ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gilenya 0.25 mg hard capsules
Gilenya 0.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gilenya 0.25 mg hard capsules

Each 0.25 mg capsule contains 0.25 mg fingolimod (as hydrochloride).

Gilenya 0.5 mg hard capsules

Each 0.5 mg capsule contains 0.5 mg fingolimod (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Gilenya 0.25 mg hard capsules

Capsule of 16 mm with ivory opaque cap and body, with black radial imprint “FTY 0.25mg” on cap and black radial band on body.

Gilenya 0.5 mg hard capsules

Capsule of 16 mm with bright yellow opaque cap and white opaque body; imprint with black ink, “FTY0.5 mg” on cap and two radial bands imprinted on the body with yellow ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1).

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

4.2 Posology and method of administration

The treatment should be initiated and supervised by a physician experienced in multiple sclerosis.

Posology

In adults, the recommended dose of fingolimod is one 0.5 mg capsule taken orally once daily.

In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight:
- Paediatric patients with body weight ≤40 kg: one 0.25 mg capsule taken orally once daily.
- Paediatric patients with body weight >40 kg: one 0.5 mg capsule taken orally once daily.

Paediatric patients who start on 0.25 mg capsules and subsequently reach a stable body weight above 40 kg should be switched to 0.5 mg capsules.

When switching from a 0.25 mg to a 0.5 mg daily dose, it is recommended to repeat the same first dose monitoring as for treatment initiation.

The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:
- 1 day or more during the first 2 weeks of treatment.
- more than 7 days during weeks 3 and 4 of treatment.
- more than 2 weeks after one month of treatment.

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned (see section 4.4).

Special populations

Elderly population
Gilenya should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy (see section 5.2).

Renal impairment
Fingolimod was not studied in patients with renal impairment in the multiple sclerosis pivotal studies. Based on clinical pharmacology studies, no dose adjustments are needed in patients with mild to severe renal impairment.

Hepatic impairment
Gilenya must not be used in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.3). Although no dose adjustments are needed in patients with mild or moderate hepatic impairment, caution should be exercised when initiating treatment in these patients (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of fingolimod in children aged below 10 years have not yet been established. No data are available. There are very limited data available in children between 10–12 years old (see sections 4.4, 4.8 and 5.1).

Method of administration

This medicinal product is for oral use.

Gilenya can be taken with or without food (see section 5.2).

The capsules should always be swallowed intact, without opening them.

4.3 Contraindications

- Immunodeficiency syndrome.
- Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies).
- Severe active infections, active chronic infections (hepatitis, tuberculosis).
- Active malignancies.
- Severe liver impairment (Child-Pugh class C).
- Patients who in the previous 6 months had myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure (see section 4.4).
- Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia or class III anti-arrhythmic medicinal products (see section 4.4).
- Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not wear a pacemaker (see section 4.4).
- Patients with a baseline QTc interval ≥ 500 msec (see section 4.4).
- During pregnancy and in women of childbearing potential not using effective contraception (see sections 4.4 and 4.6).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Bradyarrhythmia

Initiation of treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete AV block (see sections 4.8 and 5.1).

After the first dose, the decline in heart rate starts within one hour, and is maximal within 6 hours. This post-dose effect persists over the following days, although usually to a milder extent, and usually abates over the next weeks. With continued administration, the average heart rate returns towards baseline within one month. However individual patients may not return to baseline heart rate by the end of the first month. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. If necessary, the decrease in heart rate induced by fingolimod can be reversed by parenteral doses of atropine or isoprenaline.

All patients should have an ECG and blood pressure measurement performed prior to and 6 hours after the first dose of Gilenya. All patients should be monitored for a period of 6 hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurement. Continuous (real time) ECG monitoring during this 6 hour period is recommended.

The same precautions as for the first dose are recommended when patients are switched from the 0.25 mg to the 0.5 mg daily dose.

Should post-dose bradyarrhythmia-related symptoms occur, appropriate clinical management should be initiated and monitoring should be continued until the symptoms have resolved. Should a patient require pharmacological intervention during the first-dose monitoring, overnight monitoring in a medical facility should be instituted and the first-dose monitoring should be repeated after the second dose of Gilenya.

If the heart rate at 6 hours is the lowest since the first dose was administered (suggesting that the maximum pharmacodynamic effect on the heart may not yet be manifest), monitoring should be extended by at least 2 hours and until heart rate increases again. Additionally, if after 6 hours, the heart rate is <45 bpm in adults, <55 bpm in paediatric patients aged 12 years and above, or <60 bpm in paediatric patients aged 10 to below 12 years, or the ECG shows new onset second degree or higher grade AV block or a QTc interval ≥500 msec, extended monitoring (at least overnight monitoring), should be performed, and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring (at least overnight monitoring).

The effects on heart rate and atrioventricular conduction may recur on re-introduction of fingolimod treatment depending on duration of the interruption and time since start of treatment. The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted (see section 4.2).

Very rare cases of T-wave inversion have been reported in adult patients treated with fingolimod. In case of T-wave inversion, the prescriber should ensure that there are no associated myocardial ischaemia signs or symptoms. If myocardial ischaemia is suspected, it is recommended to seek advice from a cardiologist.

Due to the risk of serious rhythm disturbances or significant bradycardia, Gilenya should not be used in patients with sino-atrial heart block, a history of symptomatic bradycardia, recurrent syncope or cardiac arrest, or in patients with significant QT prolongation (QTc>470 msec [adult female], QTc >460 msec [paediatric female] or >450 msec [adult and paediatric male]), uncontrolled hypertension or severe sleep apnoea (see also section 4.3). In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks, and advice from a cardiologist sought prior to initiation of treatment in order to determine the most appropriate monitoring. At least overnight extended monitoring is recommended for treatment initiation (see also section 4.5).

Fingolimod has not been studied in patients with arrhythmias requiring treatment with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Class Ia and class III antiarrhythmic medicinal products have been associated with cases of torsades de pointes in patients with bradycardia (see section 4.3).

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 which may decrease heart rate (e.g. ivabradine, digoxin, anticholinesteratic agents or pilocarpine). Since the initiation of fingolimod treatment is also associated with slowing of the heart rate (see also section 4.8, Bradyarrhythmia), concomitant use of these substances during treatment initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with Gilenya should not be initiated in patients who are concurrently treated with these substances (see also section 4.5). In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment with Gilenya is considered, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products prior to initiation of treatment. If the heart-rate-lowering treatment cannot be stopped, cardiologist's advice should be sought to determine appropriate first dose monitoring, at least overnight extended monitoring is recommended (see also section 4.5).

<u>QT interval</u>

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 limit of the 90% CI ≤13.0 ms. There is no dose- or exposure-response relationship of fingolimod and QTcI prolongation. There is no consistent signal of increased incidence of QTcI outliers, either absolute or change from baseline, associated with fingolimod treatment.

The clinical relevance of this finding is unknown. In the multiple sclerosis studies, clinically relevant effects on prolongation of the QTc-interval have not been observed but patients at risk for QT prolongation were not included in clinical studies.

Medicinal products that may prolong QTc interval are best avoided in patients with relevant risk factors, for example, hypokalaemia or congenital QT prolongation.

Immunosuppressive effects

Fingolimod has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas and other malignancies, particularly those of the skin. Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis (see also section 4.4 “Infections” and “Cutaneous neoplasms” and section 4.8 “Lymphomas”).

Infections

A core pharmacodynamic effect of fingolimod is a dose-dependent reduction of the peripheral lymphocyte count to 20-30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues (see section 5.1).

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. Assessments of CBC are also recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte count $<0.2x10^9$/l, if confirmed, should lead to treatment interruption until recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count $<0.2x10^9$/l.

Initiation of treatment with Gilenya should be delayed in patients with severe active infection until resolution.

The immune system effects of Gilenya may increase the risk of infections, including opportunistic infections (see section 4.8). Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. When evaluating a patient with a suspected infection that could be serious, referral to a physician experienced in treating infections should be considered. During treatment, patients should be instructed to report promptly symptoms of infection to their physician.

Suspension of 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.

Elimination of fingolimod following discontinuation of therapy may take up to two months and vigilance for infection should therefore be continued throughout this period. Patients should be instructed to report symptoms of infection up to 2 months after discontinuation of fingolimod.

Herpes viral infection

Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex and varicella zoster viruses have occurred with Gilenya at any time during treatment. If herpes encephalitis, meningitis or meningoencephalitis occur, Gilenya should be discontinued and appropriate treatment for the respective infection should be administered.

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 fingolimod 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). Initiation of treatment with fingolimod should be postponed for 1 month to allow full effect of vaccination to occur.

Cryptococcal meningitis
Cases of cryptococcal meningitis (a fungal infection), sometimes fatal, 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). Patients with symptoms and signs consistent with cryptococcal meningitis (e.g. headache accompanied by mental changes such as confusion, hallucinations, and/or personality changes) should undergo prompt diagnostic evaluation. If cryptococcal meningitis is diagnosed, fingolimod should be suspended and appropriate treatment should be initiated. A multidisciplinary consultation (i.e. infectious disease specialist) should be undertaken if re-initiation of fingolimod is warranted.

Progressive multifocal leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) has been reported under fingolimod treatment since marketing authorisation (see section 4.8). PML is an opportunistic infection caused by John Cunningham virus (JCV), which may be fatal or result in severe disability. Cases of PML have occurred after approximately 2-3 years of monotherapy treatment without previous exposure to natalizumab. Although the estimated risk appears to increase with cumulative exposure over time, an exact relationship with the duration of treatment is unknown. Additional PML cases have occurred in patients who had been treated previously with natalizumab, which has a known association with PML. PML can only occur in the presence of a JCV infection. If JCV testing is undertaken, it should be considered that the influence of lymphopenia on the accuracy of anti-JCV antibody testing has not been studied in fingolimod-treated patients. It should also be noted that a negative anti-JCV antibody test does not preclude the possibility of subsequent JCV infection. Before initiating treatment with fingolimod, a baseline MRI should be available (usually within 3 months) as a reference. MRI findings may be apparent before clinical signs or symptoms. During routine MRI (in accordance with national and local recommendations), physicians should pay attention to PML suggestive lesions. MRI may be considered as part of increased vigilance in patients considered at increased risk of PML. Cases of asymptomatic PML based on MRI findings and positive JCV DNA in the cerebrospinal fluid have been reported in patients treated with fingolimod. If PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with fingolimod should be suspended until PML has been excluded.

Human papilloma virus infection
Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with fingolimod in the post-marketing setting (see section 4.8). Due to the immunosuppressive properties of fingolimod, vaccination against HPV should be considered prior to treatment initiation with fingolimod taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care.

Macular oedema

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

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

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

Liver injury

Increased hepatic enzymes, in particular alanine aminotransaminase (ALT) but also gamma glutamyltransferase (GGT) and aspartate transaminase (AST) have been reported in multiple sclerosis patients treated with fingolimod. Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have also been reported. 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. In clinical trials, elevations 3-fold the upper limit of normal (ULN) or greater in ALT occurred in 8.0% of adult patients treated with fingolimod 0.5 mg compared to 1.9% of placebo patients. Elevations 5-fold the ULN occurred in 1.8% of patients on fingolimod and 0.9% of patients on placebo. In clinical trials, fingolimod was discontinued if the elevation exceeded 5 times the ULN. Recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to fingolimod. In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of fingolimod.

Fingolimod has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and should not be used in these patients (see section 4.3).

Due to the immunosuppressive properties of fingolimod, initiation of treatment should be delayed in patients with active viral hepatitis until resolution.

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment. In the absence of clinical symptoms, liver transaminases and serum bilirubin should be monitored at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter until 2 months after Gilenya discontinuation. In the absence of clinical symptoms, if liver transaminases are greater than 3 but less than 5 times the ULN without increase in serum bilirubin, more frequent monitoring including serum bilirubin and alkaline phosphatase (ALP) measurement should be instituted to determine if further increases occur and in order to discern if an alternative aetiology of hepatic dysfunction is present. If liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin, Gilenya should be discontinued. Hepatic monitoring should be continued. If serum levels return to normal (including if an alternative cause of the hepatic dysfunction is discovered), Gilenya may be restarted based on a careful benefit-risk assessment of the patient.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have liver enzymes and bilirubin checked promptly and treatment should be discontinued if significant liver injury is confirmed. 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 of developing elevated liver function tests when taking Gilenya, caution in the use of Gilenya should be exercised in patients with a history of significant liver disease.

Blood pressure effects

Patients with hypertension uncontrolled by medication were excluded from participation in premarketing clinical trials and special care is indicated if patients with uncontrolled hypertension are treated with Gilenya.

In MS clinical trials, patients treated with fingolimod 0.5 mg had an average increase of approximately 3 mmHg in systolic pressure, and approximately 1 mmHg in diastolic pressure, first detected approximately 1 month after treatment initiation, and persisting with continued treatment. In the two-year placebo-controlled study, hypertension was reported as an adverse event in 6.5% of patients on fingolimod 0.5 mg and in 3.3% of patients on placebo. Therefore, blood pressure should be regularly monitored during treatment.

Respiratory effects

Minor dose-dependent reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (DLCO) were observed with fingolimod treatment starting at month 1 and remaining stable thereafter. Gilenya should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease (see section 4.8).

Posterior reversible encephalopathy syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported at the 0.5 mg dose in clinical trials and in the post-marketing setting (see section 4.8). 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 ischaemic 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 or immunomodulatory therapies

There have been no studies performed to evaluate the efficacy and safety of fingolimod when switching patients from teriflunomide, dimethyl fumarate or alemtuzumab treatment to Gilenya. When switching patients from another disease modifying therapy to Gilenya, the elimination half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A CBC is recommended prior to initiating Gilenya to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

Gilenya can generally be started immediately after discontinuation of interferon or glatiramer acetate.

For dimethyl fumarate, the washout period should be sufficient for CBC to recover before treatment with Gilenya is started.

Due to the long elimination half-life of natalizumab, elimination 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 from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide summary of product characteristics is recommended or alternatively washout period should not be shorter than 3.5 months. Caution regarding potential concomitant immune effects is required when switching patients from natalizumab or teriflunomide to Gilenya.

Alemtuzumab has profound and prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with Gilenya after alemtuzumab is not recommended unless the benefits of such treatment clearly outweigh the risks for the individual patient.

A decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration.

Co-administration with potent CYP450 inducers

The combination of fingolimod with potent CYP450 inducers should be used with caution. Concomitant administration with St John's Wort is not recommended (see section 4.5).

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). Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, and then every 6 to 12 months taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions are detected.

Since there is a potential risk of malignant skin growths, patients treated with fingolimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Lymphomas
There have been cases of lymphoma in clinical studies and the post-marketing setting (see section 4.8). 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. A fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma has also been observed. If lymphoma is suspected, treatment should be discontinued.

Women of childbearing potential

Due to risk to the foetus, fingolimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for 2 months after treatment discontinuation (see sections 4.3 and 4.6 and the information contained in the Physician Information Pack).

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 treatment should be considered by the physician on a case-by-case basis taking into account individual benefits and risks.

Return of disease activity (rebound) after fingolimod discontinuation

In the post-marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping fingolimod. This has generally been observed within 12 weeks after stopping fingolimod, but has also been reported up to 24 weeks after fingolimod discontinuation. Caution is therefore indicated when stopping fingolimod therapy. If discontinuation of fingolimod is deemed necessary, the possibility of recurrence of exceptionally high disease activity should be considered and patients should be monitored for relevant signs and symptoms and appropriate treatment initiated as required (see "Stopping therapy" below).

Stopping therapy

If a decision is made to stop treatment with Gilenya a 6 week interval without therapy is needed, based on half-life, to clear fingolimod from the circulation (see section 5.2). Lymphocyte counts progressively return to normal range within 1-2 months of stopping therapy in most patients (see section 5.1) although full recovery can take significantly longer in some patients. Starting other therapies during this interval will result in concomitant exposure to fingolimod. Use of immunosuppressants soon after the discontinuation of Gilenya may lead to an additive effect on the immune system and caution is therefore indicated.

Caution is also indicated when stopping fingolimod therapy due to the risk of a rebound (see "Return of disease activity (rebound) after fingolimod discontinuation" above). If discontinuation of Gilenya is deemed necessary, patients should be monitored during this time for relevant signs of a possible rebound.

Interference with serological testing

Since fingolimod reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with Gilenya. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes.

Paediatric population

The safety profile in paediatric patients is similar to that in adults and the warnings and precautions for adults therefore also apply to paediatric patients.

In particular, the following should be noted when prescribing Gilenya to paediatric patients:
- Precautions should be followed at the time of the first dose (see "Bradyarrhythmia" above). The same precautions as for the first dose are recommended when patients are switched from the 0.25 mg to the 0.5 mg daily dose.
- In the controlled paediatric trial D2311, cases of seizures, anxiety, depressed mood and depression have been reported with a higher incidence in patients treated with fingolimod compared to patients treated with interferon beta-1a. Caution is required in this subgroup population (see "Paediatric population" in section 4.8).
- Mild isolated bilirubin increases have been noted in paediatric patients on Gilenya.
- It is recommended that paediatric patients complete all immunisations in accordance with current immunisation guidelines before starting Gilenya therapy (see "Infections" above).
- There are very limited data available in children between 10–12 years old, less than 40 kg or at Tanner stage <2 (see sections 4.8 and 5.1). Caution is required in these subgroups due to very limited knowledge available from the clinical study.
- Long-term safety data in the paediatric population are not available.

4.5 Interaction with other medicinal products and other forms of interaction

Anti-neoplastic, immunomodulatory or immunosuppressive therapies

Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects (see sections 4.3 and 4.4).

Caution should also be exercised when switching patients from long-acting therapies with immune effects such as natalizumab, teriflunomide or mitoxantrone (see section 4.4). In multiple sclerosis clinical studies the concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection.

Vaccination

During and for up to two months after treatment with Gilenya vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided (see sections 4.4 and 4.8).

Bradycardia-inducing substances

Fingolimod has been studied in combination with atenolol and diltiazem. When fingolimod was used with atenolol in an interaction study in healthy volunteers, there was an additional 15% reduction of heart rate at fingolimod treatment initiation, an effect not seen with diltiazem. Treatment with Gilenya should not be initiated in patients receiving beta blockers, or other substances which may decrease heart rate, such as class Ia and III antiarrhythmics, calcium channel blockers (such as verapamil or diltiazem), ivabradine, digoxin, anticholinesteratic agents or pilocarpine because of the potential additive effects on heart rate (see sections 4.4 and 4.8). If treatment with Gilenya is considered in such patients, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering medicinal products or appropriate monitoring for treatment initiation, at least overnight monitoring is recommended, if the heart-rate-lowering medication cannot be stopped.

Pharmacokinetic interactions of other substances on fingolimod

Fingolimod is metabolised mainly by CYP4F2. Other enzymes like CYP3A4 may also contribute to its metabolism, notably in the case of strong induction of CYP3A4. Potent inhibitors of transporter proteins are not expected to influence fingolimod disposition. Co-administration of fingolimod with ketoconazole resulted in a 1.7-fold increase in fingolimod and fingolimod phosphate exposure (AUC) by inhibition of CYP4F2. Caution should be exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin).

Co-administration of carbamazepine 600 mg twice daily at steady-state and a single dose of fingolimod 2 mg reduced the AUC of fingolimod and its metabolite by approximately 40%. Other strong CYP3A4 enzyme inducers, for example rifampicin, phenobarbital, phenytoin, efavirenz and St. John’s Wort, may reduce the AUC of fingolimod and its metabolite at least to this extent. As this could potentially impair the efficacy, their co-administration should be used with caution. Concomitant administration with St. John’s Wort is however not recommended (see section 4.4).

Pharmacokinetic interactions of fingolimod on other substances

Fingolimod is unlikely to interact with substances mainly cleared by the CYP450 enzymes or by substrates of the main transporter proteins.

Co-administration of fingolimod with ciclosporin did not elicit any change in the ciclosporin or fingolimod exposure. Therefore, fingolimod is not expected to alter the pharmacokinetics of medicinal products that are CYP3A4 substrates.

Co-administration of fingolimod with oral contraceptives (ethinylestradiol and levonorgestrel) did not elicit any change in oral contraceptive exposure. No interaction studies have been performed with oral contraceptives containing other progestagens, however an effect of fingolimod on their exposure is not expected.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Fingolimod is contraindicated in women of childbearing potential not using effective contraception (see section 4.3). Therefore, before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available and counselling should be provided regarding the serious risk to the foetus. Women of childbearing potential must use effective contraception during treatment and for 2 months after discontinuation of Gilenya, since fingolimod takes approximately 2 months to eliminate from the body after treatment discontinuation (see section 4.4).

Specific measures are also included in the Physician Information Pack. These measures must be implemented before fingolimod is prescribed to female patients and during treatment.

When stopping fingolimod therapy for planning a pregnancy the possible return of disease activity should be considered (see section 4.4).

Pregnancy

Based on human experience, post-marketing data suggest that use of fingolimod is associated with a 2-fold increased risk of major congenital malformations when administered during pregnancy compared with the rate observed in the general population (2-3%; EUROCAT).

The following major malformations were most frequently reported:
- Congenital heart disease such as atrial and ventricular septal defects, tetralogy of Fallot
- Renal abnormalities
- Musculoskeletal abnormalities

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

Animal studies have shown reproductive toxicity including foetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect (see section 5.3). Furthermore, the receptor affected by fingolimod (sphingosine 1-phosphate receptor) is known to be involved in vascular formation during embryogenesis.

Consequently, fingolimod is contraindicated during pregnancy (see section 4.3). Fingolimod should be stopped 2 months before planning a pregnancy (see section 4.4). If a woman becomes pregnant during treatment, fingolimod must be discontinued. Medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment and ultrasonography examinations should be performed.

Breast-feeding

Fingolimod is excreted in milk of treated animals during lactation (see section 5.3). Due to the potential for serious adverse reactions to fingolimod in nursing infants, women receiving Gilenya should not breastfeed.

Fertility

Data from preclinical studies do not suggest that fingolimod would be associated with an increased risk of reduced fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions (incidence ≥10%) at the 0.5 mg dose were headache (24.5%), hepatic enzyme increased (15.2%), diarrhoea (12.6%), cough (12.3%), influenza (11.4%), sinusitis (10.9%) and back pain (10.0%).

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials and derived from post-marketing experience via spontaneous case reports or literature cases are shown below. Frequencies were defined using the following convention: 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Infections and infestations	
Very common:	Influenza Sinusitis
Common:	Herpes viral infections Bronchitis Tinea versicolor
Uncommon:	Pneumonia
Not known:	Progressive multifocal leukoencephalopathy (PML)** Cryptococcal infections**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Common:	Basal cell carcinoma
Uncommon:	Malignant melanoma****
Rare:	Lymphoma*** Squamous cell carcinoma****
Very rare:	Kaposi's sarcoma****
Not known	Merkel cell carcinoma***
Blood and lymphatic system disorders	
Common:	Lymphopenia Leucopenia
Uncommon:	Thrombocytopenia
Not known:	Autoimmune haemolytic anaemia*** Peripheral oedema***
Immune system disorders	
Not known:	Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation***
Psychiatric disorders	
Common:	Depression
Uncommon:	Depressed mood

Nervous system disorders	
Very common:	Headache
Common:	Dizziness Migraine
Uncommon:	Seizure
Rare:	Posterior reversible encephalopathy syndrome (PRES)*
Not known:	Severe exacerbation of disease after fingolimod discontinuation***
Eye disorders	
Common:	Vision blurred
Uncommon:	Macular oedema
Cardiac disorders	
Common:	Bradycardia Atrioventricular block
Very rare:	T-wave inversion***
Vascular disorders	
Common:	Hypertension
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough
Common:	Dyspnoea
Gastrointestinal disorders	
Very common:	Diarrhoea
Uncommon:	Nausea***
Hepatobiliary disorders	
Not known:	Acute hepatic failure***
Skin and subcutaneous tissue disorders	
Common:	Eczema Alopecia Pruritus
Musculoskeletal and connective tissue disorders	
Very common:	Back pain
Common:	Myalgia Arthralgia
General disorders and administration site conditions	
Common:	Asthenia
Investigations	
Very common:	Hepatic enzyme increased (increased alanine transaminase, gamma glutamyltransferase, aspartate transaminase)
Common:	Weight decreased*** Blood triglycerides increased
Uncommon:	Neutrophil count decreased
* The frequency category was based on an estimated exposure of approximately 10,000 patients to fingolimod in all clinical trials. ** PML and cryptococcal infections (including cases of cryptococcal meningitis) have been reported in the post-marketing setting (see section 4.4). *** Adverse reactions from spontaneous reports and literature **** 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.	

Description of selected adverse reactions

Infections

In multiple sclerosis clinical studies the overall rate of infections (65.1%) at the 0.5 mg dose was similar to placebo. However, lower respiratory tract infections, primarily bronchitis and to a lesser extent herpes infection and pneumonia were more common in fingolimod-treated patients. Some cases of disseminated herpes infection, including fatal cases, have been reported even at the 0.5 mg dose.

In the post-marketing setting, cases of infections with opportunistic pathogens, such as viral (e.g. varicella zoster virus [VZV], John Cunningham virus [JCV] causing Progressive Multifocal Leukoencephalopathy, herpes simplex virus [HSV]), fungal (e.g. cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported, some of which have been fatal (see section 4.4).

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with fingolimod in the post-marketing setting (see section 4.4). Due to the immunosuppressive properties of fingolimod, vaccination against HPV should be considered prior to treatment initiation with fingolimod taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care.

Macular oedema
In multiple sclerosis clinical studies macular oedema occurred in 0.5% of patients treated with the recommended dose of 0.5 mg and 1.1% of patients treated with the higher dose of 1.25 mg. The majority of cases 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 ophthalmological examination. The macular oedema generally improved or resolved spontaneously after discontinuation of treatment. 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 (17% with a history of uveitis vs. 0.6% without a history of uveitis). Gilenya has not been studied in multiple sclerosis patients with diabetes mellitus, a disease which is associated with an increased risk for macular oedema (see section 4.4). In renal transplant clinical studies in which patients with diabetes mellitus were included, therapy with fingolimod 2.5 mg and 5 mg resulted in a 2-fold increase in the incidence of macular oedema.

Bradyarrhythmia
Initiation of treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays. In multiple sclerosis clinical studies the maximal decline in heart rate was seen within 6 hours after treatment initiation, with declines in mean heart rate of 12-13 beats per minute for fingolimod 0.5 mg. Heart rate below 40 beats per minute in adults, and below 50 beats per minute in paediatric patients, was rarely observed in patients on fingolimod 0.5 mg. The average heart rate returned towards baseline within 1 month of chronic treatment. Bradycardia was generally asymptomatic but some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue and/or palpitations, which resolved within the first 24 hours after treatment initiation (see also sections 4.4 and 5.1).

In multiple sclerosis clinical studies first-degree atrioventricular block (prolonged PR interval on ECG) was detected after treatment initiation in adult and paediatric patients. In adult clinical trials it occurred in 4.7% of patients on fingolimod 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% adult patients on fingolimod 0.5 mg. In the post-marketing setting, isolated reports of transient, spontaneously resolving complete AV block have been observed during the six hour monitoring 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 the first 24 hours after treatment initiation. Although most patients did not require medical intervention, one patient on fingolimod 0.5 mg received isoprenaline for 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 medicinal products and/or pre-existing disease. The relationship of such events to Gilenya is uncertain.

Blood pressure
In multiple sclerosis clinical studies fingolimod 0.5 mg was associated with an average increase of approximately 3 mmHg in systolic pressure and approximately 1 mmHg in diastolic pressure, manifesting approximately 1 month after treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6.5% of patients on fingolimod 0.5 mg and in 3.3% of patients on placebo. In the post-marketing setting, cases of hypertension have been reported within the first month of treatment initiation and on the first day of treatment that may require treatment with antihypertensive agents or discontinuation of Gilenya (see also section 4.4, Blood pressure effects).

Liver function
Increased hepatic enzymes have been reported in adult and paediatric multiple sclerosis patients treated with Gilenya. In clinical studies 8.0% and 1.8% of adult patients treated with fingolimod 0.5 mg experienced an asymptomatic elevation in serum levels of ALT of ≥3x ULN (upper limit of normal) and ≥5x ULN, respectively. Recurrence of liver transaminase elevations has occurred upon re-challenge in some patients, supporting a relationship to the medicinal product. In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months. ALT levels returned to normal within approximately 2 months after discontinuation of treatment. In a small number of patients (N=10 on 1.25 mg, N=2 on 0.5 mg) who experienced ALT elevations ≥5x ULN and who continued on fingolimod therapy, the ALT levels returned to normal within approximately 5 months (see also section 4.4, Liver function).

Nervous system disorders
In clinical studies, rare events involving the nervous system occurred in patients treated with fingolimod at higher doses (1.25 or 5.0 mg) including ischaemic and haemorrhagic strokes and neurological atypical disorders, such as acute disseminated encephalomyelitis (ADEM)-like events.

Cases of seizures, including status epilepticus, have been reported with the use of fingolimod in clinical studies and in the post-marketing setting.

Vascular disorders
Rare cases of peripheral arterial occlusive disease occurred in patients treated with fingolimod at higher doses (1.25 mg).

Respiratory system
Minor dose-dependent reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (DLCO) were observed with Gilenya treatment starting at month 1 and remaining stable thereafter. At month 24, the reduction from baseline values in percentage 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 (see also section 4.4, Respiratory effects).

Lymphomas
There have been cases of lymphoma of different varieties, in both clinical studies and the post-marketing setting, including a fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma. The incidence of non-Hodgkin's lymphoma (B-cell and T-cell) cases was higher in clinical trials than expected in the general population. Some T-cell lymphoma cases were also reported in the post-marketing setting, including cases of cutaneous T-cell lymphoma (mycosis fungoides) (see also section 4.4, Malignancies).

Haemophagocytic syndrome
Very rare cases of haemophagocytic syndrome (HPS) with fatal outcome have been reported in patients treated with fingolimod in the context of an infection. HPS is a rare condition that has been described in association with infections, immunosuppression and a variety of autoimmune diseases.

Paediatric population

In the controlled paediatric trial D2311 (see section 5.1), the safety profile in paediatric patients (10 to below 18 years of age) receiving fingolimod 0.25 mg or 0.5 mg daily was overall similar to that seen in adult patients. There were, nevertheless, more neurological and psychiatric disorders observed in the study. Caution is needed in this subgroup due to very limited knowledge available from the clinical study.

In the paediatric study, cases of seizures were reported in 5.6% of fingolimod-treated patients and 0.9% of interferon beta-1a-treated patients.

Depression and anxiety are known to occur with increased frequency in the multiple sclerosis population. Depression and anxiety have also been reported in paediatric patients treated with fingolimod.

Mild isolated bilirubin increases have been noted in paediatric patients on fingolimod.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses up to 80 times the recommended dose (0.5 mg) were well tolerated in healthy adult 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 upon treatment initiation. The decline in heart rate usually starts within one hour of the first dose, and is steepest within 6 hours. The negative chronotropic effect of Gilenya persists beyond 6 hours and progressively attenuates over subsequent days of treatment (see section 4.4 for details). There have been reports of slow atrioventricular conduction, with isolated reports of transient, spontaneously resolving complete AV block (see sections 4.4 and 4.8).

If the overdose constitutes first exposure to Gilenya, it is important to monitor patients with a continuous (real time) ECG and hourly measurement of heart rate and blood pressure, at least during the first 6 hours (see section 4.4).

Additionally, if after 6 hours the heart rate is <45 bpm in adults, <55 bpm in paediatric patients aged 12 years and above, or <60 bpm in paediatric patients aged 10 years to below 12 years, or if the ECG at 6 hours after the first dose shows second degree or higher AV block, or if it shows a QTc interval ≥500 msec, monitoring should be extended at least for overnight and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring including overnight monitoring.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA27

Mechanism of action

Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptor 1 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptor 1 located on neural cells in the central nervous system (CNS). By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. Animal studies have shown that 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 act via interaction with S1P receptors on neural cells.

Pharmacodynamic effects

Within 4-6 hours after the first dose of fingolimod 0.5 mg, the lymphocyte count decreases to approximately 75% of baseline in peripheral blood. With continued daily dosing, the lymphocyte count continues to decrease over a two-week period, reaching a minimal count of approximately 500 cells/microlitre or approximately 30% of baseline. Eighteen percent of patients reached a minimal count below 200 cells/microlitre 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.

Fingolimod causes a transient reduction in heart rate and decrease in atrioventricular conduction at treatment initiation (see sections 4.4 and 4.8). The maximal decline in heart rate is seen within 6 hours post dose, with 70% of the negative chronotropic effect achieved on the first day. With continued administration heart rate returns to baseline within one month. The decrease in heart rate induced by fingolimod can be reversed by parenteral doses of atropine or isoprenaline. Inhaled salmeterol has also been shown to have a modest positive chronotropic effect. With initiation of fingolimod treatment there is an increase in atrial premature contractions, but there is no increased rate of atrial fibrillation/flutter or ventricular arrhythmias or ectopy. Fingolimod treatment is not associated with a decrease in cardiac output. Autonomic responses of the heart, including diurnal variation of heart rate and response to exercise are not affected by fingolimod treatment.

S1P4 could partially contribute to the effect but was not the main receptor responsible for the lymphoid depletion. The mechanism of action of bradycardia and vasoconstriction were also studied *in vitro* in guinea pigs and isolated rabbit aorta and coronary artery. It was concluded that bradycardia could be mediated primarily by activation of inward-rectifying potassium channel or G-protein activated inwardly rectifying K^+ channel (IKACh/GIRK) and that vasoconstriction seems to be mediated by a Rho kinase and calcium dependent mechanism.

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

Clinical efficacy and safety

The efficacy of fingolimod has been demonstrated in two studies which evaluated once-daily doses of fingolimod 0.5 mg and 1.25 mg in adult patients with relapsing-remitting multiple sclerosis (RRMS). Both studies included adult patients who had experienced ≥2 relapses in the prior 2 years or ≥1 relapse during the prior year. Expanded Disability Status Score (EDSS) was between 0 and 5.5. A third study targeting the same adult patient population was completed after registration of Gilenya.

Study D2301 (FREEDOMS) was a 2-year randomised, double-blind, placebo-controlled Phase III study of 1,272 patients (n=425 on 0.5 mg, 429 on 1.25 mg, 418 on placebo). Median values for baseline characteristics were: age 37 years, disease duration 6.7 years, and EDSS score 2.0. Outcome results are shown in Table 1. There were no significant differences between the 0.5 mg and the 1.25 mg doses as regards either endpoint.

Table 1 Study D2301 (FREEDOMS): main results

	Fingolimod 0.5 mg	**Placebo**
Clinical endpoints		
Annualised relapse rate (primary endpoint)	0.18**	0.40
Percentage of patients remaining relapse-free at 24 months	70%**	46%
Proportion with 3-month Confirmed Disability Progression† Hazard ratio (95% CI)	17% 0.70 (0.52, 0.96)*	24%
MRI endpoints		
Median (mean) number of new or enlarging T2 lesions over 24 months	0.0 (2.5)**	5.0 (9.8)
Median (mean) number of Gd-enhancing lesions at month 24	0.0 (0.2)**	0.0 (1.1)
Median (mean) % change in brain volume over 24 months	-0.7 (-0.8)**	-1.0 (-1.3)
† Disability progression defined as 1-point increase in EDSS confirmed 3 months later ** $p<0.001$, *$p<0.05$ compared to placebo All analyses of clinical endpoints were intent-to-treat. MRI analyses used evaluable dataset.		

Patients who completed the 24-month core FREEDOMS study could enter a dose-blinded extension study (D2301E1) and receive fingolimod. In total, 920 patients entered (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). After 12 months (month 36), 856 patients (93%) were still enrolled. Between months 24 and 36, the annualised relapse rate (ARR) for patients on fingolimod 0.5 mg in the core study who remained on 0.5 mg was 0.17 (0.21 in the core study). The ARR for patients who switched from placebo to fingolimod 0.5 mg was 0.22 (0.42 in the core study).

Comparable results were shown in a replicate 2-year randomised, double-blind, placebo-controlled Phase III study on fingolimod in 1,083 patients (n=358 on 0.5 mg, 370 on 1.25 mg, 355 on placebo) with RRMS (D2309; FREEDOMS 2). Median values for baseline characteristics were: age 41 years, disease duration 8.9 years, EDSS score 2.5.

Table 2 Study D2309 (FREEDOMS 2): main results

	Fingolimod 0.5 mg	**Placebo**
Clinical endpoints		
Annualised relapse rate (primary endpoint)	0.21**	0.40
Percentage of patients remaining relapse-free at 24 months	71.5%**	52.7%
Proportion with 3-month Confirmed Disability Progression† Hazard ratio (95% CI)	25% 0.83 (0.61, 1.12)	29%
MRI endpoints		
Median (mean) number of new or enlarging T2 lesions over 24 months	0.0 (2.3)**	4.0 (8.9)
Median (mean) number of Gd-enhancing lesions at month 24	0.0 (0.4)**	0.0 (1.2)
Median (mean) % change in brain volume over 24 months	-0.71 (-0.86)**	-1.02 (-1.28)
† Disability progression defined as 1-point increase in EDSS confirmed 3 months later ** $p<0.001$ compared to placebo All analyses of clinical endpoints were intent-to-treat. MRI analyses used evaluable dataset.		

Study D2302 (TRANSFORMS) was a 1-year randomised, double-blind, double-dummy, active (interferon beta-1a)-controlled Phase III study of 1,280 patients (n=429 on 0.5 mg, 420 on 1.25 mg, 431 on interferon beta-1a, 30 µg by intramuscular injection once weekly). Median values for baseline characteristics were: age 36 years, disease duration 5.9 years, and EDSS score 2.0. Outcome results are shown in Table 3. There were no significant differences between the 0.5 mg and the 1.25 mg doses as regards study endpoints.

Table 3 Study D2302 (TRANSFORMS): main results

	Fingolimod 0.5 mg	**Interferon beta-1a, 30 µg**
Clinical endpoints		
Annualised relapse rate (primary endpoint)	0.16**	0.33
Percentage of patients remaining relapse-free at 12 months	83%**	71%
Proportion with 3-month Confirmed Disability Progression† Hazard ratio (95% CI)	6% 0.71 (0.42, 1.21)	8%
MRI endpoints		
Median (mean) number of new or enlarging T2 lesions over 12 months	0.0 (1.7)*	1.0 (2.6)
Median (mean) number of Gd-enhancing lesions at 12 months	0.0 (0.2)**	0.0 (0.5)
Median (mean) % change in brain volume over 12 months	-0.2 (-0.3)**	-0.4 (-0.5)
† Disability progression defined as 1-point increase in EDSS confirmed 3 months later. * $p<0.01$,** $p<0.001$, compared to interferon beta-1a All analyses of clinical endpoints were intent-to-treat. MRI analyses used evaluable dataset.		

Patients who completed the 12-month core TRANSFORMS study could enter a dose-blinded extension (D2302E1) and receive fingolimod. In total, 1,030 patients entered, however, 3 of these patients did not receive treatment (n=356 continued on 0.5 mg, 330 continued on 1.25 mg, 167 switched from interferon beta-1a to 0.5 mg and 174 from interferon beta-1a to 1.25 mg). After 12 months (month 24), 882 patients (86%) were still enrolled. Between months 12 and 24, the ARR for patients on fingolimod 0.5 mg in the core study who remained on 0.5 mg was 0.20 (0.19 in the core study). The ARR for patients who switched from interferon beta-1a to fingolimod 0.5 mg was 0.33 (0.48 in the core study).

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

Further analyses of clinical trial data demonstrate consistent treatment effects in highly active subgroups of relapsing remitting multiple sclerosis patients.

Paediatric population

The efficacy and safety of once-daily doses of fingolimod 0.25 mg or 0.5 mg (dose selected based on body weight and exposure measurements) have been established in paediatric patients aged 10 to <18 years with relapsing-remitting multiple sclerosis.

Study D2311 (PARADIGMS) was a double-blind, double-dummy, active-controlled study with flexible duration up to 24 months, with 215 patients 10 to <18 years old (n=107 on fingolimod, 108 on interferon beta-1a 30 µg by intramuscular injection once weekly).

Median values for baseline characteristics were: age 16 years, median disease duration 1.5 years and EDSS score 1.5. The majority of patients were Tanner stage 2 or higher (94.4%) and were >40 kg (95.3%). Overall, 180 (84%) of patients completed the core phase on study drug (n=99 [92.5%] on fingolimod, 81 [75%] on interferon beta-1a). Outcome results are shown in Table 4.

Table 4 Study D2311 (PARADIGMS): main results

	Fingolimod 0.25 mg or 0.5 mg	**Interferon beta-1a 30 µg**
Clinical endpoints	N=107	N=107[#]
Annualised relapse rate (primary endpoint)	0.122**	0.675
Percentage of patients remaining relapse-free at 24 months	85.7**	38.8
MRI endpoints		
Annualised rate of the number of new or newly enlarging T2 lesions	n=106	n=102
Adjusted mean	4.393**	9.269
Number of Gd-enhancing T1 lesions per scan up to month 24	n=106	n=101
Adjusted mean	0.436**	1.282
Annualised rate of brain atrophy from baseline up to month 24	n=96	n=89
Least Square Mean	-0.48*	-0.80

One patient randomised to receive interferon beta-1a by intramuscular injection was unable to swallow the double-dummy medication and discontinued from study. The patient was excluded from the full analysis and safety set.
* $p<0.05$, ** $p<0.001$, compared to interferon beta-1a.
All analyses of clinical endpoints were on the full analysis set.

5.2 Pharmacokinetic properties

Pharmacokinetic data were obtained in healthy adult volunteers, in renal transplant adult patients and in multiple sclerosis adult patients.

The pharmacologically active metabolite responsible for efficacy is fingolimod phosphate.

Absorption

Fingolimod absorption is slow (t_{max} of 12-16 hours) and extensive (≥85%). The apparent absolute oral bioavailability is 93% (95% confidence interval: 79-111%). Steady-state-blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10-fold greater than with the initial dose.

Food intake does not alter C_{max} or exposure (AUC) of fingolimod. Fingolimod phosphate C_{max} was slightly decreased by 34% but AUC was unchanged. Therefore, Gilenya may be taken without regard to meals (see section 4.2).

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%).

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1,200±260 litres. A study in four healthy subjects who received a single intravenous dose of a radioiodolabelled analogue of fingolimod demonstrated that fingolimod penetrates into the brain. In a study in 13 male multiple sclerosis patients who received fingolimod 0.5 mg/day, the mean amount of fingolimod (and fingolimod phosphate) in seminal ejaculate, at steady-state, was approximately 10,000 times lower than the oral dose administered (0.5 mg).

Biotransformation

Fingolimod is transformed in humans by reversible stereoselective phosphorylation to the pharmacologically active (S)-enantiomer of fingolimod phosphate. Fingolimod is eliminated by oxidative biotransformation catalysed mainly via CYP4F2 and possibly other isoenzymes and subsequent fatty acid-like degradation to inactive metabolites. Formation of pharmacologically inactive non-polar ceramide analogues of fingolimod was also observed. The main enzyme involved in the metabolism of fingolimod is partially identified and may be either CYP4F2 or CYP3A4.

Following single oral administration of [^{14}C] fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the AUC up to 34 days post dose of total radiolabelled components, are fingolimod itself (23%), fingolimod phosphate (10%), and inactive metabolites (M3 carboxylic acid metabolite (8%), M29 ceramide metabolite (9%) and M30 ceramide metabolite (7%)).

Elimination

Fingolimod blood clearance is 6.3±2.3 l/h, and the average apparent terminal elimination half-life ($t_{1/2}$) is 6-9 days. Blood levels of fingolimod and fingolimod phosphate decline in parallel in the terminal phase, leading to 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 apparently dose proportional manner after multiple once-daily doses of 0.5 mg or 1.25 mg.

Characteristics in specific groups of patients

Gender, ethnicity and renal impairment
The pharmacokinetics of fingolimod and fingolimod-phosphate do not differ in males and females, in patients of different ethnic origin, or in patients with mild to severe renal impairment.

Hepatic impairment
In subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, and C), no change in fingolimod C_{max} was observed, but fingolimod AUC was increased respectively by 12%, 44%, and 103%. In patients with severe hepatic impairment (Child-Pugh class C), fingolimod-phosphate C_{max} was decreased by 22% and AUC was not substantially changed. The pharmacokinetics of fingolimod-phosphate were not evaluated in patients with mild or moderate hepatic impairment.

The apparent elimination half-life of fingolimod is unchanged in subjects with mild hepatic impairment, but is prolonged by about 50% in patients with moderate or severe hepatic impairment.

Fingolimod should not be used in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.3). Fingolimod should be introduced cautiously in mild and moderate hepatic impaired patients (see section 4.2).

Elderly population
Clinical experience and pharmacokinetic information in patients aged above 65 years are limited. Gilenya should be used with caution in patients aged 65 years and over (see section 4.2).

Paediatric population

In paediatric patients (10 years of age and above), fingolimod-phosphate concentrations increase in an apparent dose proportional manner between 0.25 mg and 0.5 mg.

Fingolimod-phosphate concentration at steady state is approximately 25% lower in paediatric patients (10 years of age and above) following daily administration of 0.25 mg or 0.5 mg fingolimod compared to the concentration in adult patients treated with fingolimod 0.5 mg once daily.

There are no data available for paediatric patients below 10 years old.

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 at doses of 0.15 mg/kg and higher in a 2-year study, representing an approximate 4-fold margin based on the human systemic exposure (AUC) at a daily dose of 0.5 mg.

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

Fingolimod was neither mutagenic nor clastogenic in animal studies.

Fingolimod had no effect on sperm count/motility or on fertility in male and female rats up to the highest dose tested (10 mg/kg), representing an approximate 150-fold margin based on human systemic exposure (AUC) at a daily dose of 0.5 mg.

Fingolimod was teratogenic in the rat when given at doses of 0.1 mg/kg or higher. Drug exposure in rats at this dose was similar to that in patients at the therapeutic dose (0.5 mg). The most common foetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. The teratogenic potential in rabbits could not be fully assessed, however 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 was seen at 5 mg/kg. Drug exposure in rabbits at these doses was similar to that in patients.

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.

Fingolimod was excreted in milk of treated animals during lactation at concentrations 2-fold to 3-fold higher than that found in maternal plasma. Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

Juvenile animal studies

Results from two toxicity studies in juvenile rats showed slight effects on neurobehavioural response, delayed sexual maturation and a decreased immune response to repeated stimulations with keyhole limpet haemocyanin (KLH), which were not considered adverse. Overall, the treatment-related effects of fingolimod in juvenile animals were comparable to those seen in adult rats at similar dose levels, with the exception of changes in bone mineral density and neurobehavioural impairment (reduced auditory startle response) observed at doses of 1.5 mg/kg and higher in juvenile animals and the absence of smooth muscle hypertrophy in the lungs of the juvenile rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gilenya 0.25 mg hard capsules

Capsule fill
Mannitol
Hydroxypropylcellulose
Hydroxypropylbetadex
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink
Shellac (E904)
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonia solution, concentrated (E527)

Gilenya 0.5 mg hard capsules

Capsule fill
Mannitol
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Yellow iron oxide (E172)

Printing ink
Shellac (E904)
Ethanol, anhydrous
Isopropyl alcohol
Butyl alcohol
Propylene glycol (E1520)
Purified water
Ammonia solution, concentrated (E527)
Potassium hydroxide
Black iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Dimethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Gilenya 0.25 mg hard capsules

2 years

Gilenya 0.5 mg hard capsules

2 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Gilenya 0.25 mg hard capsules

PVC/PVDC/aluminium blister packs containing 7 or 28 hard capsules.
PVC/PVDC/aluminium perforated unit dose blister packs containing 7x 1 hard capsules.

Gilenya 0.5 mg hard capsules

PVC/PVDC/aluminium blister packs containing 7, 28 or 98 hard capsules.
PVC/PVDC/aluminium blister packs containing 7 or 28 hard capsules presented in wallets or multipacks containing 84 (3 packs of 28) hard capsules presented in wallets.
PVC/PVDC/aluminium perforated unit dose blister packs containing 7x 1 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Gilenya 0.25 mg hard capsules

EU/1/11/677/007-009

Gilenya 0.5 mg hard capsules

EU/1/11/677/001-006
EU/1/11/677/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 March 2011
Date of latest renewal: 16 November 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuremberg
Germany

Lek Pharmaceuticals d.d.
Verovskova Ulica 57
Ljubljana, 1526
Slovenia

Novartis Pharmaceutical Manufacturing LLC
Verovskova Ulica 57
Ljubljana, 1000
Slovenia

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of GILENYA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each Member State (MS) where GILENYA is marketed, all physicians who intend to prescribe GILENYA are provided with an updated Physician Information Pack, including:

1. Summary of Product Characteristics (SmPC);
2. Physician's checklist for adult and pediatric patients, to consider prior to prescribing GILENYA, including information about the Pregnancy Exposure Registry;
3. The Patient / Parent / Caregiver's guide, to be provided to all patients, their parents (or legal representatives), and caregivers.
4. The pregnancy-specific patient reminder card, to be provided to all patients, their parents (or legal representatives), and caregivers, as applicable.

Physician's checklist

The physician's checklist shall contain the following key messages:

- Monitoring requirements at treatment initiation:
  Before first dose
  - Perform baseline ECG prior to the first dose of GILENYA;
  - Perform blood pressure measurement prior to the first dose of GILENYA;
  - Perform liver function test, including transaminases and bilirubin, prior to (within 6 months) treatment initiation;
  - Arrange ophthalmological assessment before starting GILENYA treatment in patients with diabetes mellitus or with a history of uveitis.
  - A negative pregnancy test result must be confirmed prior to starting treatment.

  Until 6 hours after first dose
  - Monitor the patient for 6 hours after the first dose of GILENYA has been administered for signs and symptoms of bradycardia, including hourly pulse and blood pressure checks. Continuous (real time) ECG monitoring is recommended;
  - Perform an ECG at the end of the 6-hour monitoring period.

  >6 to 8 hours after first dose
  - If, at the 6-hour time point, the heart rate is at the lowest value following the first dose, extend heart rate monitoring for at least 2 more hours and until the heart rate increases again.

- Recommendation for re-initiating GILENYA therapy after treatment interruption:
  The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:
  - One day or more during the first 2 weeks of treatment;
  - More than 7 days during weeks 3 and 4 of treatment;
  - More than 2 weeks after at least 1 month of treatment.

- Recommendation for overnight monitoring after the first dose (or if the first dose monitoring applies during treatment re-initiation):
    - Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients requiring pharmacological intervention during monitoring at treatment initiation/re-initiation. Repeat the first dose monitoring after the second dose of GILENYA;
    - Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients:
        - With third degree AV block occurring at any time;
        - Where at the 6-hour time point:
            a. Heart rate <45 bpm, <55 bpm in paediatric patients aged 12 years old and above, or <60 bpm in pediatric patients 10 to below 12 years of age;
            b. New onset second degree or higher AV block;
            c. QTc interval ≥500 msec.

- GILENYA is contraindicated in patients with:
    - Known immunodeficiency syndrome;
    - Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies);
    - Severe active infections, active chronic infections (hepatitis, tuberculosis);
    - Known active malignancies;
    - Severe liver impairment (Child-Pugh class C);
    - In the previous 6 months, myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure;
    - Severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia or class III anti-arrhythmic medicinal products;
    - Second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not wear a pacemaker;
    - Patients with a baseline QTc interval ≥500 msec;
    - Pregnant women and women of childbearing potential not using effective contraception;
    - Hypersensitivity to the active substance or to any of the excipients.

- GILENYA is not recommended in patients with:
    - Sino-atrial heart block;
    - QTc prolongation >470 msec (adult females), QTc >460 msec (pediatric females) or >450 msec (adult and pediatric males);
    - History of cardiac arrest;
    - Severe sleep apnea;
    - History of symptomatic bradycardia;
    - History of recurrent syncope;
    - Uncontrolled hypertension.

  If GILENYA treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to determine appropriate monitoring, at least overnight extended monitoring is recommended.

- GILENYA is not recommended in patients concomitantly taking medicines known to decrease the heart rate. If GILENYA treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to switch to non heart-rate-lowering therapy or, if not possible, to determine appropriate monitoring. At least overnight extended monitoring is recommended.

- GILENYA reduces peripheral blood lymphocyte counts. Peripheral lymphocyte count (CBC) should be checked in all patients prior to initiation (within 6 months or after discontinuation of prior therapy) and monitored during treatment with GILENYA. Treatment should be interrupted if lymphocyte count is confirmed as <0.2x109/L. The approved dosing of 0.5 mg once daily (or 0.25 mg once daily in pediatric patients 10 years of age and above with a body weight of ≤40 kg) when restarting Gilenya should be administered. Other dosing regimens have not been approved.

- GILENYA has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas (including mycosis fungoides) and other malignancies, particularly those of the skin. Surveillance should include vigilance for both skin malignancies and mycosis fungoides. Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis.

    - Treatment initiation in patients with severe active infection should be delayed until the infection is resolved. Suspension of treatment during serious infections should be considered. Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects. For the same reason, a decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration.

    - Vigilance for basal cell carcinoma and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma is recommended, with skin examination prior to treatment initiation and then every 6 to 12 months taking into consideration clinical judgement. Patients should be referred to a dermatologist if suspicious lesions are detected. Caution patients against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

- Specific recommendations regarding vaccination for patients initiating GILENYA treatment.

    - Check varicella zoster virus (VZV) antibody status in patients without a healthcare professional confirmed history of chickenpox or documentation of a full course of varicella vaccination. If negative, a full course of vaccination with varicella vaccine is recommended and treatment initiation should be delayed for 1 month to allow full effect of vaccination to occur.

- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during and for up to two months after treatment with GILENYA.

    - Prompt diagnostic evaluation should be performed in patient with symptoms and signs consistent with encephalitis, meningitis or meningoencephalitis; appropriate treatment, if diagnosed, should be initiated.

    - Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex virus (HSV) and VZV were reported while on GILENYA treatment.

    - Reports of cryptococcal meningitis (sometimes fatal) have been received after approximately 2-3 years of treatment, although an exact relationship with the duration of treatment is unknown.

    - Cases of progressive multifocal leukoencephalopathy (PML) have occurred after approximately 2-3 years of monotherapy treatment although an exact relationship with the duration of treatment is unknown.
      Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment with GILENYA should be suspended until PML has been excluded.

    - Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in the post-marketing setting. Cancer screening, including Pap test, and vaccination for HPV-related cancer is recommended for patients, as per standard of care.

- A full ophthalmological assessment should be considered:
    - 3-4 months after starting GILENYA therapy for the early detection of visual impairment due to drug-induced macular oedema;
    - During treatment with GILENYA in patients with diabetes mellitus or with a history of uveitis.

- GILENYA is teratogenic. It is contraindicated in women of childbearing potential (including female adolescents) not using effective contraception and in pregnant women.
    - A negative pregnancy test result must be confirmed prior to starting treatment, and it must be repeated at suitable intervals.
    - Women of child-bearing potential, including adolescent females, their parents (or legal representatives), and caregivers, should be counselled before treatment initiation and regularly thereafter about the serious risks of GILENYA to the foetus, facilitated by the pregnancy-specific patient reminder card.
    - Women of childbearing potential must use effective contraception during treatment and for two months following treatment discontinuation.
    - While on treatment, women must not become pregnant. If a woman becomes pregnant while on treatment, GILENYA must be discontinued. When stopping GILENYA therapy due to pregnancy or for planning a pregnancy, the possible return of disease activity should be considered. Medical advice should be given regarding the risk of harmful effects to the foetus associated with GILENYA treatment and ultrasonography examinations should be performed.
    - GILENYA must be stopped 2 months before planning a pregnancy.
    - Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves, in the GILENYA pregnancy registry.
- Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported. Therefore, liver function should be monitored carefully.
    - Before initiation of treatment, recent (i.e. within last 6 months) transaminase and bilirubin levels should be available;
    - During treatment, in the absence of clinical symptoms, liver transaminases and serum bilirubin should be monitored at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter until 2 months after Gilenya discontinuation;
    - During treatment, in the absence of clinical symptoms, if liver transaminases are greater than 3 but less than 5 times the upper limit of normal (ULN) without increase in serum bilirubin, more frequent monitoring including serum bilirubin and alkaline phosphatase (ALP) measurement should be instituted to determine if further increases occur and in order to discern if an alternative aetiology of hepatic dysfunction is present. If liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin, GILENYA should be discontinued. Hepatic monitoring should be continued. If serum levels return to normal (including if an alternative cause of the hepatic dysfunction is discovered), GILENYA may be restarted based on a careful benefit-risk assessment of the patient.

- The approved dosing of 0.5 mg daily (or 0.25 mg once daily in pediatric patients 10 years of age and above with a body weight of ≤40 kg) should be administered. Other dosing regimens have not been approved.

- In the post-marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping GILENYA. The possibility of recurrence of exceptionally high disease activity should be considered.

- Cases of seizure, including status epilepticus, have been reported. Physicians should be vigilant for seizures and especially in those patients with underlying conditions or with a pre-existing history or family history of epilepsy.

- Physicians should reassess on an annual basis the benefit of GILENYA treatment versus risk in each patient, especially pediatric patients.

- Physicians should provide patients/parents/caregivers with the patient/parents/caregiver guide and with the pregnancy-specific patient reminder card.

The safety profile in pediatric patients is similar to adults and therefore the warnings and precautions in adults also apply for pediatric patients.

Specifically with pediatric patients, physicians should also:
- Assess Tanner staging and measure height and weight as per standard of care;
- Perform cardiovascular monitoring;
- Take precautions when the first dose is administered / patients are switched from 0.25 to 0.5 mg daily, due to the potential for bradyarrhythmia;
- Monitor the patient for sign and symptoms of depression and anxiety;
- Emphasize treatment compliance and misuse to patients, especially about treatment interruption and the importance of repeating cardiovascular monitoring;
- Emphasize GILENYA immunosuppressive effects;
- Consider a complete vaccination schedule before starting GILENYA;
- Provide guidance on seizure monitoring.

Patient / Parent / Caregiver guide

The patient/parents/caregiver guide shall contain the following key messages:
- What GILENYA is and how it works;
- What multiple sclerosis is;
- Patients should read the package leaflet thoroughly before starting treatment and should keep it in case they need to refer to it again during treatment;
- Importance of reporting adverse reactions;
- Patients should have a baseline ECG and blood pressure measurement prior to receiving the first dose of GILENYA;
- Heart rate should be monitored for 6 or more hours after the first dose of GILENYA, including hourly pulse and blood pressure checks. Patients may be monitored with continuous ECG during the first 6 hours. An ECG at 6 hours should also be performed and, in some circumstances, monitoring may involve an overnight stay;
- Patients should call their doctor in case of treatment interruption as the first dose monitoring may need to be repeated, depending on duration of interruption and time since starting of GILENYA treatment;
- Patients should report immediately symptoms indicating low heart rate (such as dizziness, vertigo, nausea or palpitations) after the first dose of GILENYA;
- GILENYA is not recommended in patients with cardiac disease or those taking medicines concomitantly known to decrease heart rate, and they should tell any doctor they see that they are being treated with GILENYA;

- Signs and symptoms of infection, which should be immediately reported to the prescriber physician during and up to two months after GILENYA treatment, including the following:
    - Headache accompanied by stiff neck, sensitivity to light, fever, flu-like symptoms, nausea, rash, shingles and/or confusion or seizures (fits) (may be symptoms of meningitis and/or encephalitis, either caused by a fungal or viral infection);
    - Symptoms such as weakness, visual changes, or new/worsening MS symptoms (may be symptoms of progressive multifocal leukoencephalopathy [PML]).
- The need to undergo cancer screening, including Pap test, and vaccination for HPV-related cancer, as per standard of care, will be assessed by the prescriber physician;
- Any symptoms of visual impairment should be reported immediately to the prescriber during and for up to two months after the end of treatment with GILENYA;
- GILENYA is teratogenic. Women of child-bearing potential, including adolescent females, should:
    - Be informed before treatment initiation and regularly thereafter by their physician about GILENYA's serious risks to the foetus, and about the contraindication in pregnant women and in women of childbearing potential not using effective contraception, facilitated by the pregnancy-specific patient reminder card;
    - Have a negative pregnancy test before starting GILENYA;
    - Be using effective contraception during and for at least two months following discontinuation of GILENYA treatment;
    - Report immediately to the prescribing physician any (intended or unintended) pregnancy during and up to two months following discontinuation of GILENYA treatment;
- A liver function test should be performed prior to treatment initiation; liver function monitoring should be performed at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter, until 2 months after Gilenya discontinuation. Patients should inform their doctor if they notice yellowing of their skin or the whites of their eyes, abnormally dark urine, pain on the right side of the stomach area, tiredness, feeling less hungry than usual or unexplained nausea and vomiting as these can be signs of liver injury;
- Skin cancers have been reported in multiple sclerosis patients treated with GILENYA. Patients should inform their doctor immediately if any skin nodules (e.g., shiny, pearly nodules), patches or open sores that do not heal within weeks are noted. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g., unusual moles) with a change in color, shape or size over time;
- Seizure may occur. The doctor should be informed about a pre-existing history or family history of epilepsy;
- Stopping GILENYA therapy may result in return of disease activity. The prescribing physician should decide whether and how the patient should be monitored after stopping GILENYA.

Specifically for Pediatric patients:

The following should be considered:

- Physicians should assess Tanner staging and measure height and weight as per standard of care;
- Precautions should be taken during the first dose of GILENYA and when patients are switched from 0.25 to 0.5 mg daily;
- Depression and anxiety are known to occur with increased frequency in the multiple sclerosis population and have been reported also in pediatric patients treated with GILENYA;
- Cardiac monitoring guidance;
- Patients should ensure medication compliance and avoid misuse, especially treatment interruption, and repeat cardiac monitoring;
- Signs and symptoms of infection;
- Seizure monitoring guidance.

Pregnancy-specific patient reminder card

The pregnancy-specific patient reminder card shall contain the following key messages:

- GILENYA is contraindicated during pregnancy and in women of childbearing potential not using effective contraception.
- Doctors will provide counselling before treatment initiation and regularly thereafter regarding the teratogenic risk of GILENYA and required actions to minimise this risk.
- Patients must use effective contraception while taking GILENYA.
- A pregnancy test must be carried out and negative results verified by the doctor before starting treatment. It must be repeated at suitable intervals.
- Patients will be informed by their doctor of the need for effective contraception while on treatment and for 2 months after discontinuation.
- Doctors will provide counselling in the event of pregnancy and evaluation of the outcome of any pregnancy.
- While on treatment, women must not become pregnant. If a woman becomes pregnant or wants to become pregnant, GILENYA must be discontinued.
- Patients should inform their doctor straight away if there is worsening of multiple sclerosis after stopping treatment with GILENYA.
- Women exposed to GILENYA during pregnancy are encouraged to join the pregnancy exposure registry that monitors outcomes of pregnancy.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.25 mg hard capsules
fingolimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 0.25 mg fingolimod (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 hard capsules
28 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow each capsule whole

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/008 28 capsules
EU/1/11/677/009 7 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.25 mg hard capsules
fingolimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK CONTAINING SINGLE-UNIT-DOSE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.25 mg hard capsules
fingolimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 0.25 mg fingolimod (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 x 1 hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow each capsule whole

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/007 7 x 1 hard capsule

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

SINGLE-UNIT-DOSE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.25 mg hard capsules
fingolimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.5 mg hard capsules
fingolimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 0.5 mg fingolimod (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 hard capsules
28 hard capsules
98 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow each capsule whole

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/005	28 capsules
EU/1/11/677/006	98 capsules
EU/1/11/677/010	7 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.5 mg hard capsules
fingolimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK – WALLET

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.5 mg hard capsules
fingolimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 0.5 mg fingolimod (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 hard capsules
28 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow each capsule whole

To open: While pressing tab 1 firmly, pull on tab 2.

Week
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/002	7 capsules
EU/1/11/677/003	28 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK CONTAINING WALLETS (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.5 mg hard capsules
fingolimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 0.5 mg fingolimod (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 84 (3 packs of 28) hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow each capsule whole

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/004 84 capsules (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK – WALLET (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.5 mg hard capsules
fingolimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 0.5 mg fingolimod (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow each capsule whole

To open: While pressing tab 1 firmly, pull on tab 2.

Week
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/004 84 capsules (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR WALLET

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.5 mg
fingolimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK CONTAINING SINGLE-UNIT-DOSE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.5 mg hard capsules
fingolimod

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One capsule contains 0.5 mg fingolimod (as hydrochloride).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 x 1 hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow each capsule whole

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/001 7 x 1 hard capsule

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

SINGLE-UNIT-DOSE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.5 mg hard capsules
fingolimod

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Gilenya 0.25 mg hard capsules
Gilenya 0.5 mg hard capsules
fingolimod

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Gilenya is and what it is used for

What Gilenya is
Gilenya contains the active substance fingolimod.

What Gilenya is used for
Gilenya is used in adults and in children and adolescents (10 years of age and above) to treat relapsing-remitting multiple sclerosis (MS), more specifically in:
- Patients who have failed to respond despite treatment with an MS treatment.

or
- Patients who have rapidly evolving severe MS.

Gilenya does not cure MS, but it helps to reduce the number of relapses and to slow down the progression of physical disabilities due to MS.

What is multiple sclerosis
MS is a long-term condition that affects the central nervous system (CNS), comprised of the brain and spinal cord. In MS inflammation destroys the protective sheath (called myelin) around the nerves in the CNS and stops the nerves from working properly. This is called demyelination.

Relapsing-remitting MS is characterised by repeated attacks (relapses) of nervous system symptoms that reflect inflammation within the CNS. Symptoms vary from patient to patient but typically involve walking difficulties, numbness, vision problems or disturbed balance. Symptoms of a relapse may disappear completely when the relapse is over, but some problems may remain.

How Gilenya works
Gilenya helps to protect against attacks on the CNS by the immune system by reducing the ability of some white blood cells (lymphocytes) to move freely within the body and by stopping them from reaching the brain and spinal cord. This limits nerve damage caused by MS. Gilenya also reduces some of the immune reactions of your body.

2. What you need to know before you take Gilenya

Do not take Gilenya
- if you have a **lowered immune response** (due to an immunodeficiency syndrome, a disease or to medicines that suppress the immune system).
- if you have a **severe active infection or active chronic infection** such as hepatitis or tuberculosis.
- if you have an **active cancer**.
- if you have **severe liver problems**.
- **if, in the last 6 months, you have had heart attack, angina, stroke or warning of a stroke or certain types of heart failure**.
- if you have certain types of **irregular or abnormal heartbeat** (arrhythmia), including patients in whom the electrocardiogram (ECG) shows prolonged QT interval before starting Gilenya.
- **if you are taking or have recently taken medicine for irregular heartbeat** such as quinidine, disopyramide, amiodarone or sotalol.
- if you are **pregnant** or **a woman of childbearing potential not using effective contraception**.
- **if you are allergic** to fingolimod or any of the other ingredients of this medicine (listed in section 6).

If this applies to you or you are unsure, **talk to your doctor before taking Gilenya**.

Warnings and precautions
Talk to your doctor before taking Gilenya:
- **if you have severe breathing problems during sleep (severe sleep apnoea).**
- **if you have been told you have an abnormal electrocardiogram.**
- **if you suffer from symptoms of slow heart rate (e.g. dizziness, nausea, or palpitations)**.
- **if you are taking or have recently taken medicines that slow your heart rate** (such as beta blockers, verapamil, diltiazem or ivabradine, digoxin, anticholinesteratic agents or pilocarpine).
- **if you have a history of sudden loss of consciousness or fainting (syncope)**.
- **if you plan to get vaccinated**.
- **if you have never had chickenpox**.
- **if you have or have had visual disturbances** or other signs of swelling in the central vision area (macula) at the back of the eye (a condition known as macular oedema, see below), inflammation or infection of the eye (uveitis), **or if you have diabetes** (which can cause eye problems).
- **if you have liver problems**.
- if you have **high blood pressure that cannot be controlled by medicines**.
- if you have **severe lung problems** or smoker's cough.

If any of these applies to you or you are unsure, **talk to your doctor before taking Gilenya.**

Slow heart rate (bradycardia) and irregular heartbeat
At the beginning of treatment or after taking the first dose of 0.5 mg when you switch from a 0.25 mg daily dose, Gilenya causes the heart rate to slow down. As a result, you may feel dizzy or tired, or be consciously aware of your heartbeat, or your blood pressure may drop. **If these effects are severe, tell your doctor, because you may need treatment right away.** Gilenya can also cause an irregular heartbeat, especially after the first dose. Irregular heartbeat usually returns to normal in less than one day. Slow heart rate usually returns to normal within one month. During this period, no clinically significant heart rate effects are usually expected.

Your doctor will ask you to stay at the surgery or clinic for at least 6 hours, with hourly pulse and blood pressure measurements, after taking the first dose of Gilenya or after taking the first dose of 0.5 mg when you switch from a 0.25 mg daily dose, so that appropriate measures can be taken in the event of side effects that occur at the start of treatment. You should have an electrocardiogram performed prior to the first dose of Gilenya and after the 6-hour monitoring period. Your doctor may monitor your electrocardiogram continuously during that time. If after the 6-hour period you have a very slow or decreasing heart rate, or if your electrocardiogram shows abnormalities, you may need to be monitored for a longer period (at least 2 more hours and possibly overnight) until these have resolved. The same may apply if you are resuming Gilenya after a break in treatment, depending on both how long the break was and how long you had been taking Gilenya before the break.

If you have, or if you are at risk for, an irregular or abnormal heartbeat, if your electrocardiogram is abnormal, or if you have heart disease or heart failure, Gilenya may not be appropriate for you.

If you have a history of sudden loss of consciousness or decreased heart rate, Gilenya may not be appropriate for you. You will be evaluated by a cardiologist (heart specialist) to advise how you should start treatment with Gilenya, including overnight monitoring.

If you are taking medicines that can cause your heart rate to decrease, Gilenya may not be appropriate for you. You will need to be evaluated by a cardiologist, who will check whether you can be switched to alternative medicine that does not decrease your heart rate in order to allow treatment with Gilenya. If such a switch is impossible, the cardiologist will advise how you should start treatment with Gilenya, including overnight monitoring.

<u>If you have never had chickenpox</u>
If you have never had chickenpox, your doctor will check your immunity against the virus that causes it (varicella zoster virus). If you are not protected against the virus, you may need a vaccination before you start treatment with Gilenya. If this is the case, your doctor will delay the start of treatment with Gilenya until one month after the full course of vaccination is completed.

<u>Infections</u>
Gilenya lowers the white blood cell count (particularly the lymphocyte count). White blood cells fight infection. While you are taking Gilenya (and for up to 2 months after you stop taking it), you may get infections more easily. Any infection that you already have may get worse. Infections could be serious and life-threatening. If you think you have an infection, have fever, feel like you have the flu, have shingles or have a headache accompanied by stiff neck, sensitivity to light, nausea, rash, and/or confusion or seizures (fits) (these may be symptoms of meningitis and/or encephalitis caused by a fungal or herpes viral infection), contact your doctor straight away, because it could be serious and life-threatening.

If you believe your MS is getting worse (e.g. weakness or visual changes) or if you notice any new symptoms, talk to your doctor straight away, because these may be the symptoms of a rare brain disorder caused by infection and called progressive multifocal leukoencephalopathy (PML). PML is a serious condition that may lead to severe disability or death. Your doctor will consider performing an MRI scan to evaluate this condition and will decide whether you need to stop taking Gilenya.

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in patients treated with Gilenya. Your doctor will consider whether you need to have a vaccination against HPV before starting treatment. If you are a woman, your doctor will also recommend HPV screening.

<u>Macular oedema</u>
Before you start Gilenya, if you have or have had visual disturbances or other signs of swelling in the central vision area (macula) at the back of the eye, inflammation or infection of the eye (uveitis) or diabetes, your doctor may want you to undergo an eye examination.

Your doctor may want you to undergo an eye examination 3 to 4 months after starting Gilenya treatment.

The macula is a small area of the retina at the back of the eye which enables you to see shapes, colours, and details clearly and sharply. Gilenya may cause swelling in the macula, a condition that is known as macular oedema. The swelling usually happens in the first 4 months of Gilenya treatment.

Your chance of developing macular oedema is higher if you have **diabetes** or have had an inflammation of the eye called uveitis. In these cases your doctor will want you to undergo regular eye examinations in order to detect macular oedema.

If you have had macular oedema, talk to your doctor before you resume treatment with Gilenya.

Macular oedema can cause some of the same vision symptoms as an MS attack (optic neuritis). Early on, there may not be any symptoms. Be sure to tell your doctor about any changes in your vision. Your doctor may want you to undergo an eye examination, especially if:
- the centre of your vision gets blurry or has shadows;
- you develop a blind spot in the centre of your vision;
- you have problems seeing colours or fine detail.

Liver function tests
If you have severe liver problems, you should not take Gilenya. Gilenya may affect your liver function. You will probably not notice any symptoms but if you notice yellowing of your skin or the whites of your eyes, abnormally dark urine (brown coloured), pain on the right side of your stomach area (abdomen), tiredness, feeling less hungry than usual or unexplained nausea and vomiting, **tell your doctor straight away**.
If you get any of these symptoms after starting Gilenya, **tell your doctor straight away.**

Before, during and after the treatment, your doctor will request blood tests to monitor your liver function. If your test results indicate a problem with your liver you may have to interrupt treatment with Gilenya.

High blood pressure
As Gilenya causes a slight elevation of blood pressure, your doctor may want to check your blood pressure regularly.

Lung problems
Gilenya has a slight effect on the lung function. Patients with severe lung problems or with smoker's cough may have a higher chance of developing side effects.

Blood count
The desired effect of Gilenya treatment is to reduce the amount of white blood cells in your blood. This will usually go back to normal within 2 months of stopping treatment. If you need to have any blood tests, tell the doctor that you are taking Gilenya. Otherwise, it may not be possible for the doctor to understand the results of the test, and for certain types of blood test your doctor may need to take more blood than usual.

Before you start Gilenya, your doctor will confirm whether you have enough white blood cells in your blood and may want to repeat a check regularly. In case you do not have enough white blood cells, you may have to interrupt treatment with Gilenya.

Posterior reversible encephalopathy syndrome (PRES)
A condition called posterior reversible encephalopathy syndrome (PRES) has been rarely reported in MS patients treated with Gilenya. Symptoms may include sudden onset of severe headache, confusion, seizures and vision changes. Tell your doctor straight away if you experience any of these symptoms during your treatment with Gilenya, because it could be serious.

Cancer
Skin cancers have been reported in MS patients treated with Gilenya. Talk to your doctor straight away if you notice any skin nodules (e.g. shiny pearly nodules), patches or open sores that do not heal within weeks. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g. unusual moles) with a change in colour, shape or size over time. Before you start Gilenya, a skin examination is required to check whether you have any skin nodules. Your doctor will also carry out regular skin examinations during your treatment with Gilenya. If you develop problems with your skin, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you to be seen on a regular basis.

A type of cancer of the lymphatic system (lymphoma) has been reported in MS patients treated with Gilenya.

Exposure to the sun and protection against the sun
Fingolimod weakens your immune system. This increases your risk of developing cancers, in particular skin cancers. You should limit your exposure to the sun and UV rays by:
- wearing appropriate protective clothing.
- regularly applying sunscreen with a high degree of UV protection.

Unusual brain lesions associated with MS relapse
Rare cases of unusually large brain lesions associated with MS relapse have been reported in patients treated with Gilenya. In case of severe relapse, your doctor will consider performing MRI to evaluate this condition and will decide whether you need to stop taking Gilenya.

Switch from other treatments to Gilenya
Your doctor may switch you directly from beta interferon, glatiramer acetate or dimethyl fumarate to Gilenya if there are no signs of abnormalities caused by your previous treatment. Your doctor may have to do a blood test in order to exclude such abnormalities. After stopping natalizumab you may have to wait for 2-3 months before starting treatment with Gilenya. To switch from teriflunomide, your doctor may advise you to wait for a certain time or to go through an accelerated elimination procedure. If you have been treated with alemtuzumab, a thorough evaluation and discussion with your doctor is required to decide if Gilenya is appropriate for you.

Women of childbearing potential
If used during pregnancy, Gilenya can harm the unborn baby. Before you start treatment with Gilenya your doctor will explain the risk to you and ask you to do a pregnancy test in order to ensure that you are not pregnant. Your doctor will give you a card which explains why you should not become pregnant while taking Gilenya. It also explains what you should do to avoid becoming pregnant while you are taking Gilenya. You must use effective contraception during treatment and for 2 months after stopping treatment (see section “Pregnancy and breastfeeding”).

Worsening of MS after stopping Gilenya treatment
Do not stop taking Gilenya or change your dose without talking to your doctor first.

Tell your doctor straight away if you think your MS is getting worse after you have stopped treatment with Gilenya. This could be serious (see “If you stop taking Gilenya” in section 3, and also section 4, “Possible side effects”).

Elderly
Experience with Gilenya in elderly patients (over 65 years) is limited. Talk to your doctor if you have any concerns.

Children and adolescents
Gilenya is not intended for use in children below 10 years old as it has not been studied in MS patients in this age group.

The warnings and precautions listed above also apply to children and adolescents. The following information is particularly important for children and adolescents and their caregivers:
- Before you start Gilenya, your doctor will check your vaccination status. If you have not had certain vaccinations, it may be necessary for you to be given them before Gilenya can be started.
- The first time you take Gilenya, or when you switch from a 0.25 mg daily dose to a 0.5 mg daily dose, your doctor will monitor your heart rate and heartbeat (see "Slow heart rate (bradycardia) and irregular heartbeat" above).
- If you experience convulsions or fits before or whilst taking Gilenya, let your doctor know.
- If you suffer from depression or anxiety or if you become depressed or anxious while you are taking Gilenya, let your doctor know. You may need to be monitored more closely.

Other medicines and Gilenya
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Tell your doctor if you are taking any of the following medicines:
- **Medicines that suppress or modulate the immune system**, including **other medicines used to treat MS**, such as beta interferon, glatiramer acetate, natalizumab, mitoxantrone, teriflunomide, dimethyl fumarate or alemtuzumab. You must not use Gilenya together with such medicines as this could intensify the effect on the immune system (see also "Do not take Gilenya").
- **Corticosteroids,** due to a possible added effect on the immune system.
- **Vaccines**. If you need to receive a vaccine, seek your doctor's advice first. During and for up to 2 months after treatment with Gilenya, you should not receive certain types of vaccine (live attenuated vaccines) as they could trigger the infection that they were supposed to prevent. Other vaccines may not work as well as usual if given during this period.
- **Medicines that slow the heartbeat** (for example beta blockers, such as atenolol). Use of Gilenya together with such medicines could intensify the effect on heartbeat in the first days after starting Gilenya.
- **Medicines for irregular heartbeat**, such as quinidine, disopyramide, amiodarone or sotalol. You must not use Gilenya if you are taking such a medicine because it could intensify the effect on irregular heartbeat (see also "Do not take Gilenya").
- **Other medicines**:
    - protease inhibitors, anti-infectives such as ketoconazole, azole antifungals, clarithromycin or telithromycin.
    - carbamazepine, rifampicine, phenobarbital, phenytoin, efavirenz or St. John's Wort (potential risk of reduced efficacy of Gilenya).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

<u>Pregnancy</u>
Do not use Gilenya during pregnancy, if you are trying to become pregnant or if you are a woman who could become pregnant and you are not using effective contraception. If Gilenya is used during pregnancy, there is a risk of harm to the unborn baby. The rate of congenital malformations observed in babies exposed to Gilenya during pregnancy is about 2 times the rate observed in the general population (in whom the rate of congenital malformations is about 2-3%). The most frequently reported malformations included cardiac, renal and musculoskeletal malformations.

Therefore, if you are a woman of childbearing potential:
- before you start treatment with Gilenya your doctor will inform you about the risk to an unborn baby and ask you to do a pregnancy test in order to ensure that you are not pregnant,

and,
- you must use effective contraception while taking Gilenya and for two months after you stop taking it to avoid becoming pregnant. Talk to your doctor about reliable methods of contraception.

Your doctor will give you a card which explains why you should not become pregnant while taking Gilenya.

If you do become pregnant while taking Gilenya, tell your doctor straight away. Your doctor will decide to stop treatment (see "If you stop taking Gilenya" in section 3, and also section 4, "Possible side effects"). Specialised pre-natal monitoring will be performed.

Breast-feeding

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

Driving and using machines
Your doctor will tell you whether your illness allows you to drive vehicles, including a bicycle, and use machines safely. Gilenya is not expected to have an influence on your ability to drive and use machines.

However, at initiation of treatment you will have to stay at the doctor's surgery or clinic for 6 hours after taking the first dose of Gilenya. Your ability to drive and use machines may be impaired during and potentially after this time period.

3. How to take Gilenya

Treatment with Gilenya will be overseen by a doctor who is experienced in the treatment of multiple sclerosis.

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose is:

Adults:
The dose is one 0.5 mg capsule per day.

Children and adolescents (10 years of age and above):
The dose depends on body weight:
- *Children and adolescents with body weight equal to or below 40 kg*: one 0.25 mg capsule per day.
- *Children and adolescents with body weight above 40 kg*: one 0.5 mg capsule per day.

Children and adolescents who start on one 0.25 mg capsule per day and later reach a stable body weight above 40 kg will be instructed by their doctor to switch to one 0.5 mg capsule per day. In this case, it is recommended to repeat the first-dose observation period.

Do not exceed the recommended dose.

Gilenya is for oral use.

Take Gilenya once a day with a glass of water. Gilenya capsules should always be swallowed intact, without opening them. Gilenya can be taken with or without food.
Taking Gilenya at the same time each day will help you remember when to take your medicine.

If you have questions about how long to take Gilenya, talk to your doctor or your pharmacist.

If you take more Gilenya than you should
If you have taken too much Gilenya, call your doctor straight away.

If you forget to take Gilenya
If you have been taking Gilenya for less than 1 month and you forget to take 1 dose for a whole day, call your doctor before you take the next dose. Your doctor may decide to keep you under observation at the time you take the next dose.

If you have been taking Gilenya for at least 1 month and have forgotten to take your treatment for more than 2 weeks, call your doctor before you take the next dose. Your doctor may decide to keep you under observation at the time you take the next dose. However, if you have forgotten to take your treatment for up to 2 weeks, you can take the next dose as planned.

Never take a double dose to make up for a forgotten dose.

If you stop taking Gilenya
Do not stop taking Gilenya or change your dose without talking to your doctor first.

Gilenya will stay in your body for up to 2 months after you stop taking it. Your white blood cell count (lymphocyte count) may also remain low during this time and the side effects described in this leaflet may still occur. After stopping Gilenya you may have to wait for 6-8 weeks before starting a new MS treatment.

If you have to restart Gilenya more than 2 weeks after you stop taking it, the effect on heart rate normally seen when treatment is first started may re-occur and you will need to be monitored at the doctor's surgery or clinic for re-initiation of treatment. Do not restart Gilenya after stopping it for more than two weeks without seeking advice from your doctor.

Your doctor will decide whether and how you need to be monitored after stopping Gilenya. Tell your doctor straight away if you think your MS is getting worse after you have stopped treatment with Gilenya. This could be serious.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

<u>Some side effects could be or could become serious</u>
Common (may affect up to 1 in 10 people)
- Coughing with phlegm, chest discomfort, fever (signs of lung disorders)
- Herpes virus infection (shingles or herpes zoster) with symptoms such as blisters, burning, itching or pain of the skin, typically on the upper body or the face. Other symptoms may be fever and weakness in the early stages of infection, followed by numbness, itching or red patches with severe pain
- Slow heartbeat (bradycardia), irregular heart rhythm
- A type of skin cancer called basal cell carcinoma (BCC) which often appears as a pearly nodule, although it can also take other forms
- Depression and anxiety are known to occur with increased frequency in the MS population and have also been reported in paediatric patients treated with Gilenya.
- Weight loss.

Uncommon (may affect up to 1 in 100 people)
- Pneumonia with symptoms such as fever, cough, difficulty breathing
- Macular oedema (swelling in the central vision area of the retina at the back of the eye) with symptoms such as shadows or blind spot in the centre of the vision, blurred vision, problems seeing colours or details
- Reduction in blood platelets which increases risk of bleeding or bruising
- Malignant melanoma (a type of skin cancer which usually develops from an unusual mole). Possible signs of melanoma include moles which may change size, shape, elevation or colour over time, or new moles. The moles may itch, bleed or ulcerate
- Convulsion, fits (more frequent in children and adolescents than in adults)

Rare (may affect up to 1 in 1,000 people)
- A condition called posterior reversible encephalopathy syndrome (PRES). Symptoms may include sudden onset of severe headache, confusion, seizures and/or vision disturbances
- Lymphoma (a type of cancer that affects the lymph system)
- Squamous cell carcinoma: a type of skin cancer which may present as a firm red nodule, a sore with crust, or a new sore on an existing scar

Very rare (may affect up to 1 in 10,000 people)
- Electrocardiogram anomaly (T-wave inversion)
- Tumour related to infection with human herpes virus 8 (Kaposi's sarcoma)

Not known (frequency cannot be estimated from the available data)
- Allergic reactions, including symptoms of rash or itchy hives, swelling of lips, tongue or face, which are more likely to occur on the day you start Gilenya treatment
- Signs of liver disease (including liver failure), such as yellowing of your skin or the whites of your eyes (jaundice), nausea or vomiting, pain on the right side of your stomach area (abdomen), dark urine (brown coloured), feeling less hungry than usual, tiredness and abnormal liver function tests. In a very small number of cases, liver failure could lead to liver transplantation
- Risk of a rare brain infection called progressive multifocal leukoencephalopathy (PML). The symptoms of PML may be similar to an MS relapse. Symptoms might also arise that you might not become aware of by yourself, such as changes in mood or behaviour, memory lapses, speech and communication difficulties, which your doctor may need to investigate further to rule out PML. Therefore, if you believe your MS is getting worse or if you or those close to you notice any new or unusual symptoms, it is very important that you speak to your doctor as soon as possible
- Cryptococcal infections (a type of fungal infection), including cryptococcal meningitis with symptoms such as headache accompanied by stiff neck, sensitivity to light, nausea, and/or confusion
- Merkel cell carcinoma (a type of skin cancer). Possible signs of Merkel cell carcinoma include flesh-coloured or bluish-red, painless nodule, often on the face, head or neck. Merkel cell carcinoma can also present as a firm painless nodule or mass. Long-term exposure to the sun and a weak immune system can affect the risk of developing Merkel cell carcinoma.
- After Gilenya treatment is stopped, symptoms of MS can return and may become worse than they were before or during treatment.
- Autoimmune form of anaemia (decreased amount of red blood cells) where red blood cells are destroyed (autoimmune haemolytic anaemia).

If you experience any of these, **tell your doctor straight away**.

Other side effects

Very common (may affect more than 1 in 10 people)
- Infection from flu virus with symptoms such as tiredness, chills, sore throat, aching in the joints or muscles, fever
- Feeling of pressure or pain in the cheeks and forehead (sinusitis)
- Headache
- Diarrhoea
- Back pain
- Blood testing showing higher levels of liver enzymes
- Cough

Common (may affect up to 1 in 10 people)
- Ringworm, a fungal infection of the skin (tinea versicolor)
- Dizziness
- Severe headache often accompanied by nausea, vomiting and sensitivity to light (migraine)
- Low level of white blood cells (lymphocytes, leucocytes)
- Weakness
- Itchy, red, burning rash (eczema)
- Itching
- Blood fat (triglycerides) level increased
- Hair loss
- Breathlessness
- Depression
- Blurred vision (see also the section on macular oedema under "Some side effects could be or could become serious")
- Hypertension (Gilenya may cause a mild increase in blood pressure)
- Muscle pain
- Joint pain

Uncommon (may affect up to 1 in 100 people)
- Low level of certain white blood cells (neutrophils)
- Depressed mood
- Nausea

Rare (may affect up to 1 in 1,000 people)
- Cancer of the lymphatic system (lymphoma)

Not known (frequency cannot be estimated from the available data)
- Peripheral swelling

If any of these affects you severely, **tell your doctor**

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Gilenya

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and blister foil after "EXP". The expiry date refers to the last day of that month.
Do not store above 25ºC.
Store in the original package in order to protect from moisture.
Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Gilenya contains
- The active substance is fingolimod.

Gilenya 0.25 mg hard capsules
- Each capsule contains 0.25 mg fingolimod (as hydrochloride).
- The other ingredients are:
  Capsule fill: mannitol, hydroxypropylcellulose, hydroxypropylbetadex, magnesium stearate.
  Capsule shell: gelatin, titanium dioxide (E171), yellow iron oxide (E172).
  Printing ink: shellac (E904), black iron oxide (E172), propylene glycol (E1520), ammonia solution, concentrated (E527).

Gilenya 0.5 mg hard capsules
- Each capsule contains 0.5 mg fingolimod (as hydrochloride).
- The other ingredients are:
  Capsule fill: mannitol, magnesium stearate.
  Capsule shell: gelatin, titanium dioxide (E171), yellow iron oxide (E172).
  Printing ink: shellac (E904), ethanol anhydrous, isopropyl alcohol, butyl alcohol, propylene glycol (E1520), purified water, ammonia solution, concentrated (E527), potassium hydroxide, black iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171), dimethicone.

What Gilenya looks like and contents of the pack
Gilenya 0.25 mg hard capsules have an ivory opaque body and cap. "FTY 0.25mg" is imprinted on the cap with black ink and a black radial band on the body.

Gilenya 0.5 mg hard capsules have a white opaque body and bright yellow opaque cap. "FTY0.5mg" is imprinted on the cap with black ink and two bands are imprinted on the body with yellow ink.

Gilenya 0.25 mg capsules are available in packs containing 7 or 28 capsules. Not all pack sizes may be marketed in your country.

Gilenya 0.5 mg capsules are available in packs containing 7, 28 or 98 capsules or in multipacks containing 84 capsules (3 packs of 28 capsules). Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Lek Pharmaceuticals d.d.
Verovskova Ulica 57
Ljubljana, 1526
Slovenia

Novartis Pharmaceutical Manufacturing LLC
Verovskova Ulica 57
Ljubljana, 1000
Slovenia

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom (Northern Ireland)
Novartis Ireland Limited
Tel: +44 1276 698370

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.