0.001*)	-1.0 (-1.3)
Number of new or newly enlarging T2 lesions	n=264	n=245	n=251
Median (mean) number over 24 months	0.0 (2.3) (p<0.001*)	0.0 (1.6) (p<0.001*)	4.0 (8.9)
Number of Gd-enhancing lesions	n=269 (Month 24)	n=251 (Month 24)	n=256 (Month 24)
Median (mean) number at			
Month 6	0.0 (0.2)	0.0 (0.2)	0.0 (1.1)
Month 12	0.0 (0.2)	0.0 (0.2)	0.0 (1.3)
Month 24	0.0 (0.4)	0.0 (0.2)	0.0 (1.2)
	(p<0.001* at each time point)	(p<0.001* at each time point)	
Percent change in T2 lesion total volume	n=262	n= 242	n=247
Median (mean) % change over 24 months	-7.1 (13.7) (p<0.001*)	-10.1 (-7.7) (p<0.001*)	0.8 (25.1)

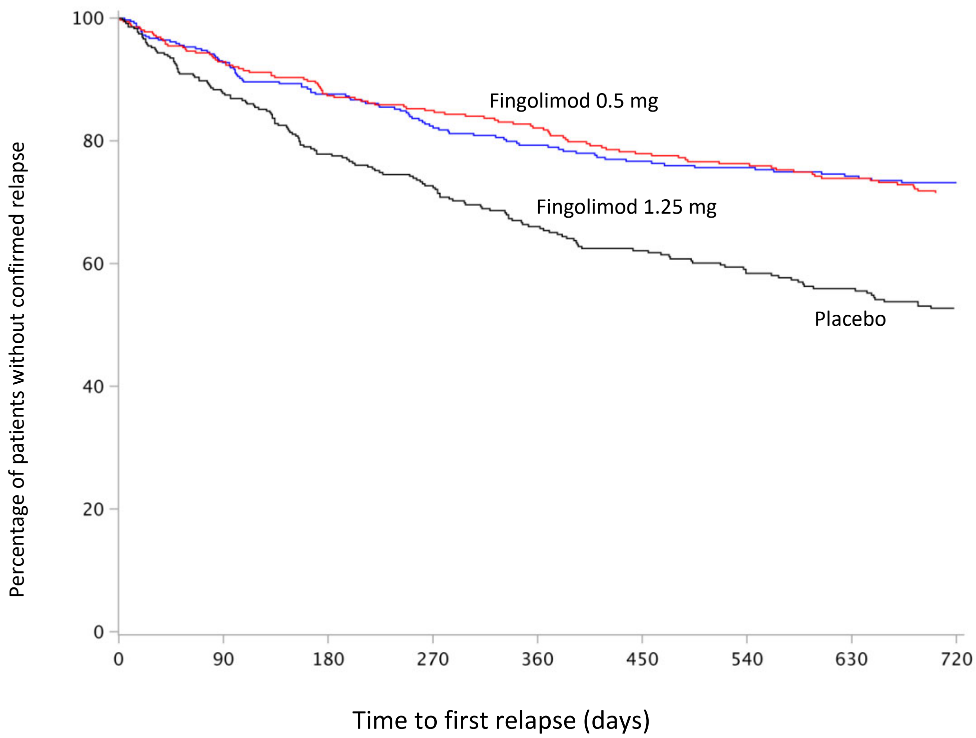
	GILENYA 0.5 mg	GILENYA 1.25 mg	Placebo
Change in T1 hypointense lesion volume	n=225	n=209	n=209
Median (mean) % change over 24 months	-9.9 (12.6) (p=0.372)	-10.9 (-4.7) (p=0.205)	-8.5 (26.4.)

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

Determination of p-values: aggregate ARR by negative binomial regression adjusted for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS; percentage of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapses 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.

[†] Additional analyses revealed that results in the overall population were not significant due to false positive progressions in the subgroup of patients with baseline EDSS=0 (n=62, 8.7% of study population). In patients with EDSS>0 (n=651; 91.3% of study population), fingolimod 0.5 mg demonstrated a clinically relevant and statistically significant reduction compared to placebo (HR= 0.70; CI (0.50, 0.98); p=0.040), consistent with study FREEDOMS.

Figure 3 Kaplan-Meier plot of time to first confirmed relapse up to Month 24 –FREEDOMS II Study (D2309) (ITT population)



Study D2302 (TRANSFORMS)

Study D2302 (TRANSFORMS) was a 1-year randomised, double-blind, double-dummy, active-controlled (interferon beta-1a 30 micrograms, intramuscular, once weekly) Phase III study in patients with relapsing-remitting multiple sclerosis who had not received natalizumab in the previous 6 months. Prior therapy with interferon-beta or glatiramer acetate up to the time of randomisation 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 GILENYA 0.5 mg, 354 days on GILENYA 1.25 mg and 361 days on interferon beta-1a IM.

The annualised 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 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-treated patients at 1 year. There were no significant differences between the 0.5 mg and 1.25 mg doses for either endpoint.

The results for this study are shown in Table 5 and Figure 4.

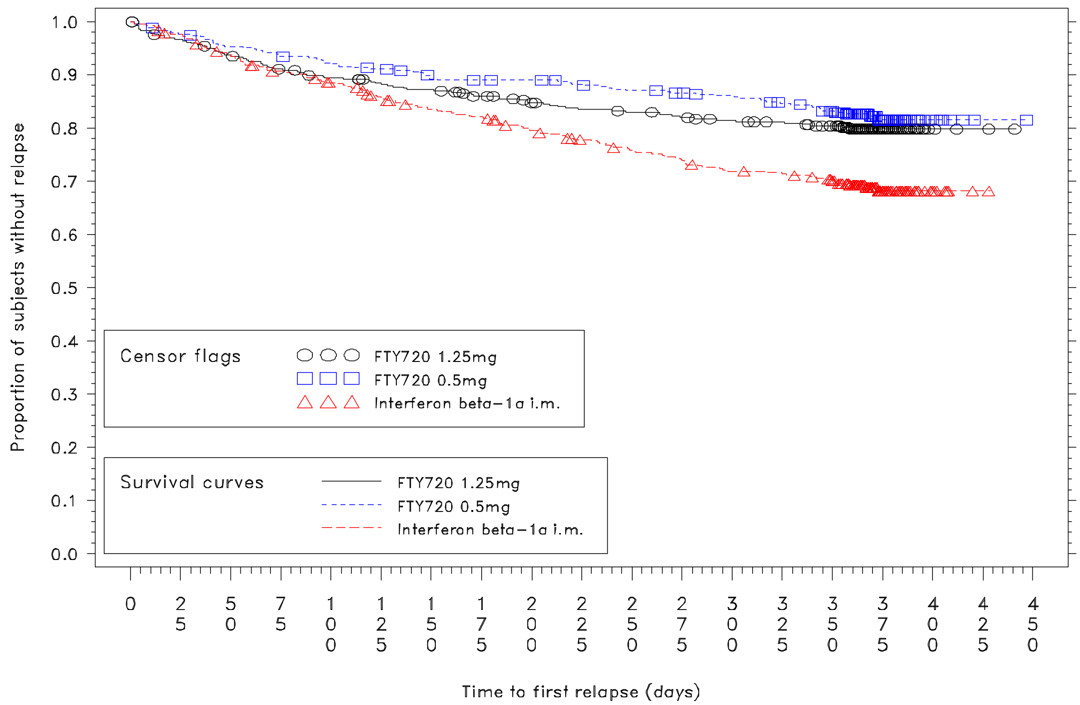
Table 5 Clinical and MRI results of TRANSFORMS Study (D2302)

	GILENYA 0.5 mg N=429	**GILENYA 1.25 mg** N=420	**Interferon beta-1a, IM 30µg,** N=431
Clinical Endpoints			
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 4 Kaplan-Meier plot for time to first confirmed relapse up to Month 12 – TRANSFORMS Study (D2302) (ITT population)



Patients who completed Study TRANSFORMS (D2302) had the option to enter a dose-blinded extension study. 1,030 patients from the core study entered the extension (Study D2302E1) and were treated with fingolimod (n=357 continued on 0.5 mg, 330 continued on 1.25 mg, 167 switched from interferon beta-1a to 0.5 mg and 176 switched from interferon beta-1a to 1.25 mg). 882 of these patients (85.9 %) had at least 12 months follow-up in the extension phase. The maximum cumulative duration of exposure to fingolimod 0.5 mg (core + extension study) was 1,594 days.

At Month 12 of the extension study, patients who received interferon beta-1a i.m. in the core study had relative reductions in ARR of 30 % after switching to fingolimod 0.5 mg (ARR ratio=0.70, p=0.06). The ARR for patients who were treated with fingolimod 0.5 mg in the core study was low during the combined core and extension study (ARR of 0.18 up to Month 24).

The pooled results of studies D2301 (FREEDOMS) and D2302 (TRANSFORMS) showed a consistent reduction in the annualised relapse rate with GILENYA compared to comparator in subgroups defined by gender, age, prior multiple sclerosis therapy, disease activity or disability levels at baseline.

5.2 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 faeces extrapolated to infinity). The apparent absolute oral bioavailability is high (93%).

Food intake does not alter Cmax or exposure (AUC) of fingolimod or fingolimod-phosphate. Therefore GILENYA may be taken without regard to meals (see DOSAGE AND ADMINISTRATION).

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

Distribution:

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

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1200 ± 260 L. A study in four healthy subjects who received a single intravenous dose of radioiodolabeled fingolimod demonstrated that fingolimod penetrates into the brain. In a study in 13 male multiple sclerosis patients who received GILENYA 0.5 mg/day at steady-state, the amount of fingolimod (and fingolimod-phosphate) in seminal ejaculate was more than 10,000 times lower than the dose administered (0.5 mg).

Metabolism:

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

Following single oral administration of [14C] 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 elimination half-life (t1/2) 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 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 faeces 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.

Pharmacokinetics in special patient groups:

Children:

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

Elderly:

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.

Renal dysfunction:
Severe renal impairment increases fingolimod Cmax and AUC by 32% and 43%, respectively, and fingolimod-phosphate Cmax 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, (Child-Pugh class A, B, and C), showed no change on fingolimod Cmax, 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. In patients with severe hepatic impairment (Child-Pugh class C), fingolimod-phosphate Cmax was decreased by 22 % and AUC increased by 38 %. The pharmacokinetics of fingolimod-phosphate was not evaluated in patients with mild or moderate hepatic impairment. 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 (Child-Pugh class A and B). Fingolimod should be used with caution in patients with severe hepatic impairment (Child-Pugh class C).

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.

5.3 Preclinical 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 maximum tolerated dose of 2.5 mg/kg, representing an approximate 50-fold margin based on human systemic exposure (AUC) at the 0.5 mg dose. 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 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 or motility, nor on fertility in male and female rats up to the highest dose tested (10 mg/kg), representing an approximate 150-fold margin based on human systemic exposure (AUC) at a daily dose of 0.5 mg.

In a toxicity study in juvenile rats, no additional target organs of toxicity were observed compared to adult rats. Repeated stimulations with Keyhole Limpet Hemocyanin (KLH) showed a moderately decreased response during the treatment period, but fully functional immune reactions at the end of an 8 week recovery period.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core:
Magnesium stearate
Mannitol
Capsule shell:
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin
Printing ink:
Shellac (E904)
Dehydrated alcohol
Isopropyl alcohol
Butyl alcohol
Propylene glycol
Purified water
Strong ammonia solution
Potassium hydroxide
Black iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Dimethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store below 30 degrees Celsius. Protect from moisture.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister packs of 7, 28 or 84 capsules. Not all presentations might be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

Novartis New Zealand Limited
PO Box 99102
Newmarket
Auckland 1149
New Zealand
Telephone: 0800 354 335
® = Registered Trademark

9 DATE OF FIRST APPROVAL

13 October 2011

10 DATE OF REVISION OF THE TEXT

14 May 2025

SUMMARY TABLE OF CHANGES

Section	Summary of changes
4.6, 4.8, 5.1	Use in pregnancy - Revision of text based on GPR and PRIM data (new human data), addition of Pharmacotherapeutic group and ATC code, editorial updates
4.8	Update to Medsafe AE reporting link

Internal Document Code
(gil140525iNZ) based on the CDS dated 12 March 2025