NOVARTIS

Gilenya®

Composition

Active substances

Fingolimod as fingolimod hydrochloride

Excipients

0.25 mg capsules:

0.25 mg fingolimod as fingolimod hydrochloride, mannitol, hydroxypropylcellulose, hydroxypropylbetadex, magnesium stearate, gelatin, titanium dioxide, yellow iron oxide, shellac, black iron oxide, propylene glycol, 28% ammonia solution.

0.5 mg capsules:

0.5 mg fingolimod as fingolimod hydrochloride, mannitol, magnesium stearate, yellow iron oxide, titanium dioxide, gelatin, shellac, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, 28% ammonia solution, potassium hydroxide, black iron oxide, dimethicone.

Pharmaceutical form and quantity of active substance per unit

Hard capsules containing 0.25 mg fingolimod (as hydrochloride).

Hard capsules containing 0.5 mg fingolimod (as hydrochloride).

Indications/Potential uses

Gilenya is indicated for the treatment of adults, adolescents and children aged 10 years and over with relapsing-remitting multiple sclerosis (MS) to reduce the frequency of relapses and delay the progression of disability.

Dosage/Administration

General populations

Dosage

In adults the recommended dose of Gilenya is one 0.5 mg capsule taken orally once daily with or without food.

In children and adolescents (aged 10 years and over) the recommended dose depends on body weight:

- Children and adolescents with a body weight of 40 kg or under: one 0.25 mg capsule taken orally once daily.

- Children and adolescents with a body weight of over 40 kg: one 0.5 mg capsule taken orally once daily.

"The strength 0.25mg supporting the age group between 10 and 18 years old with body weight of 40kg or under is not registered"

Children and adolescents who receive 0.25 mg capsules at the start of treatment should be switched to 0.5 mg capsules once a stable body weight of over 40 kg has been reached.

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

For recommendations on switching patients from other disease-modifying therapies or other immunosuppressants to Gilenya see "Prior treatment with immunosuppressant or immune-modulating therapies" under "Warnings and precautions". The duration of effect of these medicinal products must be taken into account to avoid additive immunosuppressive effects (see "Prior treatment with immunosuppressant or immune-modulating therapies" under "Warnings and precautions").

Initiation of treatment

An ECG must be carried out for all patients before the start of treatment and at the end of the 6-hour monitoring period. All patients should be monitored for signs of bradycardia and atrioventricular conduction disturbances with hourly pulse and blood pressure measurements for at least 6 hours after ingestion of the first dose. Provisions must be made for emergency cardiological treatment. Continuous real-time ECG monitoring is recommended for the first six hours after the first dose of Gilenya.

When switching the daily dose from 0.25 mg to 0.5 mg, it is recommended that administration of the first increased dose is monitored in the same way as for the first dose upon treatment initiation.

The same monitoring as for treatment initiation is recommended following treatment interruption (see "Warnings and precautions").

Certain patients require cardiac monitoring continuing beyond the first 6 hours after the start of treatment (also see "Monitoring following first dose of Gilenya – summary table" further below in this section and "Warnings and precautions"). In addition, it is the responsibility of the attending physician to decide to what extent monitoring of vital parameters/ECG will also be necessary after subsequent doses (see "Warnings and precautions").

The following table summarises the cardiac monitoring measures following the first dose of Gilenya (see also "Warnings and precautions").

Table 1 Monitoring following first dose of Gilenya – summary table

All patients	
Should be monitored for 6 hours for symptoms of bradycardia and atrioventricular conduction disturbances as follows: Hourly pulse and blood pressure measurement ECG before the start of treatment and after the 6-hour monitoring period Provisions for emergency cardiological treatment Continuous (real-time) ECG monitoring is recommended.	
Patients with abnormalities in the first 6 hours following the first dose	
In the event of symptomatic bradyarrhythmia	The patient should continue to be monitored after the 6-hour monitoring period until symptoms have fully resolved.
If heart rate reaches the lowest value 6 hours following the first dose	Cardiac monitoring should be continued until the heart rate has recovered and for a minimum of 2 hours.

If one of the following findings is present in the ECG 6 hours following the first dose: Heart rate <45 bpm Persistent new second-degree AV block or higher-degree AV block QTc interval ≥500 ms If the following ECG finding is present at any point in time during the monitoring phase following the first dose: New-onset third-degree AV block	Cardiac monitoring should be continued at least overnight.

If pharmacological treatment of bradyarrhythmia-related symptoms is required after the first dose, the patient should be monitored overnight in a medical facility. The first-dose monitoring strategy should be repeated for administration of the second dose.

Patients with pre-existing cardiac disease

In certain patient populations Gilenya should be considered only if the expected benefit outweighs the potential risks.

In predisposed patients with: Known ischaemic heart disease (including angina pectoris) Congestive heart failure Cerebrovascular disease Uncontrolled hypertension Severe untreated sleep apnoea As well as patients with a history of the following illnesses: Myocardial infarction Cardiac arrest Recurrent syncope Symptomatic bradycardia	The following should be carried out before starting treatment: A cardiologist should be consulted Suitable cardiac monitoring (at least overnight) should be determined

Patients on heart rate-lowering therapy	
In patients on: Beta blockers Calcium channel blockers (with a heart rate-lowering effect, such as verapamil or diltiazem) Other substances that lower the heart rate (e.g. ivabradine, digoxin, acetylcholinesterase inhibitors, pilocarpine)	The following should be carried out before starting treatment: A cardiologist should be consulted to examine the possibility of switching to a substance that does not slow heart rate or delay AV conduction or If the patient cannot be switched to different medication, suitable cardiac monitoring (incl. continuous ECG) should be carried out at least overnight.

Patients with QT interval prolongation	
In patients with: Significant QTc prolongation (QTc >470 ms in women, QTc >450 ms in men) before starting treatment Additional risk factors for the occurrence of QT prolongation (e.g. hypokalaemia, hypomagnesaemia or congenital long QT syndrome)	The following should be carried out before starting treatment: A cardiologist should be consulted and Suitable cardiac monitoring (incl. continuous ECG monitoring at least overnight in a medical facility) should be determined.

Special dosage instructions

Patients with hepatic impairment

No Gilenya dose adjustments are needed in patients with mild hepatic impairment (Child-Pugh class A); however, treatment should be carried out with caution (see “Hepatic function” under “Warnings and precautions” and “Pharmacokinetics”). Gilenya should not be administered to patients with moderate (Child-Pugh class B) or severe (Child-Pugh class C) hepatic impairment (see “Contraindications”).

Patients with renal impairment

No clinical data are available on safety and efficacy in patients with renal impairment.

Elderly patients

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

Children and adolescents

The safety and efficacy of Gilenya in children under 10 years of age have not been studied. Gilenya should not be used in children under 10 years of age. Only limited data are available in the ≥10 to ≤12 years age group (see "Clinical efficacy").

Ethnicity

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

Gender

No Gilenya dose adjustments are needed based on gender (see "Pharmacokinetics").

Contraindications

- Patients with myocardial infarction, unstable angina pectoris, stroke/TIA, decompensated heart failure (requiring inpatient treatment), or NYHA class III/IV heart failure in the previous six months.
- Patients with severe cardiac arrhythmias requiring antiarrhythmic treatment with class Ia and class III antiarrhythmics (see "Warnings and precautions" and "Interactions").
- Patients with second-degree Mobitz type II AV block or third-degree AV block, or sick sinus syndrome, if they do not wear a pacemaker.
- Patients with a baseline QTc interval from 500 ms (see "Warnings and precautions").
- Patients with an existing immunodeficiency syndrome.
- Patients with an increased risk of opportunistic infections, including those currently receiving immunosuppressive therapy or who are immunocompromised.

- Patients with severe active infections or active chronic bacterial, fungal or viral infections (e.g. hepatitis, tuberculosis).
- Patients with existing active malignancies, excluding patients with basal cell carcinoma of the skin.
- Patients with moderate and severe hepatic impairment/liver cirrhosis (corresponding to Child-Pugh class B and C).
- Patients with existing macular oedema.
- Gilenya is contraindicated in patients of childbearing potential without adequate contraception as well as during pregnancy and breast-feeding.
- Known hypersensitivity to fingolimod or to any of the excipients.

Warnings and precautions

Bradyarrhythmia

Initiation of Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays (see "Adverse effects" and "Pharmacodynamics"). After the first dose heart rate starts to decline within 1 hour, with the lowest value being reached within the first 6 hours or, in some patients, within 24 hours. For this reason all patients should be monitored for symptoms of bradycardia for at least the first 6 hours after the first dose of Gilenya. Subsequently, heart rate returns to baseline within one month of chronic treatment (see "Heart rate and heart rhythm" subsection under "Pharmacodynamics"). In patients receiving 0.5 mg Gilenya the heart rate decreases by approximately 8 bpm. There have been rare reports of heart rates below 40 bpm (in adults) and below 50 bpm (in children and adolescents) (see "Adverse effects"). Patients who experienced bradycardia were generally asymptomatic but some patients developed mild to moderate symptoms such as hypotension, dizziness, fatigue, palpitations and chest pain, which usually resolved within the first 24 hours of treatment. If necessary, bradycardia can be treated with parenteral administration of atropine or isoprenaline.

Initiation of Gilenya treatment has been associated with atrioventricular (AV) conduction delays, usually first-degree AV block (prolonged PR interval on

electrocardiogram). Fewer than 0.2% of adult patients receiving 0.5 mg Gilenya developed second-degree atrioventricular block, usually Mobitz type I (Wenckebach). The conduction abnormalities were typically transient, asymptomatic, did not normally require treatment and resolved within the first 24 hours of treatment. Isolated cases of transient, spontaneously resolving complete AV block have been reported during post-marketing use of Gilenya (see "Adverse effects" and "Pharmacodynamics").

First-dose cardiac monitoring measures (also see "Summary table" under "Dosage/Administration")

In all patients an ECG should be carried out before the first dose and at the end of the 6-hour monitoring period. On initiation of Gilenya treatment all patients should be monitored for a period of 6 hours, with hourly pulse and blood pressure measurements, for symptoms of bradycardia. In addition, continuous (real-time) ECG monitoring is recommended during the first six hours.

Should symptomatic bradyarrhythmia occur after the first dose, suitable measures must be taken and the patient must continue to be monitored following the 6-hour monitoring period until symptoms have fully resolved.

If a patient requires pharmacological treatment during the monitoring period following the first dose, he or she should be monitored overnight in a medical facility and the first-dose monitoring strategy should be repeated after the second dose of Gilenya.

If, at the end of the 6-hour monitoring period following the first dose, the heart rate reaches the lowest value following administration (suggesting that the maximum pharmacodynamic effect on the heart has not yet been achieved), monitoring should be continued until the heart rate has recovered and for a minimum of 2 hours.

When switching the daily dose from 0.25 mg to 0.5 mg in children and adolescents, the same precautions should be taken as for the first dose.

In addition, continued cardiac monitoring, at least overnight, is required if any of the following criteria are met:

- New-onset third-degree AV block at any point in time during the monitoring phase following treatment initiation
- 6 hours after treatment initiation, the presence of:
    - Heart rate <45 bpm in adults, <55 bpm in adolescents and children aged 12 years and over or <60 bpm in children aged 10 or 11 years and over
    - The lowest heart rate since the start of monitoring, meaning the maximum pharmacodynamic effect has not yet been achieved
    - Persistent new second-degree AV block or higher-degree AV block
    - QTc interval ≥500 ms.

In certain patient populations Gilenya should be considered only if the expected benefit outweighs the potential risks. Bradycardia may be poorly tolerated in patients with known ischaemic heart disease (including angina pectoris), a history of myocardial infarction, patients with congestive heart failure and patients with cerebrovascular disease. If treatment with Gilenya is being considered, a cardiologist should be consulted prior to initiation of treatment to determine suitable cardiac monitoring (at least overnight) (see "Interactions").

Due to the risk of serious cardiac rhythm disturbances Gilenya should not be used in patients with sino-atrial block or a history of symptomatic bradycardia or recurrent syncope.

Since significant bradycardia may be poorly tolerated in patients with a history of cardiac arrest, uncontrolled hypertension or severe untreated sleep apnoea, Gilenya should not be used in these patients.

Experience with Gilenya is limited in patients receiving treatment with beta blockers, calcium channel blockers with a heart rate-lowering effect (e.g. verapamil or diltiazem) or other substances that may decrease heart rate (e.g. ivabradine, digoxin, acetylcholinesterase inhibitors, pilocarpine). Since the initiation of Gilenya treatment is also associated with slowing of the heart rate (see "Bradyarrhythmia"), concomitant use of these substances during

initiation of Gilenya treatment may lead to severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with Gilenya should generally not be initiated in patients who are concurrently treated with such substances. If treatment with Gilenya is being considered, a cardiologist should be consulted to examine the possibility of switching to medicinal products that do not slow the heart rate or delay AV conduction and to determine the most suitable monitoring measures for treatment initiation. Patients for whom such a switch is not an option should at the very least be monitored overnight with continuous ECG monitoring (see “Interactions”).

The effects on heart rate and atrioventricular conduction may recur on reintroduction of Gilenya treatment depending on the duration of treatment interruption and the length of previous Gilenya treatment.

The same precautions as for the first dose are recommended if 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 the first month of treatment
- - If the period of treatment interruption is shorter than the above, the treatment should be continued with the next dose as planned.

QT prolongation

QT interval prolongation has been observed in some patients exposed to Gilenya (individual patients with QTcF prolongation between 30 and 60 ms; no QTcF prolongation >60 ms and no individual values >500 ms). Patients at risk of QTc prolongation were not included in clinical studies. The clinical relevance of these findings is unclear.

Since initiation of Gilenya treatment decreases the heart rate and prolongs the QT interval, treatment with Gilenya is contraindicated in patients with a baseline QTc interval from 500 ms (see “Contraindications”).

Use of Gilenya should be avoided in the following patient populations if possible. If, however, treatment with Gilenya is being considered, a cardiologist should be consulted before treatment to determine suitable cardiac monitoring (incl. continuous ECG monitoring at least overnight in a medical facility):

- Patients with significant QTc prolongation (QTc >470 ms in adult women, QTc >460 ms in girls, QTc >450 ms in adult men and in boys) before starting treatment.
- Patients with additional risk factors for the occurrence of QT prolongation (e.g. hypokalaemia, hypomagnesaemia or congenital long QT syndrome) (see "Pharmacodynamics" and "Interactions").

Continued cardiac monitoring is necessary at least overnight in patients with a QTc interval ≥500 ms at the end of the 6-hour monitoring phase following treatment initiation (see "Dosage/Administration").

Gilenya has not been studied in patients with arrhythmias requiring treatment with class Ia (e.g. quinidine, procainamide) or class III antiarrhythmics (e.g. amiodarone, sotalol). Class Ia and class III antiarrhythmics have been associated with cases of torsade de pointes in patients with bradycardia, among others. Since initiation of Gilenya treatment decreases the heart rate, Gilenya must not be used concomitantly with such medicinal products (see "Contraindications").

Infections

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

The immune system effects of Gilenya (see "Pharmacokinetics") may increase the risk of infections, including opportunistic infections (see "Adverse effects").

Before initiation of Gilenya treatment a recent complete blood count (i.e. within the last 6 months or after discontinuation of prior therapy) should be available.

In addition, it is recommended that a complete blood count (including differential blood count) be performed at month 3 and regularly (at least annually) thereafter during treatment as well as at the first sign of an infection. If a total lymphocyte count of $<0.1 \times 10^9$/l is confirmed, treatment should be

paused until improvement. If the total lymphocyte count is <0.2 x 10^9/l, close monitoring of the differential blood count is required at least every 3 months.

Patients with severe active infections or active chronic infections should not start therapy with Gilenya (see "Contraindications") and should wait until the infection has resolved before initiating therapy.

Appropriate diagnostic and therapeutic measures must therefore be employed immediately in patients who develop signs of infection during treatment, particularly if infection with herpes virus is suspected. Because the elimination of fingolimod after discontinuation of treatment may take up to 2 months, monitoring for infection must be continued throughout this period (see "Discontinuation of therapy" below). Antineoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects. Specific decisions regarding the dosage and duration of treatment with corticosteroids must be based on clinical judgement. In the phase III clinical studies co-administration of a short course of corticosteroids with fingolimod (up to 5 days as per study protocols) did not increase the overall rate of infection compared to placebo. Based on these data short courses of corticosteroids (up to 5 days) can be used in combination with Gilenya (see "Adverse effects" and "Interactions").

Patients receiving Gilenya should be instructed to report symptoms of infection to their physician. Suspension of treatment with Gilenya should be considered if a patient develops a serious infection and a benefit-risk assessment should be undertaken prior to re-initiation of therapy.

Progressive multifocal leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have been documented in the post-marketing setting (see "Adverse effects"). PML is an opportunistic infection caused by the JC virus and 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.

At the start of treatment with fingolimod, an MRI scan (generally no older than 3 months) is recommended as a reference. During routine MRI (in accordance with national and local recommendations) physicians should be vigilant for lesions that may be suggestive of PML. MRI may be considered as part of close monitoring of patients considered at increased risk of PML.

Physicians should be vigilant for symptoms suggestive of PML such as speech and gait disturbances, personality changes or MRI findings.

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

MRI findings suggestive of PML may be apparent before the onset of clinical signs or symptoms. Cases of PML diagnosed on the basis of MRI findings and JCV DNA detected in CSF, in the absence of clinical signs or specific symptoms of PML, have been reported in patients treated with MS drugs associated with a risk of PML, including Gilenya.

Cases of PML have occurred without prior natalizumab therapy after approximately 2-3 years of treatment. The estimated risk appears to increase with cumulative exposure over time, but an exact relationship with the duration of treatment is not known. Additionally, PML cases have occurred in patients previously treated with natalizumab (natalizumab is associated with an increased risk of PML).

The incidence rate for PML appears to be higher for patients in Japan; the reasons are currently unknown.

Cryptococcal infections

Cases of cryptococcal infections, including cryptococcal meningitis, have been reported in the post-marketing setting (see “Adverse effects”). Most cases occurred after approximately 2-3 years of treatment. However, an exact relationship with the duration of treatment is not known. Cryptococcal meningitis can be fatal. For this reason patients with signs and symptoms consistent with cryptococcal meningitis (headache accompanied by stiff neck,

photosensitivity, nausea and/or confusion) should undergo prompt diagnostic evaluation. If cryptococcal meningitis is diagnosed, appropriate treatment should be initiated.

Human papilloma virus infection

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

Vaccination

Vaccination may be less effective during and for up to 2 months after stopping treatment with Gilenya (see "Discontinuation of therapy" below). The use of live attenuated vaccines must be avoided.

For children and adolescents please also see the "Children and adolescents" subsection.

Prior to Gilenya treatment patients must be assessed for their immunity to varicella (chickenpox). It is recommended that patients without a medically confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo testing for antibodies against the varicella zoster virus (VZV) before starting Gilenya therapy. In antibody-negative patients a full course of vaccination with varicella vaccine is recommended before starting treatment with Gilenya (see "Adverse effects"). Treatment with Gilenya should not be initiated until 1 month after vaccination to ensure the full efficacy of the vaccination.

Macular oedema

Macular oedema with or without visual symptoms has been reported in 0.5% of patients treated with 0.5 mg Gilenya (see "Adverse effects"), occurring predominantly in the first 3-4 months of treatment. An ophthalmological examination – with an assessment of the ocular fundus, including the macula – must be carried out prior to, and 3-4 months after, initiation of Gilenya

treatment. The patient's eyesight should be checked every 6 months by the attending neurologist. If patients report visual disturbances at any time while on Gilenya therapy, an evaluation of the ocular fundus, including the macula, should be carried out. Regular ophthalmological examinations should be carried out during treatment with Gilenya in patients with diabetes mellitus or a history of uveitis and in patients with a history of macular oedema (see "Contraindications").

Hepatic function

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with Gilenya.

Liver values should be monitored 1, 3, 6, 9 and 12 months after the start of treatment with Gilenya and periodically thereafter even in the absence of clinical symptoms.

Increased hepatic enzymes, particularly alanine aminotransferase (ALT), have occurred during fingolimod therapy. In clinical studies in adult MS patients elevations in ALT more than 3-fold the upper limit of normal (ULN) occurred in 8.0% of patients (placebo 1.9%). Elevations more than 5-fold the ULN occurred in 1.8% of patients on fingolimod (placebo 0.9%) in clinical studies and treatment was discontinued in these cases. Recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to fingolimod. Close monitoring is indicated if transaminase levels (particularly ALT) are shown to rise by more than 5 times the ULN. Gilenya should be discontinued if there is repeated evidence of transaminase levels (particularly ALT) rising by more than 5 times the ULN and should not be reinstituted until the values have returned to normal.

Ingestion of other potentially hepatotoxic medicinal products/substances (including alcoholic drinks) should be avoided. Patients with liver cirrhosis and hepatic impairment (Child-Pugh class B and C) should not be treated with Gilenya. In addition, no treatment should be given to patients with acute or chronic active hepatitis B infection due to the risk of exacerbation of the viral hepatic disease (also see "Contraindications").

Patients who develop symptoms suggestive of hepatic impairment during treatment such as unexplained vomiting or jaundice should have their liver

enzymes checked immediately and Gilenya should be discontinued if significant hepatic injury is confirmed (see "Liver function" under "Adverse effects"). Resumption of therapy will be dependent on whether or not another cause of liver injury is determined and on the benefits to the patient of resuming therapy versus the risks of recurrence of hepatic impairment.

Blood pressure

In MS clinical studies patients treated with 0.5 mg fingolimod had an average increase of approximately 3 mmHg in systolic blood pressure and approximately 1 mmHg in diastolic pressure, first detected approximately 1 month after treatment initiation and persisting during treatment. Blood pressure should be regularly monitored during treatment with Gilenya.

Posterior reversible encephalopathy syndrome

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

Lung function

A dose-dependent reduction in FEV_1 and DLCO (diffusing capacity) was observed as early as the first month after the start of Gilenya treatment and remained stable thereafter. After 24 months of therapy the reduction in predicted FEV_1 as a percentage of the baseline value was 2.7% for 0.5 mg fingolimod and 1.2% for placebo. For DLCO the reductions from baseline after 24 months of treatment were 3.3% for 0.5 mg fingolimod and 2.7% for placebo. The changes in FEV_1 seem reversible following discontinuation of treatment. Data on the reversibility of DLCO changes following discontinuation of treatment are limited. In controlled clinical studies in MS patients dyspnoea occurred in 5% of those given 0.5 mg fingolimod and 4% of those given placebo. Some patients discontinued treatment with Gilenya due to unexplained dyspnoea in the (uncontrolled) extension studies. Gilenya

has not been studied in MS patients with impaired lung function. Patients with symptoms suggestive of a pulmonary disorder must be examined by a specialist (with testing to include spirometry and determination of DLCO).

Cutaneous malignancies

Basal cell carcinoma (BCC) and other cutaneous neoplasms such as malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma have been reported in patients treated with Gilenya (see "Adverse effects"). All patients, particularly those with an increased risk of malignant cutaneous neoplasms, but including those without such an increased risk should undergo dermatological examinations prior to the start of treatment with Gilenya and regularly during the further course of treatment.

Since there is a potential risk of malignant cutaneous neoplasms, patients treated with Gilenya should be warned against unprotected exposure to sunlight. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy

Lymphoma

Patients receiving immunosuppressants are generally at increased risk of developing lymphoma or other malignant neoplasms. There have been reports of lymphoma in clinical studies and in the post-marketing setting. The cases reported were heterogeneous in nature, mainly involving non-Hodgkin's lymphomas, including B-cell and T-cell lymphomas. Cases of cutaneous T-cell lymphoma (mycosis fungoides) have also been observed (see "Adverse effects").

Changes in the lymphocyte count

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

Prior treatment with immunosuppressant or immune-modulating therapies

There have been no clinical studies to evaluate the safety and efficacy of Gilenya when switching from teriflunomide, dimethyl fumarate or alemtuzumab to Gilenya.

When switching from other disease-modifying therapies, the elimination half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A recent (i.e. since discontinuation of the previous therapy) complete blood count should be available prior to initiating Gilenya to ensure any immune effects of the previous therapy (i.e. cytopenia) have resolved.

Interferon beta, glatiramer acetate or dimethyl fumarate

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

Natalizumab or teriflunomide

Due to the long elimination half-life of natalizumab or teriflunomide caution regarding potential additive immune effects is required when switching patients from these therapies to Gilenya. It is recommended that the timing of introduction of Gilenya be carefully considered on a case-by-case basis.

Elimination of natalizumab usually takes up to 2-3 months after 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 is described in the teriflunomide prescribing information.

Alemtuzumab

Due to the characteristics and duration of the immunosuppressive effect of alemtuzumab, which are described in the prescribing information, initiating treatment with Gilenya after alemtuzumab is not recommended unless the benefit of Gilenya treatment clearly outweighs the risks for the individual patient.

Return of disease activity (rebound) after Gilenya discontinuation

Cases of severe exacerbation of disease, including fulminant relapses, have been reported after stopping Gilenya in the post-marketing setting. This was generally observed within 12 weeks after stopping Gilenya, but was also reported up to 24 weeks after Gilenya discontinuation and beyond. Therefore,

caution is required when stopping Gilenya therapy (see “Discontinuation of therapy” below). After discontinuation of Gilenya patients must be monitored for relevant signs and symptoms of increased disease activity. Appropriate treatment must be initiated as required.

Tumefactive lesions

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

Discontinuation of therapy

If a decision is made to stop treatment with Gilenya, it must be borne in mind that fingolimod remains in the blood and has pharmacodynamic effects such as decreased lymphocyte counts for up to 2 months following the last dose. Lymphocyte counts typically return to the normal range within 1-2 months of stopping therapy (see “Pharmacokinetics”). Monitoring for infections should also be continued for up to 2 months and patients should continue to report any sign of infection during this period. Starting other therapies during this period will result in concomitant exposure to fingolimod. Use of immunosuppressants shortly after discontinuation of Gilenya may lead to an additive effect on the immune system and caution is therefore required.

(See “Return of disease activity (rebound) after Gilenya discontinuation”.)

Children and adolescents (10 years of age and over)

The safety profile in children and adolescents is similar to that in adults and the warnings and precautions for adults therefore also apply to children and adolescents. In particular, the following should be noted when prescribing Gilenya to children and adolescents:

– Precautions should be followed when administering the first dose (see “Bradyarrhythmia”). The same precautions as for the first dose are also recommended when patients are switched from the 0.25 mg daily dose to the 0.5 mg daily dose.

– In the controlled paediatric study (D2311) seizures, anxiety, depressed mood and depression have been reported more frequently in patients treated with fingolimod than in patients treated with interferon beta-1a. Therefore, particular caution is required in this patient subgroup (see "Children and adolescents" in "Adverse effects").

– Mild isolated bilirubin increases have been noted in children and adolescents on Gilenya.

– It is recommended to only start Gilenya treatment in children and adolescents once all scheduled vaccinations have been carried out in accordance with the relevant vaccination guidelines.

– There are only very limited data on use in children between 10-12 years old, children weighing less than 40 kg or children at Tanner stage <2 (see "Adverse effects" and "Clinical efficacy"). Particular caution is required in these subgroups of children and adolescents due to the very limited findings available from the clinical study.

– Long-term safety data in children and adolescents are not available.

Children and adolescents (under 10 years of age)

Safety and efficacy in patients under 10 years of age have not been studied. Gilenya should therefore not be used in children under 10 years of age.

Pregnancy, women of childbearing potential, risk to the fetus and contraception

Gilenya is contraindicated during pregnancy, in women of childbearing potential without adequate contraception and during breast-feeding (see "Contraindications"). Due to the potential high risk to the fetus a pregnancy test should be performed in women of childbearing potential prior to the start of treatment with Gilenya and be negative. Medical counselling should be provided regarding the risk of treatment-related adverse effects on the fetus. Women should not become pregnant and an effective method of contraception must be used during treatment and for 2 months after the end of treatment (see "Contraindications", "Pregnancy/Breast-feeding" and the section above: "Return of disease activity (rebound) after Gilenya discontinuation".)

Interactions

Pharmacokinetic interactions

Fingolimod is primarily degraded by cytochrome P450 4F2 (CYP4F2) and possibly other CYP4F isoenzymes. *In vitro* studies on hepatocytes have shown that CYP3A4 may contribute to the metabolism of fingolimod if CYP3A4 is highly stimulated.

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

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

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

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2 and ABCB1 (P-gp) mRNA and CYP3A, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP4F2 activity in primary human hepatocytes. Fingolimod did not induce mRNA or activity of the different CYP450 enzymes and ABCB1 with respect to the vehicle control. Therefore, no clinically relevant induction of the tested CYP450 enzymes or ABCB1 (P-gp) by fingolimod is expected at therapeutic concentrations. *In vitro* experiments showed no evidence of CYP induction by fingolimod phosphate.

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

Based on *in vitro* data, fingolimod and fingolimod phosphate are not expected to inhibit the uptake of co-medications and/or biological active substances transported by organic anion transporters (OATP1B1, OATP1B3) or sodium taurocholate co-transporting polypeptides (NTCP). Similarly, they are not

expected to inhibit the efflux of co-medications and/or biological active substances transported by the breast cancer resistance protein (BCRP), bile salt export pump (BSEP) or multidrug resistance-associated protein 2 (MRP2) or released via P glycoprotein (P-gp) at therapeutic concentrations.

Oral contraceptives

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

Ciclosporin

The pharmacokinetics of single-dose fingolimod were not altered during co-administration with ciclosporin at steady state, nor were ciclosporin steady-state pharmacokinetics altered by single-dose or multi-dose (28 days) fingolimod administration. These data suggest that fingolimod neither reduces nor increases the clearance of medicinal products mainly cleared by CYP3A4 and that it is unlikely that the inhibition of CYP3A4 will reduce the clearance of fingolimod. The potent inhibition of transporters P gp, MRP2, OATP1B1 OATP C does not influence fingolimod disposition.

Ketoconazole

Co-administration of 200 mg ketoconazole twice daily at steady state and a single 5 mg dose of fingolimod led to an increase (1.7-fold) in the AUC of fingolimod and fingolimod phosphate by inhibition of CYP4F2.

Isoprenaline, atropine, atenolol and diltiazem

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

Carbamazepine

The co-administration of 600 mg carbamazepine twice daily at steady state and a single dose of 2 mg fingolimod had a weak effect on the AUC of fingolimod and fingolimod phosphate (decreasing both by approximately 40%), indicating that concomitant use of carbamazepine may reduce the efficacy of fingolimod.

Other potent CYP3A4 enzyme inducers (e.g. rifampicin, phenobarbital, phenytoin, oxcarbazepine, efavirenz and St. John's wort) may reduce the AUC of fingolimod and its metabolite to at least a comparable extent and may impair the efficacy of fingolimod if taken concomitantly.

Laboratory tests

Since fingolimod reduces blood lymphocyte counts via redistribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be used to evaluate the lymphocyte subset status of a patient treated with Gilenya.

Laboratory tests requiring circulating mononuclear cells require larger blood volumes due to the reduction in the number of circulating lymphocytes.

Pharmacodynamic interactions

Antineoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids) should not be co-administered due to the risk of additive immune system effects (see "Warnings and precautions"). Specific decisions regarding the dosage and duration of concomitant treatment with corticosteroids should be based on clinical judgement. In the phase III clinical studies co-administration of a short course of corticosteroids with fingolimod (up to 5 days as per study protocols) did not increase the overall rate of infection compared to placebo (see "Warnings and precautions" and "Adverse effects").

Caution is required when switching patients from long-acting therapies with immune effects such as natalizumab, teriflunomide or mitoxantrone to Gilenya (see "Prior treatment with immunosuppressant or immune-modulating therapies" under "Warnings and precautions").

When fingolimod is used with atenolol, there is an additional 15% reduction in the heart rate following initiation of treatment with fingolimod. This effect is not seen with diltiazem.

Treatment with Gilenya should not be initiated in patients receiving beta blockers, calcium channel blockers with a heart rate-lowering effect (e.g. verapamil or diltiazem) or other substances that may decrease heart rate (e.g. ivabradine, digoxin, acetylcholinesterase inhibitors, pilocarpine) due to the potential additive effect on heart rate. If treatment with Gilenya is being considered, a cardiologist should be consulted at the start of treatment regarding a switch to medicinal products that do not slow the heart rate. Patients whose medication cannot be switched should be monitored using continuous ECG monitoring at least overnight (see "Warnings and precautions" and "Dosage/Administration"). Gilenya is contraindicated in patients taking class Ia or class III antiarrhythmics (see "Contraindications").

The efficacy of vaccination may be limited during and for up to 2 months after treatment with Gilenya. The use of live attenuated vaccines may carry the risk of infection and must therefore be avoided during Gilenya treatment and for up to 2 months after the end of Gilenya treatment (see "Adverse effects" and "Warnings and precautions").

Effect of Gilenya on other medicinal products

Population pharmacokinetics analysis of potential drug-drug interactions

A population pharmacokinetics evaluation performed in multiple sclerosis patients did not provide evidence of a significant effect of fluoxetine and paroxetine (potent CYP2D6 inhibitors) on fingolimod or fingolimod phosphate concentrations. Administration of carbamazepine reduces concentrations of fingolimod phosphate by less than 30%. In addition, the following commonly prescribed substances had no clinically relevant effect (≤20%) on fingolimod or fingolimod phosphate concentrations: baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin, corticosteroids and oral contraceptives.

Pregnancy/Breast-feeding

Women of childbearing potential/contraception for women

Fingolimod is contraindicated in women of childbearing potential without adequate contraception (see "Contraindications"). Therefore, women of childbearing potential must test negative for pregnancy before starting treatment with Gilenya. Women of childbearing potential must be advised of the potential serious consequences for the unborn child and of the need for effective contraception during treatment and for 2 months after the completion of treatment with Gilenya. Since it takes approximately 2 months to eliminate Gilenya from the body after stopping treatment (see "Warnings and precautions"), the potential risk to the fetus may persist. Therefore, contraception must be continued during this period (see "Contraindications").

If treatment with Gilenya is discontinued due to a pregnancy or planned pregnancy, see the "Warnings and precautions" section and the "Return of disease activity (rebound) after Gilenya discontinuation" and "Discontinuation of therapy" subsections.

Pregnancy

Women should not become pregnant during treatment and an effective method of contraception must be used (see "Contraindications"). If a woman becomes pregnant while taking Gilenya, Gilenya should be discontinued. Animal studies have shown reproductive toxicity including fetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect (see "Preclinical data"). Furthermore, the receptor affected by fingolimod (sphingosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. It is not currently known whether cardiovascular malformations occur in humans.

There are no adequate and well-controlled studies of fingolimod in pregnant women.

Available human data (post-marketing data and pregnancy registry information) suggest that Gilenya use is associated with an increased prevalence of major congenital malformation compared to the general population. Women should not become pregnant during treatment and are advised to use an effective method of contraception. If a woman becomes pregnant while taking Gilenya, treatment with Gilenya must be discontinued. Patients must be informed about the harmful effects on the fetus, and a medical

follow-up examination should be performed (e.g. ultrasound). The possibility of serious exacerbation of the disease should also be considered in patients discontinuing Gilenya because of pregnancy or planned pregnancy. Such patients should consult their doctor on potential alternative treatments (see "Warnings and precautions").

Data from pregnancy registries in Canada, EU countries and South America have shown that the risk of birth defects in the MS population is similar to that in the general population. Based on data from a pregnancy registry in the USA the risk of miscarriage and stillbirth appears to be similar in the MS population and the general population.

In more than 600 prospective pregnancies with live births, stillbirths or termination of pregnancy due to fetal anomaly with maternal exposure to fingolimod during pregnancy that were reported in the post-marketing setting, the proportion of major congenital malformations was approximately 5%. The prevalence of major congenital malformation in the general population is 2 to 4%. The pattern of malformations reported with Gilenya is similar to that in the general population. The commonest major malformations are:

- Congenital heart disease such as atrial and ventricular septal defects, tetralogy of Fallot
- Renal abnormalities
- Musculoskeletal abnormalities

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

Labour and delivery

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

Breast-feeding

Fingolimod is contraindicated during breast-feeding (see "Contraindications"). Fingolimod passes into the milk of treated animals during lactation. There are no data on the effects of Gilenya on breast-fed children or on milk production. Since many active substances pass into human milk, and due to the potential for serious adverse drug reactions in breast-fed infants exposed to fingolimod, women receiving Gilenya must not breast-feed.

Pregnancy testing

Women of childbearing potential should take a pregnancy test before starting treatment with Gilenya.

Fertility

Animal studies have not shown any evidence that fingolimod is associated with an increased risk of reduced fertility (see "Preclinical data").

Effects on ability to drive and use machines

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

Adverse effects

Summary of the safety profile

The cohort used to characterise the safety profile of Gilenya originates from two placebo-controlled phase III clinical studies and an active-controlled phase III clinical study of adult patients with relapsing-remitting multiple sclerosis. It included a total of 2,431 adult patients treated with Gilenya (0.5 or 1.25 mg dose). Study D2301 (FREEDOMS) was a 2-year placebo-controlled clinical study in 854 adult multiple sclerosis patients treated with fingolimod (placebo: 418 adult patients). Study D2309 (FREEDOMS II) was a 2-year placebo-controlled clinical study in 728 adult multiple sclerosis patients treated with fingolimod (placebo: 355). In the pooled data from these two studies the most serious adverse reactions to the recommended therapeutic dose of 0.5 mg were infections, macular oedema and transient atrioventricular block following treatment initiation. The most frequent adverse reactions (incidence ≥10%) at the 0.5 mg dose were headache, increased liver enzymes, diarrhoea, cough, influenza, sinusitis and back pain. The most frequent adverse event occurring in patients given 0.5 mg Gilenya at an incidence greater than 1% and leading to discontinuation of treatment was increased ALT (2.2%).

The adverse reactions in study D2302 (TRANSFORMS), a 1-year active-controlled study in 849 adult patients with multiple sclerosis treated with fingolimod or the comparator interferon beta-1a, were generally similar to

those in the placebo-controlled studies, taking into account the differences in study duration.

Frequencies of adverse effects from the pooled data of the two placebo-controlled studies FREEDOMS and FREEDOMS II

Adverse effects are listed according to MedDRA system organ class. Frequencies were defined as follows: *Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).* Within each frequency grouping adverse reactions are given in order of decreasing seriousness.

Infections and infestations

Very common: Influenza viral infections (11%, placebo 8%), sinusitis (11%, placebo 8%).

Common: Bronchitis, herpes zoster, tinea versicolor.

Uncommon: Pneumonia.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Common: Basal cell carcinoma.

Uncommon: Malignant melanoma.

Rare: Lymphoma, squamous cell carcinoma.

Very rare: Kaposi's sarcoma.

Blood and lymphatic system disorders

Common: Leucopenia, lymphopenia.

Psychiatric disorders

Common: Depression.

Uncommon: Depressed mood.

Nervous system disorders

Very common: Headache (25%, placebo 23%).

Common: Dizziness, migraine.

Uncommon: Seizure.

Rare: Posterior reversible encephalopathy syndrome (PRES)*.

Eye disorders

Common: Blurred vision.

Uncommon: Macular oedema.

Cardiac disorders

Common: Bradycardia, atrioventricular block.

Vascular disorders

Common: Hypertension.

Respiratory, thoracic and mediastinal disorders

Very common: Cough (12%, placebo 11%).

Common: Dyspnoea.

Gastrointestinal disorders

Very common: Diarrhoea (13%, placebo 10%).

Hepatobiliary disorders

Very common: Increased liver enzymes (increased ALT, GGT, AST) (15%, placebo 4%).

Skin and subcutaneous tissue disorders

Common: Eczema, pruritus.

Musculoskeletal and connective tissue disorders

Very common: Back pain (10%, placebo 9%).

General disorders and administration site conditions

Common: Asthenia.

Investigations

Common: Increased blood triglycerides.

*Not reported in the FREEDOMS, FREEDOMS II and TRANSFORMS studies. The frequency category is based on the incidence among the approx. 10,000 fingolimod patients from all clinical studies.

Post-marketing adverse effects

Infections and infestations

Cryptococcal infections (including cryptococcal meningitis).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Merkel cell carcinoma.

Immune system disorders

Hypersensitivity reactions such as rash, urticaria and angioedema upon treatment initiation.

Nervous system disorders

Severe exacerbation of disease after Gilenya discontinuation (see “Warnings and precautions”).

Gastrointestinal disorders

Nausea.

Musculoskeletal and connective tissue disorders

Myalgia, arthralgia.

Investigations

Weight decreased

Description of selected adverse reactions

Infections

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

There have been very rare fatal cases of VZV infections in the context of prolonged concomitant use of corticosteroids (more than 5 days) for the treatment of MS relapses. However, a causal relationship between the concomitant treatment and fatal outcome has not been established. In the phase III clinical studies co-administration of a short course of corticosteroids

with fingolimod (up to 5 days as per study protocols) did not increase the overall rate of infection compared to placebo (see “Warnings and precautions” and “Interactions”).

There have been very rare cases of other herpes virus infections with fatal outcome. A causal relationship with Gilenya has not been established.

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported during treatment with Gilenya in the post-marketing setting (see “Warnings and precautions”).

In the post-marketing setting cases of infection with opportunistic pathogens, including viral (e.g. VZV, JCV causing PML, HSV), fungal (e.g. cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacteria) pathogens, have been reported, some of which were fatal (see “Warnings and precautions”).

Macular oedema

In clinical studies macular oedema occurred in 0.5% of patients treated with the recommended Gilenya dose of 0.5 mg and in 1.1% of patients treated with the higher 1.25 mg dose.

The majority of cases in multiple sclerosis clinical studies occurred within the first 3-4 months of therapy. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed during a routine ophthalmological examination. The macular oedema generally improved or resolved spontaneously after discontinuation of the medicinal product. The risk of recurrence following resumption of treatment has not been evaluated.

The incidence of macular oedema is increased in MS patients with a history of uveitis (approximately 20% with a history of uveitis vs 0.6% without a history of uveitis).

Bradyarrhythmia

Initiation of Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays (see “Dosage/Administration”, “Warnings and precautions” and “Pharmaco-dynamics”).

In multiple sclerosis clinical studies the mean maximum decrease in heart rate was reached within 6 hours after the first dose, with a decline in mean heart rate of 8 bpm with 0.5 mg Gilenya. The second dose may result in a slight further decrease. Heart rates below 40 bpm were rare in patients given 0.5 mg Gilenya. Heart rate returned to baseline within the first month of chronic dosing.

In clinical studies first-degree AV block (prolonged PR interval on electrocardiogram) occurred following treatment initiation in 4.7% of patients receiving 0.5 mg Gilenya, in 2.8% of patients receiving interferon beta-1a IM and in 1.6% of patients in the placebo group. Second-degree AV block was determined in fewer than 0.2% of patients treated with 0.5 mg Gilenya. In the post-marketing setting isolated cases of transient, spontaneously resolving complete AV block have been reported during the 6-hour monitoring period following Gilenya administration. The conduction abnormalities observed both in clinical studies and the post-marketing setting were typically transient, asymptomatic and resolved within 24 hours following the start of treatment. Although most patients did not require medical intervention, one patient who had received the 0.5 mg dose in a clinical study was treated with isoprenaline for an asymptomatic second-degree Mobitz type I atrioventricular block.

In the post-marketing setting isolated delayed-onset events, including transient asystole and unexplained death, occurred within 24 hours of the first dose. A conclusive assessment of these cases was confounded by concomitant medications and/or pre-existing disease. The causal relationship of such events to Gilenya is uncertain.

Blood pressure

In multiple sclerosis clinical studies 0.5 mg Gilenya was associated with a mild average increase of 1 mmHg in mean arterial pressure manifesting approximately 2 months after treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6.5% of patients on 0.5 mg Gilenya and in 3.3% of patients on placebo.

Hepatic function

Increased liver enzyme levels, mainly alanine aminotransferase (ALT) levels, were detected in multiple sclerosis patients treated with Gilenya. In multiple

sclerosis clinical studies 8.0% and 1.8% of patients treated with 0.5 mg Gilenya experienced an asymptomatic elevation in serum levels of ALT of at least 3x ULN or at least 5x ULN, respectively, in most cases within 6-9 months. Serum ALT levels returned to the normal range within approximately 2 months after discontinuation of Gilenya. In the few patients who continued on Gilenya therapy and who experienced liver transaminase elevations of ≥5x ULN, i.e. 10 patients given 1.25 mg Gilenya and 2 patients given 0.5 mg Gilenya, it took approximately 5 months for the levels to return to normal (see "Warnings and precautions").

Respiratory disorders

A dose-dependent reduction in values for FEV_1 and DLCO (diffusing capacity) has been observed during treatment with Gilenya (see "Warnings and precautions" and "Pharmacokinetics").

Seizures

Seizures, including status epilepticus, have been reported with Gilenya treatment both in clinical studies and in the post-marketing setting. It is unknown whether these events were related to the symptoms of multiple sclerosis alone, related to Gilenya or a combination of both.

Vascular events

In phase III clinical studies rare cases of peripheral arterial occlusive disease occurred in patients treated with Gilenya at higher doses (1.25 or 5.0 mg). Rare cases of ischaemic and haemorrhagic strokes have also been reported with 0.5 mg Gilenya in clinical studies and in the post-marketing setting, although a causal relationship has not been established.

Cutaneous neoplasms

In the pooled data from both placebo-controlled clinical studies basal cell carcinoma occurred in 14/783 (1.8%) of patients treated with 0.5 mg fingolimod and 5/776 (0.6%) of patients treated with placebo. Other cases of malignant cutaneous neoplasms (e.g. melanoma) have occurred in patients taking Gilenya in clinical studies and in the post-marketing setting. Patients at risk of malignant cutaneous neoplasms should undergo dermatological

examinations prior to the start of treatment with Gilenya and regularly during the further course of treatment.

Lymphoma

There have been cases of lymphoma (including a fatal case of Epstein-Barr virus (EBV)-positive B-cell lymphoma) reported in clinical studies and in the post-marketing setting. The cases reported were heterogeneous, mainly including non-Hodgkin's lymphomas such as B-cell and T-cell lymphomas. The incidence of B- and T-cell lymphomas was higher in the clinical studies than would be expected in the general population. Cases of cutaneous T-cell lymphoma (mycosis fungoides) have been observed.

Children and adolescents (10 years of age and over)

In a controlled paediatric study the safety profile in children and adolescents (10 years of age to under 18 years of age) receiving 0.25 mg or 0.5 mg of Gilenya once daily was almost identical to that in adult patients.

However, seizures occurred in 5.6% of patients treated with fingolimod and 0.9% of patients treated with interferon beta-1a in the paediatric study. Depression and anxiety are known to occur with increased frequency in patients with multiple sclerosis. Depression and anxiety have also been reported in paediatric patients who received fingolimod.

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

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product.

Overdose

Single doses up to 80 times the recommended dose (0.5 mg) were studied in healthy volunteers. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort, which was clinically consistent with small airway reactivity.

Fingolimod can induce bradycardia and cause AV conduction delays. The decline in heart rate normally starts within 1 hour of the first dose and generally reaches a maximum within 6 hours. Subsequently, heart rate usually

returns to baseline within one month of chronic treatment (see “Warnings and precautions”). There have been reports of slow atrioventricular conduction with isolated reports of transient, spontaneously resolving complete AV block (see “Warnings and precautions” and “Adverse effects”).

Signs and symptoms

If an overdose with Gilenya occurs, it is important to also monitor for symptoms of bradycardia and bradyarrhythmia. If the overdose occurs at the beginning of treatment, it is important to monitor patients with continuous (real-time) ECG monitoring and hourly pulse and blood pressure measurements for at least the first 6 hours. The same measures as for first-dose monitoring apply (see “Table 1: Monitoring following first dose of Gilenya” under “Dosage/Administration”, and “Warnings and precautions”).

Management

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

Properties/Actions

ATC code

L04AA27

Mechanism of action

Fingolimod is a sphingosine-1-phosphate receptor modulator. The active substance is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds in the low nanomolar concentration range to sphingosine-1-phosphate (S1P) receptors 1, 3 and 4 on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptors 1, 3 and 5 on neural cells in the central nervous system (CNS). By acting as a functional antagonist of S1PR on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. This redistribution reduces the infiltration of pathogenic lymphocytes, including proinflammatory Th17 cells, into the CNS, where they are involved in nerve inflammation and nervous tissue damage. Animal studies and *in vitro* experiments indicate that fingolimod may also exert beneficial effects in

multiple sclerosis via interaction with S1P receptors on neural cells. Fingolimod penetrates the CNS in humans and animals and has been shown to reduce astrogliosis, demyelination and neuronal loss. Moreover, fingolimod increases BDNF (brain-derived neurotrophic factor) levels in the cortex, hippocampus and striatum of the brain, supporting neuronal survival and improving motor functions.

Pharmacodynamics

Immune system

Effects on blood immune cell counts: Within 4-6 hours of the first 0.5 mg dose of fingolimod the lymphocyte count decreases to approximately 75% of baseline. With continued daily dosing the lymphocyte count continues to decrease over a 2-week period, reaching a nadir count of approximately 500 cells/µl or approximately 30% of baseline. 18% of patients reached a nadir of <200 cells/µl on at least one occasion. Low lymphocyte counts are maintained with chronic daily dosing. The majority of T and B lymphocytes regularly traffic through lymphoid organs, so these are the cells most affected by fingolimod. Approximately 15-20% of T lymphocytes have an effector memory phenotype, meaning these cells are important for peripheral immune surveillance. Since this lymphocyte subset does not traffic through lymphoid organs, it is not affected by fingolimod. Peripheral lymphocyte counts increase within days of stopping fingolimod treatment and normal counts are typically reached within 1 to 2 months. Chronic fingolimod dosing leads to a mild decrease in the neutrophil count to approximately 80% of baseline. Monocytes are unaffected by fingolimod.

Heart rate and heart rhythm

Fingolimod causes a transient reduction in heart rate and atrioventricular conduction at the start of treatment (see “Adverse effects”). The maximum decline in heart rate occurs 4-5 hours post dose, with 70% of the negative chronotropic effect achieved on the first day. With continuous treatment heart rate usually returns to baseline values within 1 month.

Fingolimod treatment does not affect the autonomic responses of the heart, nor does it affect diurnal variations in heart rate or response to exercise.

With initiation of fingolimod treatment there is an increase in premature atrial contractions, but there is no increase in the rate of atrial fibrillation/flutter, ventricular arrhythmias or ectopy. Treatment with fingolimod does not lower cardiac output.

The decrease in heart rate induced by fingolimod can be reversed by atropine, isoprenaline or salmeterol.

Potential to prolong the QT interval

In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady state, when the negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTcI, with the upper bound of the 90% CI at ≤13.0 ms. There is no dose- or exposure-response relationship between fingolimod and QTcI prolongation and there is no consistent signal of an increased incidence of QTcI outliers, either absolute or as a change from baseline, associated with fingolimod treatment. However, in study 1 QTcF prolongation between 30-60 ms occurred after the initial 0.5 mg dose of fingolimod in 6.6% of patients (placebo: 2.4%) and in 13.9% (placebo: 6.7%) of patients during the further course of treatment. The clinical relevance is unknown.

Pulmonary system

Fingolimod treatment with single or multiple doses of 0.5 or 1.25 mg for 2 weeks is not associated with a detectable increase in airway resistance as measured by FEV_1 or FEF_{25-75}. However, single doses ≥5 mg (10 times the recommended dose) resulted in a dose-dependent increase in airway resistance. Fingolimod treatment with multiple doses of 0.5, 1.25 or 5 mg does not result in impaired oxygenation, oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Patients being treated with fingolimod have a normal response to inhaled beta-agonists.

Clinical efficacy

The efficacy of Gilenya has been demonstrated in two studies that evaluated once-daily doses of 0.5 mg and 1.25 mg Gilenya in adult patients with relapsing-remitting multiple sclerosis. Both studies included patients who had experienced at least 2 clinical relapses during the 2 years prior to

randomisation or at least 1 clinical relapse during the year prior to randomisation and had an expanded disability status scale (EDSS) score between 0 and 5.5. A third study with the same type of patients was concluded after registration of Gilenya.

The efficacy and safety of once-daily doses of 0.25 mg or 0.5 mg Gilenya (dose selected based on body weight and exposure measurements) were studied in children and adolescents aged from 10 to under 18 years with relapsing-remitting multiple sclerosis.

Study D2301 (FREEDOMS)

Study D2301 (FREEDOMS) was a 2-year randomised, double-blind, placebo-controlled phase III study in patients with relapsing-remitting multiple sclerosis who had not received interferon-beta or glatiramer acetate for at least 3 months prior to the start of the study and had not received natalizumab for at least 6 months prior to the start of the study.

Median age was 37 years, median disease duration was 6.7 years and median EDSS score at baseline was 2.0. Patients were randomised to receive 0.5 mg Gilenya (n=425), 1.25 mg Gilenya (n=429), or placebo (n=418) for up to 24 months. Median duration of treatment was 717 days on 0.5 mg Gilenya, 715 days on 1.25 mg Gilenya and 718.5 days on placebo.

The primary endpoint was the annualised relapse rate.

The annualised relapse rate (ARR) was statistically significantly lower in patients treated with Gilenya than in the placebo group. The key secondary endpoint was the time to 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (increase of at least 0.5 points for patients with baseline EDSS of 5.5), sustained for 3 months. Time to onset of 3-month confirmed disability progression was statistically significantly delayed with Gilenya treatment compared to placebo. There were no statistically significant differences between the 0.5 mg and 1.25 mg doses for any endpoint.

The results for this study are shown in Table 2 and Figure 1.

Table 2 Clinical results and MRI results in FREEDOMS study

NOVARTIS

	0.5 mg Gilenya	Placebo
Clinical endpoints	N=425	N=418
Annualised relapse rate (primary endpoint)	0.18 (p<0.001*)	0.40
Relative reduction (%)	54	
Percentage of patients remaining relapse-free at 24 months	70.4 (p<0.001*)	45.6
Risk of disability progression		
Hazard ratio (95% CI) (3-month confirmed)	0.70 (0.52, 0.96) (p=0.024*)	
Hazard ratio (95% CI) (6-month confirmed)	0.63 (0.44, 0.90) (p=0.012*)	
MRI endpoints		
Number of new or newly enlarging T2 lesions	n=370	n=339
Median (mean) number over 24 months	0.0 (2.5) (p<0.001*)	5.0 (9.8)
Number of Gd-enhancing lesions	n=369 (month 24)	n=332 (month 24)
Median (mean) number at		
Month 6	0.0 (0.2)	0.0 (1.3)
Month 12	0.0 (0.2)	0.0 (1.1)
Month 24	0.0 (0.2) (p<0.001* at each time point)	0.0 (1.1)
Percent change in T2 lesion total volume	n=368	n=339
Median (mean) % change over 24 months	-1.7 (10.6) (p<0.001*)	8.6 (33.8)
Change in T1 hypointense lesion volume	n=346	n=305
Median (mean) % change over 24 months	0.0 (8.8) (p=0.012*)	1.6 (50.7)
Percent change in brain volume	n=357	n=331
Median (mean) % change over 24 months	-0.7 (-0.8) (p<0.001*)	-1.0 (-1.3)

All analyses of clinical endpoints were carried out in the intent-to-treat (ITT) population. MRI analyses used evaluable datasets.

* Indicates statistical significance vs placebo at two-sided 0.05 level.

Determination of p-values: Analysis of aggregate ARR by negative binomial regression adjusting for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS

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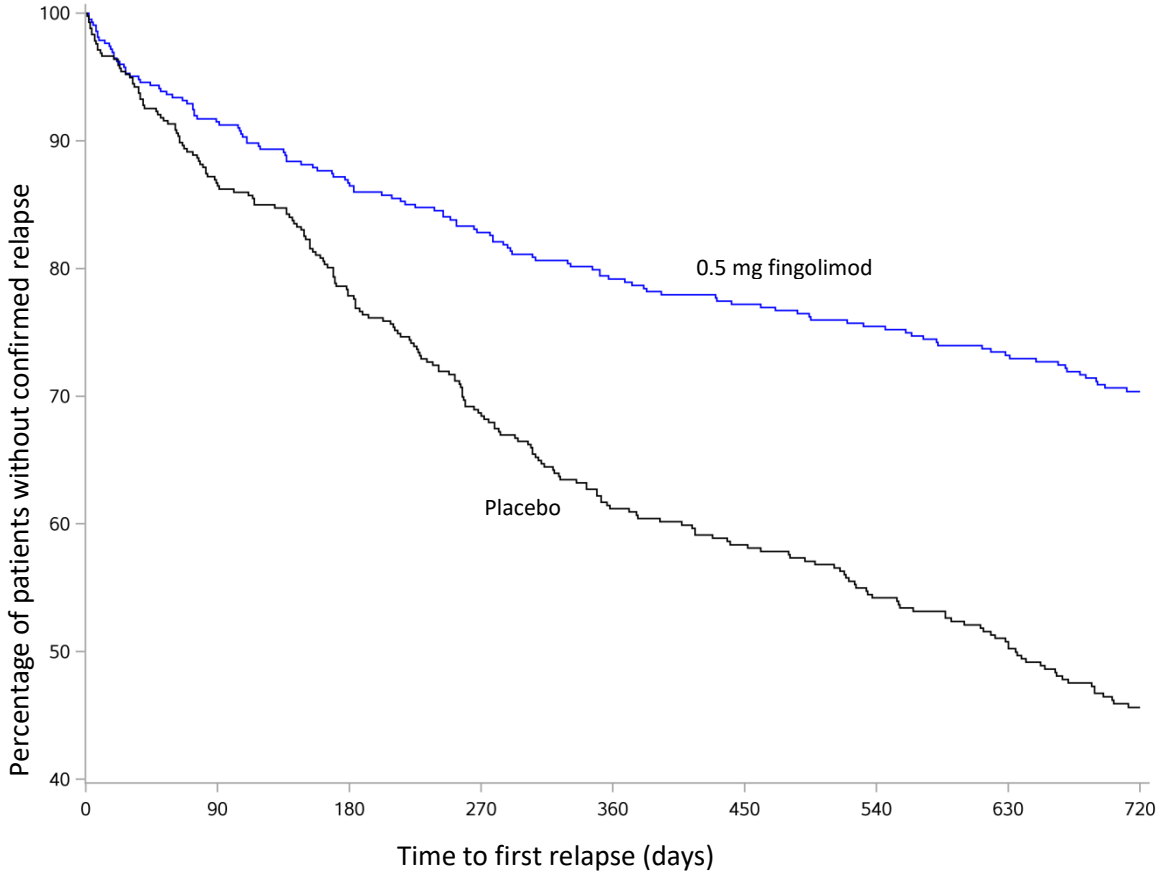
Figure 1 Kaplan-Meier plot of time to first confirmed relapse up to month 24 – FREEDOMS study (ITT population)



Patients who completed the FREEDOMS (D2301) study had the opportunity to take part in the dose-blinded extension study D2301E1. 920 patients from the main study were included in the extension study and were all treated with fingolimod (n=331 continued treatment at 0.5 mg, 289 continued treatment at 1.25 mg, 155 switched from placebo to a dose of 0.5 mg and 145 switched from placebo to a dose of 1.25 mg). After 12 months (month 36) 856 patients (93%) were still enrolled. For 811 patients in total (88.2%) follow-up data from at least 18 months of the extension phase were available.

At month 24 of the extension study the annualised relapse rate (ARR) had dropped by 55% in patients who had been included in the placebo group in the main study and were then switched to 0.5 mg fingolimod (ARR ratio: 0.45, 95% CI 0.32 to 0.62, p<0.001). Patients who had already been treated with

0.5 mg fingolimod in the main study continued to have a low ARR during the extension phase (ARR=0.10).

Between months 24 and 36 the annualised relapse rate (ARR) was 0.17 for patients on 0.5 mg fingolimod in the main study who continued to take 0.5 mg (0.21 in the main study). Patients who switched from placebo to 0.5 mg fingolimod had an ARR of 0.22 (0.42 in the main study).

Study D2309 (FREEDOMS II)

The replicated 2-year randomised, double-blind, placebo-controlled phase III study in 1,083 patients with relapsing remitting multiple sclerosis achieved comparable results to study D2301. This study was completed after fingolimod approval.

The median age was 40.5 years, the median disease duration was 8.9 years and the median EDSS score at baseline was 2.5. The results of this study are shown in Table 3 and Figure 2.

Table 3 Clinical results and MRI results from FREEDOMS II study

	0.5 mg Gilenya	Placebo
Clinical endpoints	N=358	N=355
Annualised relapse rate (primary endpoint)	0.21 (p<0.001*)	0.40
Relative reduction (in %)	48	
Percentage of relapse-free patients after 24 months	71.5 (p<0.001*)	52.7
Risk of disability progression†		
Hazard ratio (95% CI) (3-month confirmed)	0.83 (0.61, 1.12) (p=0.227)	
Hazard ratio (95% CI) (6-month confirmed)	0.72 (0.48, 1.07) (p=0.113)	
MRI endpoints		
Percentage change in brain volume	n=266	n=249
Median (mean) percentage change over 24 months	-0.7 (-0.9) (p<0.001*)	-1.0 (-1.3)
Number of new or newly enlarging T2 lesions	n=264	n=251

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	0.5 mg Gilenya	Placebo
Median (mean) number over 24 months	0.0 (2.3) (p<0.001*)	4.0 (8.9)
Number of Gd-enhancing lesions	n=269 (month 24)	n=256 (month 24)
Median (mean) number at		
Month 6	0.0 (0.2)	0.0 (1.1)
Month 12	0.0 (0.2)	0.0 (1.3)
Month 24	0.0 (0.4) (p<0.001* at each time point)	0.0 (1.2)
Percentage change in the overall volume of T2 lesions	n=262	n=247
Median (mean) percentage change over 24 months	-7.1 (13.7) (p<0.001*)	0.8 (25.1)
Change in T1 hypointense lesion volume	n=225	n=209
Median (mean) percentage change over 24 months	-9.9 (12.6) (p=0.372)	-8.5 (26.4)

All analyses of clinical endpoints were carried out on the intent-to-treat cohort. MRI analyses used the evaluable dataset.
* Statistical significance vs placebo at two-sided 0.05 level.

Determination of p-values: Analysis of aggregate ARR by negative binomial regression adjusted for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS.

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

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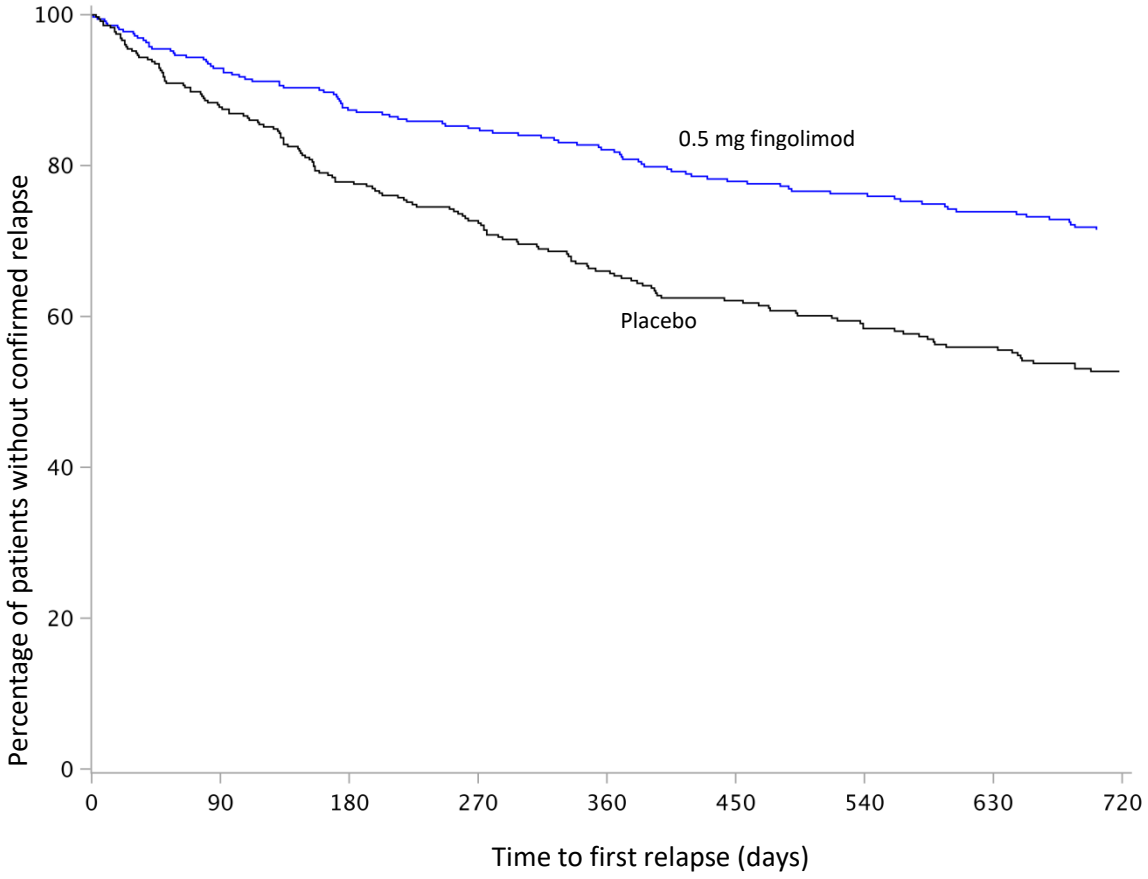
Figure 2 Kaplan-Meier curves for time to first confirmed relapse up to month 24 – FREEDOMS II study (ITT cohort)



None of the endpoints demonstrated statistically significant differences between the 0.5 mg and 1.25 mg doses.

Study D2302 (TRANSFORMS)

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

Median age was 36 years, median disease duration was 5.9 years and median EDSS score at baseline was 2.0. Patients were randomised to receive 0.5 mg Gilenya (n=431), 1.25 mg Gilenya (n=426) or 30 µg interferon beta-1a IM once weekly (n=435) for up to 12 months. Median time on study drug was

365 days (0.5 mg Gilenya), 354 days (1.25 mg Gilenya) and 361 days (interferon beta-1a).

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

Table 4 Clinical results and MRI results from the TRANSFORMS study

	0.5 mg Gilenya	Interferon beta-1a, 30 µg
Clinical endpoints	N=429	N=431
Annualised relapse rate (primary endpoint)	0.16 (p<0.001*)	0.33
Relative reduction (%)	52	
Percentage of patients remaining relapse-free at 12 months	82.5 (p<0.001*)	70.1
Risk of disability progression		
Hazard ratio (95% CI) (3-month confirmed)	0.71 (0.42, 1.21) (p=0.209)	
MRI endpoints		
Number of new or newly enlarging T2 lesions	n=380	n=365
Median (mean) number over 12 months	0.0 (1.7) (p=0.004*)	1.0 (2.6)
Number of Gd-enhancing lesions	n=374	n=354
Median (mean) number after 12 months	0.0 (0.2) (p<0.001*)	0.0 (0.5)
Percent change in brain volume	n=368	n=359
Median (mean) percentage change over 12 months	-0.2 (-0.3) (p<0.001*)	-0.4 (-0.5)

All analyses of clinical endpoints were carried out in the intent-to-treat (ITT) population. MRI analyses used evaluable datasets.

* Indicates statistical significance vs interferon beta-1a IM at two-sided 0.05 level.

Determination of p-values: Analysis of aggregate ARR by negative binomial regression adjusted for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS.

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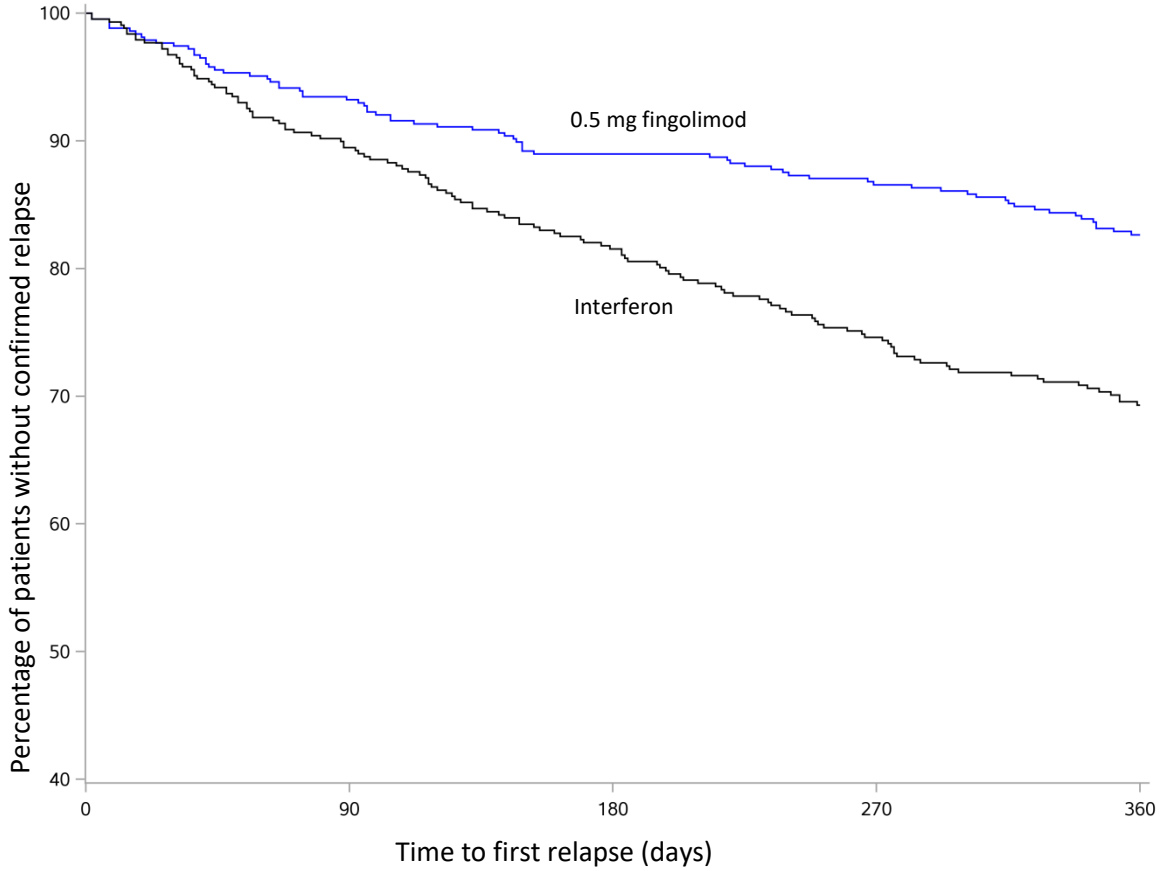
Figure 3 Kaplan-Meier plot of time to first confirmed relapse up to month 12 – TRANSFORMS study (ITT population)



There were no statistically significant differences between the 0.5 mg and 1.25 mg doses for any endpoint.

Patients who completed the TRANSFORMS (D2302) study had the opportunity to take part in the dose-blinded extension study (D2301E1). A total of 1,030 patients were included from the main study and treated with fingolimod (n=357 continued treatment at 0.5 mg, 330 continued treatment at 1.25 mg, 167 switched from interferon beta-1a to 0.5 mg and 176 switched from interferon beta-1a to 1.25 mg). For 822 of these patients (85.9%) follow-up data from at least 12 months of the extension phase were available.

At month 12 of the extension study patients who had received interferon beta-1a IM in the main study and were then switched to 0.5 mg fingolimod had relative reductions in ARR of 30% (ARR ratio=0.70, p=0.06). Patients who had already been treated with 0.5 mg fingolimod in the main study

continued to have a low ARR during the main and extension phase (ARR=0.18 up to month 24).

Between months 12 and 24 the ARR was 0.20 for patients on 0.5 mg fingolimod in the main study who continued to take 0.5 mg (0.19 in the main study). Patients who switched from interferon beta-1a to 0.5 mg fingolimod had an ARR of 0.33 (0.48 in the main study).

Overall, the results of studies D2301 (FREEDOMS) and D2302 (TRANSFORMS) showed a consistent reduction in the annualised relapse rate vs comparator in the subgroups defined by gender, age, prior MS therapy, disease activity or disability levels at baseline.

Study D2311 (PARADIGMS) in children and adolescents aged 10 years and over

Study D2311 (PARADIGMS) was a double-blind, randomised, active-controlled, multicentre, parallel-group study with a flexible duration of up to 24 months to investigate the efficacy and safety of fingolimod (n=107) compared to interferon beta-1a (n=107) in children and adolescents with relapsing-remitting MS aged from 10 to under 18 years. Prior therapy with interferon beta, dimethyl fumarate or glatiramer acetate up to the time of randomisation was permitted. Patients with at least one clinical relapse in the previous year or at least 2 clinical relapses in the 2 years prior to randomisation or MRI evidence of ≥1 Gd-enhancing lesion within 6 months prior to randomisation and an EDSS of between 0 and 5.5 were included. Neurological evaluations were performed at screening, then every 3 months and at the time of a suspected relapse. The MRI evaluations were performed at screening, then every 6 months throughout the study. The primary endpoint was the annualised relapse rate.

The median age was 16 years, the median disease duration since onset of the first symptom was 1.5 years and the median EDSS score at baseline was 1.5. Patients were randomised and received either fingolimod or interferon beta-1a administered intramuscularly once weekly for up to 24 months. Few patients were included in the ≥10 to ≤12 years age group (n=13 on Gilenya) and in the ≤40 kg weight category (n=9 on Gilenya), meaning that only limited efficacy and safety data are available in these patient populations. The median

treatment duration with the study drug was 634 days for fingolimod and 547 days for interferon beta-1a.

The primary endpoint, the annualised relapse rate (ARR), was statistically significantly lower in patients treated with fingolimod than in those who received interferon beta-1a (81.9% relative reduction in ARR). The key secondary endpoint, the annualised number of new or newly enlarging T2 lesions up to month 24, was also statistically significantly lower in patients treated with fingolimod than in those who received interferon beta-1a, as was the number of Gd-enhancing T1 lesions per scan up to month 24. Fingolimod also led to a statistically significant reduction in the annualised brain atrophy rate from baseline up to month 24. An additional post-hoc analysis showed that fingolimod led to a statistically significant increase in time to 3-month confirmed disability progression compared to interferon beta-1a.

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

Table 5 Clinical and MRI results from the PARADIGMS study

	Fingolimod 0.25 mg or 0.5 mg	**Interferon beta-1a IM 30 µg**
Clinical endpoints	N=107	N=107[#]
Annualised relapse rate (primary endpoint)	0.122 (p<0.001*)	0.675
Relative reduction (in percent)	81.9	
Percentage of patients remaining relapse-free up to month 24	85.7 (p<0.001*)	38.8
Risk of disability progression		
Hazard ratio (95% CI) (3-month confirmed)	0.23 (0.08, 0.66) (p=0.007*)	
Hazard ratio (95% CI) (6-month confirmed)	0.20 (0.04; 0.93) (p=0.040**)	
MRI endpoints		
Annualised number of new or newly enlarging T2 lesions	n=106	n=102
Adjusted mean	4.393 (p<0.001*)	9.269
Relative reduction (percent)	52.6	

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	Fingolimod 0.25 mg or 0.5 mg	Interferon beta-1a IM 30 µg
Number of Gd-enhancing T1 lesions per scan up to month 24	n=105	n=95
Adjusted mean	0.436 (p<0.001*)	1.282
Relative reduction (percent)	66.0	
Annualised brain atrophy rate from baseline up to month 24	n=96	n=89
Least square mean	-0.48 (p=0.014*)	-0.80

All analyses of clinical endpoints were carried out on the full analysis set. MRI analyses used the evaluable dataset.

[#] 1 patient was randomised to treatment with 30 µg interferon beta-1a IM once weekly but was unable to swallow the additional dose of placebo required as part of the double-dummy method and was taken out of the study. This patient was excluded from the full analysis and safety set.

* Indicates statistical significance vs interferon beta-1a IM at two-sided 0.05 level.

** Post-hoc analysis, Cox's proportional hazards model. p=0.180 in log-rank test.

Determination of p-values: Aggregate ARR: by negative binomial regression, adjusted for treatment, country, puberty status (the stratification factor in the interactive voice response system (IVRS)) and number of relapses in previous 2 years (offset: time in the study); percentage of patients remaining relapse-free: using a Kaplan-Meier estimate; risk of disability progression: using Cox's proportional hazards model, adjusted for treatment, country, puberty status (the stratification factor in the IVRS) and number of relapses in previous 2 years; annualised number of new/newly enlarging T2 lesions: by negative binomial regression, adjusted for treatment, region, puberty status (the stratification factor in the IVRS) and number of T2 lesions at baseline (offset: time in the study); number of Gd-enhancing lesions per scan: by negative binomial regression with the cumulative number of Gd-enhancing T1 lesions on all scheduled post-baseline MRI scans during the study as a response variable, adjusted for treatment, country, puberty status (the stratification factor in the IVRS) and the number of Gd-enhancing T1 lesions at baseline (offset: number of MRI scans); annualised brain atrophy rate: using an ANCOVA model, adjusted for treatment, region, puberty status (the stratification factor in the IVRS) and baseline whole brain volume.

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Fig. 4 **Kaplan-Meier plot of time to first confirmed relapse up to month 24 – PARADIGMS study (full analysis set)**

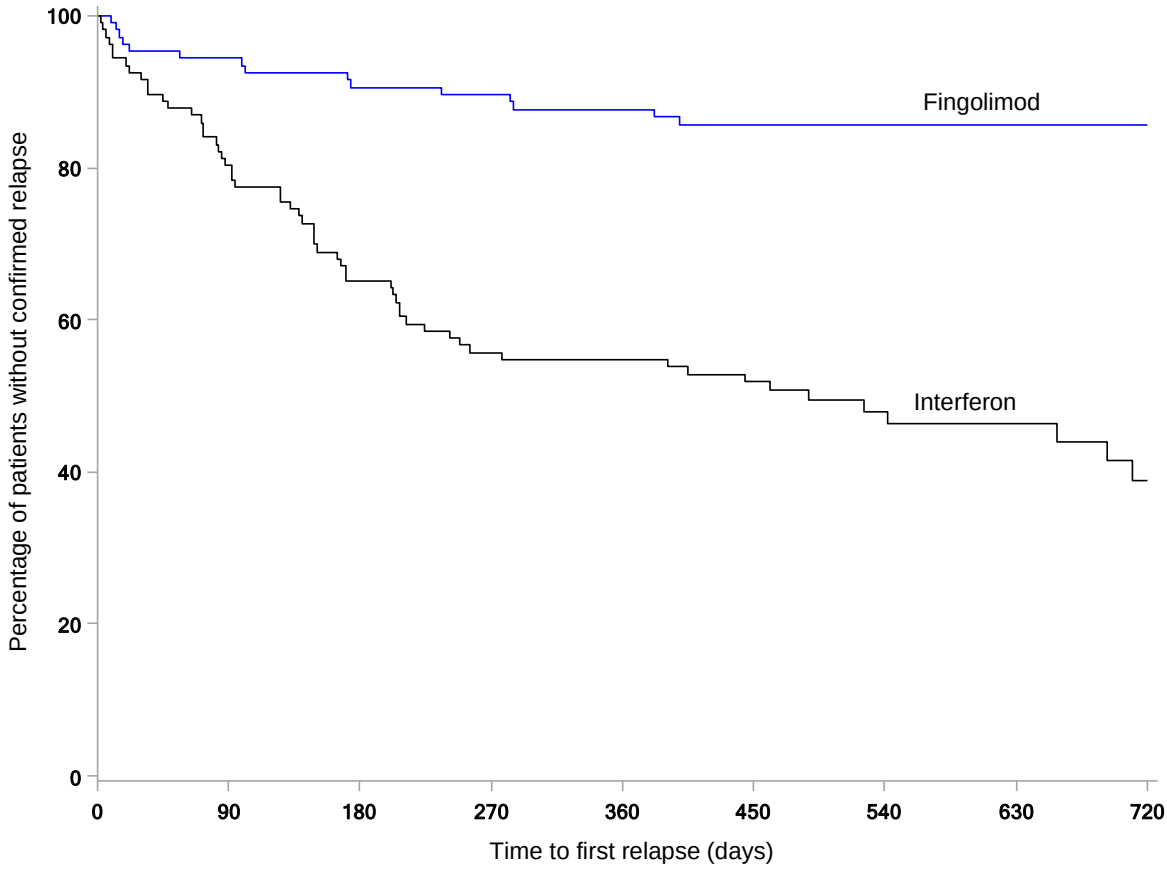

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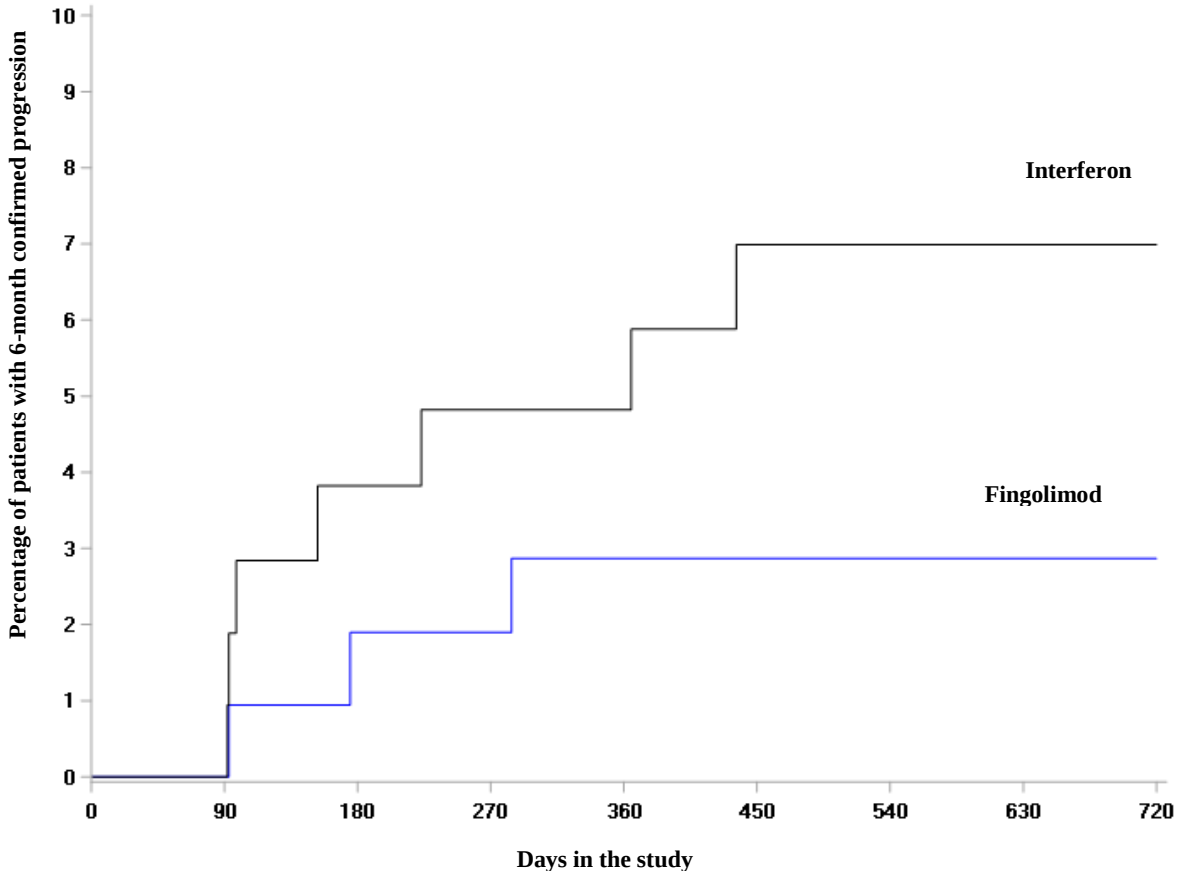
Fig. 5 **Kaplan-Meier plot of time to 6-month confirmed disability progression – PARADIGMS study (full analysis set)**



Pharmacokinetics

Absorption

Fingolimod absorption is slow (t_{max} of 12-16 hours) and extensive (≥85%, based on the amount of radioactivity excreted in the urine and the amount of metabolites excreted in the faeces extrapolated to infinity). The apparent absolute oral bioavailability is high (93%).

Food intake does not alter C_{max} or exposure (AUC) of fingolimod. Gilenya may therefore be taken independently of meals (see "Dosage/Administration").

Steady-state blood concentrations are reached within 1 to 2 months of once-daily administration and are approximately 10 times greater than after the first dose.

Distribution

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

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1200 ± 260 l. A study with 4 healthy volunteers who received fingolimod radiolabelled with iodine as an intravenous single dose showed that fingolimod penetrates into the brain. In a study on 13 male patients with multiple sclerosis who received 0.5 mg Gilenya per day at steady state the amount of fingolimod (and fingolimod phosphate) in the ejaculate was over 10,000 times lower than the dose administered (0.5 mg).

Metabolism

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

Following single oral administration of [^{14}C]-fingolimod the major fingolimod-related components in blood – as assessed by their contribution to the AUC relative to the total contribution of all radiolabelled components up to 816 hours post dose – are fingolimod itself (23.3%), fingolimod phosphate (10.3%) and inactive metabolites (M3 carboxylic acid metabolite (8.3%), M29 ceramide metabolite (8.9%) and M30 ceramide metabolite (7.3%)).

Elimination

Fingolimod blood clearance is 6.3 ± 2.3 l/hour and the average apparent terminal elimination half-life ($t_{1/2}$) is 6-9 days. Blood levels of fingolimod

phosphate decline in parallel with those of fingolimod in the terminal phase, yielding similar half-lives for both substances.

After oral administration about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod phosphate are not excreted intact in the urine but are the major components in the faeces, with amounts representing less than 2.5% of the dose in each case. After 34 days the recovery of the administered dose is 89%.

Linearity/non-linearity

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

In children and adolescents fingolimod phosphate levels increase in an apparently dose-proportional manner after multiple, once-daily doses of 0.25 mg or 0.5 mg fingolimod.

Pharmacokinetics in special populations

Ethnicity

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

Gender

Gender has no influence on fingolimod and fingolimod phosphate pharmacokinetics.

Hepatic dysfunction

The pharmacokinetics of a single dose (1 or 5 mg) of fingolimod in patients with mild, moderate and severe hepatic impairment (Child-Pugh class A, B and C) were unchanged in terms of fingolimod C_{max} but AUC increased by 12%, 44% and 103%, respectively. The apparent elimination half-life is unchanged in mild hepatic impairment but is prolonged by 49-50% in moderate and severe hepatic impairment. In patients with severe hepatic impairment (Child-Pugh class C) fingolimod phosphate C_{max} was decreased

by 22% and AUC increased by 38%. Fingolimod phosphate pharmacokinetics were not determined in patients with mild or moderate hepatic impairment.

Renal dysfunction

Severe renal impairment increases fingolimod C_{max} and AUC by 32% and 43%, respectively, and fingolimod phosphate C_{max} and AUC by 25% and 14%, respectively. The apparent elimination half-life is unchanged for both analytes. No Gilenya dose adjustments are needed in patients with renal impairment.

Elderly patients

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

Children and adolescents

The concentration of fingolimod phosphate at steady state is lower in children and adolescents than in adults.

The safety and efficacy of Gilenya in children and adolescents below 10 years of age have not been studied.

Preclinical data

The preclinical safety profile of fingolimod was assessed in mice, rats, dogs and monkeys. The major target organs were the lymphoid system (lymphopenia and lymphoid atrophy), lungs (increased weight, smooth muscle hypertrophy at the bronchoalveolar junction) and heart (negative chronotropic effect, increase in blood pressure, perivascular changes and myocardial degeneration) in several species, the blood vessels (vasculopathy) in rats only and the pituitary, forestomach, liver, adrenals, gastrointestinal tract and nervous system at high doses only (often associated with signs of general toxicity) in several species.

Mutagenicity and carcinogenicity

Fingolimod was not mutagenic in an Ames test and in a L5178Y mouse lymphoma cell line *in vitro*. No clastogenic effects were seen *in vitro* in V79 Chinese hamster lung cells. Fingolimod induced numerical (polyploidy) chromosomal aberrations in V79 cells at concentrations of 3.7 µg/ml and above. Fingolimod was not clastogenic in the *in vivo* micronucleus tests in mice and rats.

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

Reproductive toxicity

Fingolimod had no effect on sperm count/motility, nor on fertility in male and female rats up to the highest dose tested (10 mg/kg), representing an approximately 150-fold higher margin based on human systemic exposure (AUC) at the 0.5 mg dose.

Fingolimod was teratogenic in rats when given at doses of 0.1 mg/kg or higher. The most common fetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. An increase in the rate of post-implantation fetal loss was observed at doses of 1 mg/kg and higher. A decrease in the number of viable fetuses was observed at doses of 3 mg/kg. Fingolimod was not teratogenic in rabbits, but increased embryofetal mortality was seen at doses of 1.5 mg/kg and higher, as well as fetal growth retardation and a decrease in the number of viable fetuses at 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 the milk of treated animals during lactation. Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

Juvenile animal studies

Results from two toxicity studies in juvenile rats showed minor effects on bone mineral density and neurobehavioural response as well as a slight delay in sexual maturity and a minor reduction in immune response to repeated stimulations with keyhole limpet haemocyanin (KLH). These effects were not considered adverse events. Overall, the treatment-related effects of fingolimod in juvenile animals were comparable to those observed in adult rats at a similar dosage, with the exception of the absence of smooth muscle hypertrophy in the lungs of the juvenile rats. The no observed adverse effect levels (NOAEL) in juvenile animals were primarily determined by unspecific effects on body weight or food consumption rather than overt toxicity.

Other information

Incompatibilities

Not applicable.

Shelf life

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

Special precautions for storage

Do not store above 30°C.

Store in the original pack.

Keep the container in the outer carton in order to protect the contents from moisture.

Keep out of the reach of children.

Pack sizes

0.25 mg capsules: blister pack containing 7 or 28.

0.5 mg capsules: blister pack containing 28 or 98.

Not all Pack sizes and strengths are marketed in all countries.

Manufacturer

Novartis Pharma Stein AG, Stein, Switzerland

NOVARTIS

For

Novartis Pharma AG

Lichtstrasse 35 Basle, Switzerland

Information last revised

February 2020

Novartis Pharma AG, Basle, Switzerland

This is a medicament

– A medicament is a product, which affects your health, and its consumption contrary to instructions is dangerous for you.

– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

– The doctor and the pharmacist are experts in medicine, its benefits and risks.

– Do not by yourself interrupt the period of treatment prescribed for you.

– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacist