Product Information as approved by the CHMP on 17 December 2015, pending endorsement by the European Commission

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 the 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 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

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

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

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.
Severe liver impairment (Child-Pugh class C).
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 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 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.

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, 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).

Very rare cases of T-wave inversion have been reported in 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, 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 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).

The effects on heart rate and atrioventricular conduction may recur on re-introduction of Gilenya

treatment depending on duration of the interruption and time since start of Gilenya treatment. 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.

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 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.

Patients need to be assessed for their immunity to varicella (chickenpox) prior to Gilenya treatment. It is recommended that patients without a health care professional confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo antibody testing to varicella zoster virus (VZV) before initiating Gilenya therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with Gilenya (see section 4.8). 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, including opportunistic 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.

Isolated cases of cryptococcal meningitis (a fungal infection) have been reported in the post-

marketing setting (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 (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. 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. 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. If PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with fingolimod should be suspended until PML has been excluded.

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 0.5% 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). 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

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 Gilenya. In clinical trials, elevations 3-fold the upper limit of normal (ULN) or greater in ALT occurred in 8.0% of 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.

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 6.5% of patients on fingolimod 0.5 mg and in 3.3% of patients on placebo. Therefore, blood pressure should be regularly monitored during treatment 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).

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 Gilenya when switching patients from teriflunomide, dimethyl fumarate or alemtuzumab treatment to Gilenya. When switching patients from another disease modifying therapy to Gilenya, the 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 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).

Basal cell carcinoma
Basal cell carcinoma (BCC) has 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, after at least one year and then at least yearly taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions are detected.

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, 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 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, 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
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
The safety population of Gilenya is derived from two Phase III placebo-controlled clinical studies and one Phase III active-controlled clinical study in patients with relapsing remitting multiple sclerosis. It includes a total of 2,431 patients on Gilenya (0.5 or 1.25 mg). Study D2301 (FREEDOMS) was a 2-year placebo-controlled clinical study in 854 patients treated with fingolimod (placebo: 418). Study D2309 (FREEDOMS II) was a 2-year placebo-controlled clinical study in 728 multiple sclerosis patients treated with fingolimod (placebo: 355). In the pooled data from these two studies the most serious adverse 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 influenza, sinusitis, headache, diarrhoea, back pain, hepatic enzyme increased and cough. The most frequent adverse reaction reported for Gilenya 0.5 mg leading to treatment interruption was ALT elevations (2.2%). 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 placebo-controlled studies, taking into account the differences in study duration.

Adverse reactions reported with Gilenya 0.5 mg in Studies D2301 (FREEDOMS) and D2309 (FREEDOMS II) 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).

Tabulated list of adverse reactions

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
Rare***:	Lymphoma
Blood and lymphatic system disorders	
Common:	Lymphopenia
	Leucopenia
Not known***:	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
Rare*:	Posterior reversible encephalopathy syndrome (PRES)
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
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:	Hepatic enzyme increased (increased ALT, Gamma glutamyltransferase, Aspartate transaminase)
Common:	Blood triglycerides increased
Uncommon:	Neutrophil count decreased

* Not reported in Studies FREEDOMS, FREEDOMS II and TRANSFORMS. The frequency category was based on an estimated exposure of approximately 10, 000 patients to fingolimod in all clinical trials.

** PML and cryptococcal infections (including isolated cases of cryptococcal meningitis) have been reported in the post-marketing setting (see section 4.4).

*** Adverse drug reactions from spontaneous reports and literature

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 Gilenya-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 (see section 4.4).

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 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. 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. 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 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% 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 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 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 6.5% 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 multiple sclerosis patients treated with Gilenya. In clinical studies 8.0% and 1.8% of patients treated with Gilenya 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 Gilenya. 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 Gilenya 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.

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.

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 lymphoma (B-cell and T-cell) cases was higher in clinical trials than expected in the general population.

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.

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 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 (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.

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. A third study targeting the same 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.

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. 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 Gilenya 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 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 25°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, 28 or 98 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/677/001-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17.03.2011

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. MANUFACTURER 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. 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

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

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 outcomes Intensive Monitoring Program and 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.
  - Perform blood pressure measurement prior to the first dose of GILENYA.
  - 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
  - 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-initiation of 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.
  - treatment is interrupted for more than 7 days during weeks 3 and 4 of treatment.
  - treatment is interrupted for 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:
    - 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. 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.

- 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.

- That their heart rate will need to 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 a continuous ECG during the first 6 hours. They will need an ECG at 6 hours and in some circumstances monitoring may involve an overnight stay.

- The need to call the doctor in case of treatment interruption as the 1st dose monitoring may need to be repeated depending on duration of the interruption and time since start of GILENYA treatment.

- 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 below 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
98 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 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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 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
Frimley Business Park
Camberley GU16 7SR
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

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 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
Frimley Business Park
Camberley GU16 7SR
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

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 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
Frimley Business Park
Camberley GU16 7SR
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

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 x 1 hard capsule

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 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

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

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

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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
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 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.

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 you are allergic** to fingolimod or any of the other ingredients of this medicine (listed in section 6).

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

Warnings and precautions
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 or have recently taken medicine for irregular heartbeat** such as quinidine, disopyramide, amiodarone or sotalol.
- **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, **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 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 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 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.

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, feel like you have the flu, or have a headache accompanied by stiff neck, sensitivity to light, nausea, and/or confusion (these may be symptoms of meningitis), contact your doctor right away. 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 as soon as possible, 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.

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 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 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.

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, if you experience any of these symptoms during your treatment with Gilenya.

Basal cell carcinoma (BCC)
A type of skin cancer called basal cell carcinoma (BCC) has been reported in MS patients treated with Gilenya. Talk to your doctor if you notice any skin nodules (e.g. shiny pearly nodules), patches or open sores that do not heal within weeks (these may be signs of BCC). 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.

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

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. 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.
    - carbamazepine, rifampicine, phenobarbital, phenytoin, efavirenz or St. John's Wort (potential risk of reduced efficacy).

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 this medicine exactly as your doctor has told you. 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, 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.

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.

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.

Some side effects could be or could become serious
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.

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

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).

Very rare (may affect up to 1 in 10,000 people):
- Electrocardiogram anomaly (T-wave inversion).

Isolated cases:
- 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.

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.
- 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.

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)

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):
- Blood vessel disorders
- Nervous system disorders
- 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 any pack that 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. 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, 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.

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

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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.