Product Information as approved by the CHMP on 19 April 2012, pending endorsement by the European Commission

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 mg fingolimod (as hydrochloride).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

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 adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon.
  These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

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
The recommended dose of Gilenya is one 0.5 mg capsule taken orally once daily. Gilenya can be taken with or without food.

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

Patients can switch directly from beta interferon or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related abnormalities, e.g. neutropenia.

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
Gilenya 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).

Diabetic patients
Gilenya has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. Gilenya should be used with caution in these patients due to a potential increase in the risk of macular oedema (see sections 4.4 and 4.8). Regular ophthalmological examinations should be conducted in these patients to detect macular oedema.

Paediatric population
The safety and efficacy of Gilenya in children aged 0 to 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

4.3 Contraindications

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, except for patients with cutaneous basal cell carcinoma.
Severe liver impairment (Child-Pugh class C).
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Bradyarrhythmia
Initiation of Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, 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 steepest within 6 hours. The negative chronotropic effect of Gilenya persists beyond 6 hours and progressively attenuates over subsequent days of treatment. With continued administration, heart rate returns to baseline within one 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.

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.

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, 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).

Due to the risk of serious rhythm disturbances, Gilenya should not be used in patients with second degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope, or in patients with significant QT prolongation (QTc>470msec (female) or >450msec (male)). Since significant bradycardia may be poorly tolerated in patients with known ischaemic heart disease (including angina pectoris), cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension or severe untreated sleep apnoea, Gilenya should not be used in these patients. In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment is considered, advice from a cardiologist should be 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).

Gilenya 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. Since initiation of Gilenya treatment results in decreased heart rate, Gilenya should not be used concomitantly with these medicinal products.

Experience with Gilenya is limited in patients receiving concurrent therapy with beta blockers, heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine). Since the initiation of Gilenya treatment is also associated with slowing of the heart rate (see also section 4.8, Bradyarrhythmia), concomitant use of these substances during Gilenya initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment with Gilenya should 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 medication 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).

If therapy is discontinued for more than 2 weeks, the effects on heart rate and atrioventricular conduction may recur on re-introduction of Gilenya treatment and the same precautions as for treatment initiation should apply.

QT interval

In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTcI, with the upper 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.

Infections
A core pharmacodynamic effect of Gilenya 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) should be available. Assessments of CBC are also recommended periodically during treatment, 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.

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

The immune system effects of Gilenya may increase the risk of infections (see section 4.8). Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. During treatment, patients receiving Gilenya should be instructed to report 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.

Macular oedema
Macular oedema with or without visual symptoms has been reported in 0.4% 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). Gilenya has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. It is recommended that multiple sclerosis patients with diabetes mellitus or a history of uveitis undergo an ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy.

Continuation of Gilenya 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 Gilenya 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 function
During clinical trials, elevations 3-fold the upper limit of normal (ULN) or greater in liver transaminases occurred in 8% of patients treated with fingolimod 0.5 mg compared to 2% of placebo patients. Elevations 5-fold the ULN occurred in 2% of patients on fingolimod and 1% 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.

Gilenya 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 with Gilenya. In the absence of clinical symptoms, liver transaminases should be monitored at Months 1, 3, 6, 9 and 12 on therapy and periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurement. With repeated confirmation of liver transaminases above 5 times the ULN, treatment with Gilenya should be interrupted and only re-commenced once liver transaminase values have normalised.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have liver enzymes checked and Gilenya should be discontinued if significant liver injury is confirmed (for example liver transaminase levels greater than 5-fold the ULN and/or serum bilirubin elevations). Resumption of therapy will be dependent on whether or not another cause of liver injury is determined and on the benefits to patient of resuming therapy versus the risks of recurrence of liver dysfunction.

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.

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.

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 6.1% of patients on fingolimod 0.5 mg and in 3.8% of patients on placebo. Therefore, blood pressure should be regularly monitored during treatment with Gilenya.

Respiratory effects
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. Gilenya should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease (see also section 4.8).

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

Due to the long half-life of natalizumab, concomitant exposure, and thus concomitant immune effects, could occur for up to 2-3 months following discontinuation of natalizumab if Gilenya was immediately started. Therefore caution is required when switching patients from natalizumab to Gilenya.

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

Stopping therapy
If a decision is made to stop treatment with Gilenya 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 (see section 5.1). 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.

4.5 Interaction with other medicinal products and other forms of interaction

Anti-neoplastic, immunosuppressive or immune-modulating therapies
Anti-neoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects (see sections 4.3 and 4.4). Caution is also indicated when switching patients from long-acting therapies with immune effects, such as natalizumab 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.

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 ivabradine, verapamil or diltiazem), 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. Co-administration of fingolimod with ketoconazole resulted in a 1.7-fold increase in fingolimod and fingolimod phosphate exposure (AUC). Caution should be exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin).

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. Potent inhibitors of transporter proteins are not expected to influence fingolimod disposition.

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.

It is not known whether the concomitant administration of strong CYP450 inducers may decrease the exposure to fingolimod and fingolimod P.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in females
Before initiation of Gilenya treatment, women of childbearing potential should be counselled regarding the potential for serious risk to the foetus and the need for effective contraception during treatment with Gilenya. Since it takes approximately two months to eliminate fingolimod from the body on stopping treatment (see section 4.4), the potential risk to the foetus may persist and contraception should be continued during that period.

Pregnancy
Before initiation of treatment in women of childbearing potential a negative pregnancy test result needs to be available. While on treatment, women should not become pregnant and active contraception is recommended. If a woman becomes pregnant while taking Gilenya, discontinuation of Gilenya is recommended.

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. There are very limited data from the use of fingolimod in pregnant women.

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

Breast-feeding
Fingolimod is excreted in milk of treated animals during lactation at concentrations 2-3-fold higher than that found in maternal plasma (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

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

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

4.8 Undesirable effects

Summary of the safety profile
A total of 1,703 patients on Gilenya (0.5 or 1.25 mg) constituted the safety population in the two Phase III studies in patients with relapsing-remitting multiple sclerosis (see section 5.1). Study D2301 (FREEDOMS) was a 2-year placebo-controlled clinical study in 854 patients treated with fingolimod (placebo: 418). In this study the most serious adverse reactions on Gilenya 0.5 mg were infections, macular oedema and transient atrioventricular block at treatment initiation. The most frequent adverse reactions (incidence ≥10%) on Gilenya 0.5 mg were headache, influenza, diarrhoea, back pain, liver enzyme elevations and cough. The most frequent adverse reaction reported for Gilenya 0.5 mg leading to treatment interruption was serum transaminase elevations (3.8%). The adverse reactions in Study D2302 (TRANSFORMS), a 1-year study in 849 patients treated with fingolimod which used interferon beta-1a as comparator, were generally similar to Study D2301, taking into account the differences in study duration.

Adverse reactions reported with Gilenya 0.5 mg in Studies D2301 (FREEDOMS) and D2302 (TRANSFORMS) 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 ranked in order of decreasing seriousness.

Tabulated list of adverse reactions

Infections and infestations	
Very common:	Influenza viral infections
Common:	Herpes viral infections
	Bronchitis
	Sinusitis
	Gastroenteritis
	Tinea infections
Uncommon:	Pneumonia
Blood and lymphatic system disorders	
Common:	Lymphopenia
	Leucopenia
Psychiatric disorders	
Common:	Depression
Uncommon:	Depressed mood
Nervous system disorders	
Very common:	Headache
Common:	Dizziness
	Paraesthesia
	Migraine
Eye disorders	
Common:	Vision blurred
	Eye pain
Uncommon:	Macular oedema*
Cardiac disorders	
Common:	Bradycardia
	Atrioventricular block
Vascular disorders	
Common:	Hypertension
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough
Common:	Dyspnoea
Gastrointestinal disorders	
Very common:	Diarrhoea
Skin and subcutaneous tissue disorders	
Common:	Eczema
	Alopecia
	Pruritus
Musculoskeletal and connective tissue disorders	
Very common:	Back pain
General disorders and administration site conditions	
Common:	Asthenia
Investigations	
Very common:	Alanine transaminase (ALT) increased
Common:	Gamma-glutamyl transferase (GGT) increased
	Hepatic enzyme increased
	Liver function test abnormal
	Blood triglycerides increased
	Weight decreased
Uncommon:	Neutrophil count decreased

* Not reported in Study D2301 (FREEDOMS) with Gilenya 0.5 mg. Frequency category is based on the incidence with Gilenya 0.5 mg (0.5% vs. 0.2% in the interferon beta-1a group) in Study D2302 (TRANSFORMS).

Description of selected adverse reactions

Infections

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

Two fatal cases of herpes infection occurred at the higher 1.25 mg dose: A case of herpes simplex encephalitis in a patient in whom initiation of acyclovir therapy was delayed by one week, and a case of primary disseminated varicella zoster infection in a patient not previously exposed to varicella receiving concomitant high-dose steroid therapy for a multiple sclerosis relapse.

Macular oedema

In multiple sclerosis clinical studies macular oedema occurred in 0.4% 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 Gilenya. 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 Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays (see sections 4.4 and 5.1). 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 Gilenya 0.5 mg. Heart rate below 40 beats per minute was rarely observed in patients on Gilenya 0.5 mg. Heart rate returned to baseline within 1 month of chronic treatment. Bradycardia was generally asymptomatic but some patients experienced mild to moderate symptoms, including dizziness, fatigue and/or palpitations, which resolved within the first 24 hours after treatment initiation.

In multiple sclerosis clinical studies first-degree atrioventricular block (prolonged PR interval onECG) was detected after treatment initiation in 4.7% of patients on fingolimod 0.5 mg, in 2.8% of patients on intramuscular interferon beta-1a, and in 1.5% of patients on placebo. Second-degree atrioventricular block was detected in less than 0.5% patients on Gilenya 0.5 mg. In the post-marketing setting, isolated reports of transient, spontaneously resolving complete AV block have been observed during the six hour monitoring period with 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 Gilenya 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 Gilenya 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 6.1% of patients on fingolimod 0.5 mg and in 3.8% 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 transaminases
In multiple sclerosis clinical studies 8% and 2% of patients treated with Gilenya 0.5 mg experienced asymptomatic elevation in serum levels of hepatic transaminases ≥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. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of Gilenya. In a small number of patients (N=10 on 1.25 mg, N=2 on 0.5 mg) who experienced liver transaminase elevations ≥5x ULN and who continued on Gilenya therapy, the elevations returned to normal within approximately 5 months (see also section 4.4, Liver function).

Nervous system disorders
Rare events involving the nervous system which occurred in patients treated with fingolimod at higher doses (1.25 or 5.0 mg) include ischaemic and haemorrhagic strokes and posterior reversible encephalopathy syndrome. Neurological atypical disorders have also been reported, such as acute disseminated encephalomyelitis (ADEM)-like events.

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 3.1% for fingolimod 0.5 mg and 2.0% for placebo, a difference that resolved after treatment discontinuation. For DLCO the reductions at Month 24 were 3.8% for fingolimod 0.5 mg and 2.7% for placebo.

Lymphomas
Three cases of lymphoma, including one fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma, have been reported in a population of more than 4,000 patients (approximately 10,000 patient years) exposed to fingolimod during the clinical programme in multiple sclerosis at, or above, the recommended dose of 0.5 mg. This incidence of 3 in 10,000 patient years (95% CI: 0.6-8.8 per 10,000 patient years) compares to a background incidence of 1.9 in 10,000 patient years in the general population.

4.9 Overdose

No cases of overdose have been reported. However, single doses up to 80 times the recommended dose (0.5 mg) were well tolerated in healthy volunteers. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with small airway reactivity.

Fingolimod can induce bradycardia 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 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: 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. 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. This redistribution reduces the infiltration of pathogenic lymphocyte cells into the central nervous system, where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and *in vitro* experiments indicate that fingolimod may also 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 in the first 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.

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 Gilenya has been demonstrated in two studies which evaluated once-daily doses of fingolimod 0.5 mg and 1.25 mg in patients with relapsing-remitting multiple sclerosis (RRMS). Both studies included 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.

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†	17%	24%
Hazard ratio (95% CI)	0.70 (0.52, 0.96)*	
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.		

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 2. There were no significant differences between the 0.5 mg and the 1.25 mg doses as regards study endpoints.

Table 2: 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†	6%	8%
Hazard ratio (95% CI)	0.71 (0.42, 1.21)	
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.		

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.

The European Medicines Agency has deferred the obligation to submit the results of studies with Gilenya in one or more subsets of the paediatric population in multiple sclerosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

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 mainly via the cytochrome P450 4F2 isoenzyme and subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive non-polar ceramide analogues of fingolimod. 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 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
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.

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).

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
There are limited data available from a renal transplant study that included 7 children above 11 years of age (study FTY720A0115). The comparison of these data to those in adult healthy volunteers is of limited relevance and no valid conclusions can be drawn regarding the pharmacokinetic properties of fingolimod in children.

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. 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.

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

Environmental Risk Assessment (ERA)
A risk for the environment due to use of Gilenya by patients with relapsing multiple sclerosis is not expected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core:
Magnesium stearate
Mannitol

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

Printing ink:
Shellac (E904)
Dehydrated alcohol
Isopropyl alcohol
Butyl alcohol
Propylene glycol
Purified water
Strong ammonia solution
Potassium hydroxide
Black iron oxide (E172)
Yellow iron oxide (E172)

Titanium dioxide (E171)
Dimethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PVC/PVDC/aluminium blister packs containing 7 or 28 hard capsules or multipacks containing 84 (3 packs of 28) hard capsules.
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

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/001-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17.03.2011

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuremberg
Germany

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

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where GILENYA is marketed, at launch and after launch all physicians who intend to prescribe GILENYA are provided with an updated physician information pack containing the following elements:

- The Summary of Product Characteristics
- Physician’s checklist prior to prescribing GILENYA
- Information about the Fingolimod Pregnancy Exposure Registry

- Patient reminder card

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 (or when the last dose of GILENYA was more than two weeks previously).
  - Perform blood pressure measurement prior to the first dose of GILENYA (or when the last dose of GILENYA was more than two weeks previously).
  - Perform a liver function test prior to treatment initiation.
  - Arrange ophthalmological assessment prior to initiation with GILENYA in patients with diabetes mellitus or with a history of uveitis.

  Until 6 hours after first dose (or if the last dose of GILENYA was more than two weeks previously)
  - 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 (or if the last dose of GILENYA was more than two weeks previously)
  - 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 overnight monitoring after the first dose (or if the last dose of GILENYA was more than two weeks previously).

  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.
  - With third degree AV block occurring at any time.
  - Where at the 6-hour time point:
    - Heart rate <45 bpm.
    - New onset second degree or higher AV block.
    - QTc interval ≥500 msec.

- That GILENYA is not recommended in patients with:
  - Second degree Mobitz Type II or higher AV block
  - Sick-sinus syndrome
  - Sino-atrial heart block
  - QTc prolongation >470 msec (females) or >450 msec (males)
  - Ischaemic cardiac disease including angina pectoris
  - Cerebrovascular disease
  - History of myocardial infarction
  - Congestive heart failure
  - History of cardiac arrest
  - Severe sleep apnoea
  - 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 Class Ia or Class III anti-arrhythmic medicines.

- GILENYA is not recommended in patients concomitantly taking medicines which are 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. There is a need to check the patient's peripheral lymphocyte count (CBC) prior to initiation and to monitor during treatment with GILENYA.

- GILENYA may increase the risk of infections. 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. Concomitant treatment with immunosuppressants or immune-modulating medicines should be avoided.

- The need to instruct patients to report signs and symptoms of infections immediately to their prescriber during and for up to two months after treatment with GILENYA.

- Specific recommendations regarding vaccination for patients initiating or currently on GILENYA treatment.

- The need for a full ophthalmological assessment 3-4 months after starting GILENYA therapy for the early detection of visual impairment due to drug-induced macular oedema.

- The need for ophthalmological assessment during treatment with GILENYA in patients with diabetes mellitus or with a history of uveitis.

- The teratogenic risk of GILENYA: the importance of avoiding pregnancy when undergoing treatment with GILENYA and the need for a negative pregnancy test result prior to treatment initiation. This should be repeated at suitable intervals.

- The need to advise women of child-bearing potential on the serious risk to the foetus and the need to practice effective contraception during treatment and for at least two months following discontinuation of treatment with GILENYA.

- The need for liver function monitoring at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter.

- The need to provide patients with the patient reminder card.

The patient reminder card shall contain the following key messages:

- That they will have a baseline ECG and blood pressure measurement prior to the first dose of GILENYA (or when the last dose of GILENYA has been administered more than two weeks ago).

- That their heart rate will need to be monitored for 6 or more hours after the first dose of GILENYA (or when the last dose of GILENYA has been administered more than two weeks ago), including hourly pulse and blood pressure checks. They will need an ECG at 6 hours and in some circumstances monitoring may involve an overnight stay.

- The need to 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.

- The signs and symptoms of infection and the need to report these immediately to the prescriber during and up to two months after treatment with GILENYA.

- The need to report any symptoms of visual impairment immediately to the prescriber during and for up to two months after the end of treatment with GILENYA.

- That GILENYA is teratogenic so women with childbearing potential must:
  - Have a negative pregnancy test.
  - Be using effective contraception during and for at least two months following discontinuation of treatment with GILENYA.
  - Report any (intended or unintended) pregnancy during and two months following discontinuation of treatment with GILENYA immediately to the prescriber.

- The need for a liver function test prior to treatment initiation and for liver function monitoring at months 1, 3, 6, 9 and 12 during GILENYA therapy and periodically thereafter.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
Conduct of a prospective cohort study assessing the incidence of cardiovascular adverse events in patients starting GILENYA treatment for relapsing remitting multiple sclerosis based on a CHMP approved protocol.	Final Study report by 15 December 2020

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 0.5 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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/005 28 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.5 mg

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

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.5 mg

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 containing 84 (3 packs of 28) hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.5 mg

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 comprising 3 cartons, each containing 28 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.5 mg

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 hard capsules (in single-unit-dose blisters)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°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
Wimblehurst Road
Horsham
West Sussex, RH12 5AB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/001 7 capsules (in single-unit-dose blisters)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GILENYA 0.5 mg

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

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS FOR WALLET

1. NAME OF THE MEDICINAL PRODUCT

GILENYA 0,5 mg

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

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 0.5 mg hard capsules
Fingolimod

Read all of this leaflet carefully before you start taking this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT GILENYA IS AND WHAT IT IS USED FOR

What Gilenya is
The active substance of Gilenya is fingolimod.

What Gilenya is used for
Gilenya is used in adults to treat relapsing-remitting multiple sclerosis (MS), more specifically in:
Patients who have failed to respond despite treatment with beta-interferon (another 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.

2. 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** (unless it is a type of skin cancer called basal cell carcinoma).
- if you have **severe liver problems**.
- **if you are allergic** (hypersensitive) to fingolimod or any of the other ingredients of Gilenya.

If this applies to you**, tell your doctor without taking Gilenya**.

Take special care with Gilenya
Talk to your doctor before taking Gilenya:
- **if you have irregular, abnormal heart beat.**
- **if you suffer from symptoms of slow heart rate (e.g. dizziness, nausea, or palpitations).**
- **if you have any heart problems, blocked heart blood vessels, have had a heart attack, have a history of your heart having stopped or if you have angina.**
- **If you have had a stroke.**
- **if you suffer from heart failure.**
- **if you have severe breathing problems during sleep (severe sleep apnoea).**
- **if you have been told you have an abnormal electrocardiogram.**
- **if you are taking medicine for irregular heartbeat** such as quinidine, disopyramide, amiodarone or sotalol.
- **if you are taking 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, **tell your doctor before taking Gilenya.**

Slow heart rate (bradycardia) and irregular heartbeat: At the beginning of treatment, 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 pronounced, 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.

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 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 applies if you are resuming Gilenya after a break of more than two weeks.

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 medication 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.

If you have never had chickenpox: If you have never had chickenpox, your doctor may want to 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 by one month.

Infections: 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, or feel like you have the flu, call your doctor right away.

Macular oedema: 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 cause abnormal results of liver function tests. You will probably not notice any symptoms but if you notice yellowing of your skin or the whites of your eyes, abnormal darkening of the urine 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.**

During the first twelve months of 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.

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

Use in children
Gilenya is not intended to be used in children and adolescents below 18 years old as it has not been studied in MS patients below 18 years old.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. 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 or mitoxantrone. 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').
- **Vaccines**. During and for up to 2 months after treatment with Gilenya, you should not be given 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. Your doctor may decide not to prescribe Gilenya if you are taking such a medicine because it could intensify the effect on irregular heartbeat.
- **Other medicines**: protease inhibitors, anti-infectives such as ketoconazole, azole antifungals, clarithromycin or telithromycin.

Pregnancy and breast-feeding
Before you start treatment with Gilenya your doctor may ask you to do a pregnancy test in order to ensure that you are not pregnant. You should avoid becoming pregnant while taking Gilenya or in the two months after you stop taking it because there is a risk of harm to the baby. Talk with your doctor

about reliable methods of birth control that you should use during treatment and for 2 months after you stop treatment.

If you do become pregnant while taking Gilenya, stop taking the medicine and tell your doctor straight away. You and your doctor will decide what is best for you and your baby.

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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Your doctor will tell you whether your illness allows you to drive vehicles 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 Gilenya exactly as your doctor has told you. You should check with your doctor if you are not sure.

The dose is one capsule per day. Take Gilenya once a day with a glass of water. 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.

Do not exceed the recommended dose.

Your doctor may switch you directly from beta interferon 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.

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 forget to take a dose, take the next dose as planned. Do not 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.

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

4. POSSIBLE SIDE EFFECTS

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

Side effects may occur with certain frequencies, which are defined as follows:

Very common:	affects more than 1 user in 10
Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000
Not known:	frequency cannot be estimated from the available data.

Some side effects could be or could become serious
Common:
- Cough with phlegm, chest discomfort, fever (signs of lung disorders)
- Feeling sick with nausea, vomiting, diarrhoea (signs of bowel problems)
- Herpes virus infection (shingles or herpes zoster) with symptoms such as blisters, burning, itching or pain around the mouth or genitals. Other symptoms may be fever and weakness in the early stages of infection, followed by numbness, itching, and red patches or blisters on the face or trunk
- Slow heartbeat (bradycardia), irregular heart rhythm

Uncommon:
- 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

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

Other side effects
Very common
- Infection from flu virus with symptoms such as tiredness, chills, sore throat, aching in the joints or muscles, fever
- Headache
- Diarrhoea
- Back pain
- Cough
- Increase in blood levels of a liver enzyme (ALT)

Common
- Feeling of pressure or pain in the cheeks and forehead (sinusitis)
- Fungal infections affecting the skin, hair or nails (ringworm)
- Dizziness
- Tingling or numbness
- Severe headache often accompanied by nausea, vomiting and sensitivity to light (signs of migraine)
- Low level of white blood cells (lymphocytes, leucocytes)

- Weakness
- Itchy, red, burning rash (signs of eczema)
- Hair loss
- Itching
- Weight loss
- Breathlessness
- Depression
- Eye pain
- 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)
- Increase in blood levels of hepatic enzymes
- Increase in blood levels of certain lipids (triglycerides)

Uncommon
- Low level of certain white blood cells (neutrophils)
- Depressed mood

Rare
- Blood vessel disorders
- Nervous system disorders
- Cancer of the lymphatic system (lymphoma)

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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please **tell your doctor or pharmacist**.

5. HOW TO STORE GILENYA

Keep out of the reach and sight of children.
Do not use Gilenya after the expiry date which is stated on the carton and blister foil after "EXP". The expiry date refers to the last day of the month.
Do not store above 30ºC.
Store in the original package in order to protect from moisture.
Do not use any pack that is damaged or shows signs of tampering.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Gilenya contains
- The active substance is fingolimod. Each capsule contains 0.5 mg fingolimod (as hydrochloride).
- The other ingredients are:
  Capsule core: magnesium stearate, mannitol
  Capsule shell: yellow iron oxide (E172), titanium dioxide (E171), gelatin
  Printing ink: shellac (E904), dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, black iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171), dimethicone

What Gilenya looks like and contents of the pack
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 is available in packs containing 7 or 28 capsules or in multipacks containing 84 capsules (3 packs of 28 capsules). Not all pack sizes may be marketed in your country.

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This leaflet was last approved in

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