PRESCRIBING INFORMATION

For the use of a registered medical practitioner or a hospital or a laboratory only

FINCORD
Fingolimod Capsules 0.5mg

1. NAME OF THE MEDICINAL PRODUCT

FINCORD [Fingolimod Capsules 0.5mg]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains:
Fingolimod hydrochloride USP 0.56mg eq.to
Fingolimod 0.5mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsule
Bright yellow opaque/white opaque size "3" hard gelatin capsule imprinted with "FO 0.5 mg" on the cap and two radial bands on the capsule body with yellow ink containing white to off white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fincord is indicated as monotherapy for the treatment of adult patients and paediatric patients of 10 years of age and above with the relapsing-remitting form of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the progression of physical disability.

4.2 Posology and method of administration

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

Posology

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

In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight:

- Paediatric patients with body weight ≤ 40 kg: one 0.25 mg capsule daily taken orally.
- Paediatric patients with body weight > 40 kg: one 0.5 mg capsule daily taken orally.

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

Fincord can be taken with or without food. If a dose is missed treatment should be continued with the next dose as planned.
When switching from a 0.25 mg to a 0.5 mg daily dose, it is recommended to repeat the observation after first dose.
For recommendations related to switching patients from other disease modifying therapies to Fingolimod (see section 4.4).

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

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

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

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

Paediatric population (below 10 years of age)
The safety and efficacy of Fingolimod in paediatric patients below 10 years of age have not yet been studied.

Note: Fincord is available in only one strength of 0.5mg. Fincord is not able to deliver dose regimens of Fingolimod to Paediatric patients with body weight ≤ 40 kg; other approved dosage forms and strengths of Fingolimod should be used in such cases.

Method of administration
This medicinal product is for oral use.

4.3 Contraindications

Known immunodeficiency syndrome.

Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies).
Severe active infections, active chronic infections (hepatitis, tuberculosis).
Known active malignancies, except for patients with cutaneous basal cell carcinoma. Severe liver impairment (Child-Pugh class C).
Patients who in the last 6 months had myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure.
Patients who have concomitant treatment with Class Ia or Class III anti-arrhythmic drugs (see section 4.4).
Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not have a pacemaker (see section 4.4).
Patients with a baseline QTc interval ≥500 msec (see section 4.4).
Known hypersensitivity to fingolimod or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

After the first dose, the decline in heart rate starts within one hour and is steepest within 6 hours. The negative chronotropic effect of Fingolimod persists beyond 6 hours and progressively attenuates over subsequent days of treatment. With continued administration, heart rate returns to baseline within one month. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. If necessary, the decrease in heart rate induced by fingolimod can be reversed by parenteral doses of atropine or isoprenaline.

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

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

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

If the heart rate at 6 hours is the lowest since the first dose was administered (suggesting that the maximum pharmacodynamic effect on the heart may not yet be manifest), monitoring should be extended by at least 2 hours and until heart rate increases again. Additionally, if at 6 hours, the heart rate is <45 bpm in adults, <55 bpm in paediatric patients aged 12 years and

above, or <60 bpm in paediatric patients aged 10 to below 12 years, or the ECG shows new onset second degree or higher grade AV block or a QTc interval ≥500 msec, extended monitoring (at least overnight monitoring), should be performed, and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring (at least overnight monitoring).

Due to the risk of serious cardiac rhythm disturbances, Fingolimod should not be used in patients with sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope. Since initiation of Fingolimod treatment results in decreased heart rate and therefore a prolongation of the QT interval, Fingolimod should not be used in patients with significant QT prolongation (QTc>470msec [adult females], QTc >460msec [paediatric females] or QTc >450msec [adult and paediatric males]) (see also section 4.3). Fingolimod is best avoided in patients with relevant risk factors for QT prolongation, for example, hypokalaemia, hypomagnesemia or congenital QT prolongation. Since significant bradycardia may be poorly tolerated in patients with history of cardiac arrest, uncontrolled hypertension or severe untreated sleep apnea, Fingolimod should not be used in these patients (see also section 4.3). In such patients, treatment with Fingolimod should be considered only if the anticipated benefits outweigh the potential risks. In patients for whom Fingolimod is not contraindicated, if treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy, at least overnight extended monitoring is recommended for treatment initiation (see also section 4.5).

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

Experience with Fingolimod is limited in patients receiving concurrent therapy with beta blockers, heart- rate-lowering calcium channel blockers (such as verapamilor diltiazem), or other substances that may decrease heart rate (e.g. ivabradine, digoxin, anticholinesteratic agents or pilocarpine). Since the initiation of Fingolimod treatment is also associated with slowing of the heart rate (see also section 4.8, 'Bradyarrhythmia'), concomitant use of these substances during Fingolimod initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with Fingolimod should not be initiated in patients who are concurrently treated with these substances (see also section 4.5). In such patients, treatment with Fingolimod should be considered only if the anticipated benefits outweigh the potential risks. If treatment with Fingolimod is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering medicinal products prior to initiation of treatment. If the heart-rate-lowering medication cannot be stopped, cardiologist's advice should be sought to determine appropriate first dose monitoring, at least overnight extended monitoring is recommended (see also section4.5).

If therapy is discontinued for more than 2 weeks after the first month of treatment, the effects on heart rate and atrioventricular conduction may recur on re-introduction of Fingolimod treatment and the same precautions as for the first dose should apply. Within the first 2 weeks of treatment, first dose procedures are recommended after an interruption of one day or more. During weeks 3 and 4 of treatment first dose procedures are recommended after a treatment interruption of more than 7 days.

<u>QT interval</u>

In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTcI, with the upper limit of the 90% CI ≤13.0 ms. There is no dose- or exposure-response relationship of fingolimod and QTcI prolongation. There is no consistent signal of increased incidence of QTcI outliers, either absolute or change from baseline, associated with fingolimod treatment.

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

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

Immunosuppressive effects

Fingolimod has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal (see section 4.4, Infections), and may also increase the risk of developing certain malignancies (e.g., lymphoma, basal cell carcinoma, malignant melanoma; see section 4.4, Basal cell carcinoma and other cutaneous neoplasms; and section 4.8, Lymphomas). Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis.

Infections

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

Before initiating treatment with Fingolimod, a recent complete blood count (CBC) (i.e. within 6 months) should be available. Assessments of CBC are also recommended periodically during treatment, and in case of signs of infection. Absolute lymphocyte count $<0.2x10^9$/l, if confirmed, should lead to treatment interruption until recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count $<0.2x10^9$/l.

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

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in the post-marketing setting (see section 4.8). PML is an opportunistic infection caused by JC virus, which may be fatal or result in severe disability. Cases of PML have occurred after approximately 2-3 years of treatment. Although the estimated risk appears to increase with cumulative exposure over time, an exact relationship with the duration of treatment is unknown. The incidence rate for PML appears to be higher for patients in Japan; the reasons are currently unknown. Additional PML cases have occurred in patients who had been treated previously with natalizumab, which has a known association with PML. During routine MRI (in accordance with national and local recommendations), physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, Fingolimod treatment should be suspended until PML has been excluded. MRI findings suggestive of PML may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings

and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with MS medications associated with PML, including Fingolimod.

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

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

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

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

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

Initiation of treatment with Fingolimod should be delayed in patients with severe active infection until resolution. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. During treatment, patients receiving Fingolimod should be instructed to report symptoms of infection to their physician.

Suspension of treatment with Fingolimod should be considered if a patient develops a serious infection and consideration of benefit-risk should be undertaken prior to re-initiation oftherapy.

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

Macular edema

Macular edema with or without visual symptoms has been reported in 0.4% of patients treated with fingolimod 0.5 mg, occurring predominantly in the first 3-4 months of therapy (see section 4.8). An ophthalmic evaluation is therefore recommended 3-4 months after treatment initiation. If patients report visual disturbances at any time while on therapy, an evaluation of the fundus, including the macula, should be carried out.

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular oedema (see section 4.8). Fingolimod has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. It is recommended that multiple sclerosis patients with diabetes mellitus or a history of uveitis undergo an ophthalmic evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy.

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

Liver function

Increased hepatic enzymes, mostly alanine aminotransaminase (ALT) elevation, have been reported in multiple sclerosis patients treated with Fingolimod. In clinical trials, a 3-fold the upper limit of normal (ULN) or greater elevation in ALT occurred in 8.0% of adult patients treated with Fingolimod 0.5 mg compared to 2% of placebo patients. Elevations 5-fold the ULN occurred in 2% of patients on Fingolimod 0.5 mg and 1% of patients on placebo. In clinical trials, Fingolimod was discontinued if the elevation exceeded 5 times the ULN. Recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to fingolimod.

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

In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of fingolimod.

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

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

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with Fingolimod and should be monitored periodically while on treatment and until two months after Fingolimod discontinuation. In the absence of clinical symptoms, liver transaminases should be monitored at Months 1, 3, 6, 9 and 12 on therapy and

periodically thereafter. If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurement. With repeated confirmation of liver transaminases above 5 times the ULN, treatment with Fingolimod should be interrupted and only re-commenced once liver transaminase values have normalised.

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

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

Posterior reversible encephalopathy syndrome

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

Interference with serological testing

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

Blood pressure effects

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

In MS clinical trials, patients treated with fingolimod 0.5 mg had an average increase of approximately 3 mmHg in systolic pressure, and approximately 1 mmHg in diastolic pressure, first detected approximately 1 month after treatment initiation, and persisting with continued treatment. In the two- year placebo-controlled study, hypertension was reported as an adverse event in 6.1% of patients on fingolimod 0.5 mg and in 3.8% of patients on placebo. Therefore, blood pressure should be regularly monitored during treatment with Fingolimod.

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

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

Beta interferon, or glatiramer acetate
Fingolimod can generally be started immediately after discontinuation of beta interferon, or glatiramer acetate.

Natalizumab
Due to the long elimination half-life of natalizumab, caution regarding potential additive immune effects is required when switching patients from natalizumab to Fingolimod. A careful case-by-case assessment regarding the timing of the initiation of Fingolimod treatment is recommended. Elimination of natalizumab usually takes up to 2-3 months followingdiscontinuation.

Malignancies
Cutaneous Malignancies
Basal cell carcinoma (BCC) and other cutaneous neoplasms, including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma, have been reported in patients receiving Fingolimod (see section 4.8). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Since there is a potential risk of malignant skin growths, patients treated with Fingolimod should be cautioned against exposure to sunlight without protection. Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, and then every 6 to 12 months taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions aredetected.

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

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

Return of disease activity (rebound) after Fingolimod discontinuation

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

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

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

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

Special populations
Paediatric patients (10 years of age and above)
It is recommended that paediatric patients complete all immunizations in accordance with current immunization guidelines prior to initiating Fingolimod therapy.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Anti-neoplastic, immune-modulating or immunosuppressive therapies
Anti-neoplastic, immune-modulating or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects (see sections 4.3 and 4.4). For the same reason, corticosteroids should be co-administered with caution. Specific decisions as to the dosage and duration of concomitant treatment with corticosteroids should be based on clinical judgment.

Co-administration of a short course of corticosteroids (up to 5 days) did not increase the overall rate of infection in patients treated with fingolimod. (see sections 4.4 and 4.8).
Caution should also be applied when switching patients from long-acting therapies with immune effects such as natalizumab or mitoxantrone (see section 4.4: Prior treatment with immunosuppressive or immune-modulating therapies).

Vaccination
During and for up to two months after treatment with Fingolimod capsule 0.5mg vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should therefore also be avoided during Fingolimod capsule 0.5mg treatment and for up to 2 months after treatment with Fingolimod capsule 0.5mg.
For paediatric patients, please also refer to subsection 'Paediatric patients (10 years of age and above)'.

Bradycardia-inducing substances
Fingolimod has been studied in combination with atenolol and diltiazem. When fingolimod was used with atenolol in an interaction study in healthy volunteers, there was an additional 15% reduction heart rate at fingolimod treatment initiation, an effect not seen with diltiazem. Treatment with Fingolimod capsule 0.5mg should not be initiated in patients receiving beta blockers, or other substances which may decrease heart rate, such as Class Ia and III antiarrhythmics, calcium channel blockers (such as verapamil or diltiazem), or other substances which may decrease heart rate (e.g. ivabradine or digoxin), anticholinesteratic agents or pilocarpine because of the potential additive effects on heart rate (see sections 4.4 and 4.8). If treatment with Fingolimod capsule 0.5mg is considered in such patients, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering medicinal products or appropriate monitoring for treatment initiation, at least overnight monitoring is recommended, if the heart-rate-lowering medication cannot be stopped.

Pharmacokinetic interactions of other substances on fingolimod
Fingolimod is primarily cleared *via* cytochrome CYP450 4F2 (CYP4F2) and possibly other CYP4F isoenzymes. Other enzymes like CYP3A4 may also contribute to its metabolism. Co-administration of fingolimod with ketoconazole resulted in a 1.7-fold increase in fingolimod and fingolimod phosphate exposure (AUC). Caution should be exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin).

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

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

Co-administration of fingolimod 0.5 mg with oral contraceptives (ethinylestradiol and levonorgestrel) did not elicit any change in oral contraceptive exposure. Fingolimod and fingolimod- phosphate exposure were consistent with those from previous studies. No interaction studies have been performed with oral contraceptives containing other progestagens, however an effect of fingolimod on their exposure is not expected.

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

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

4.6 Pregnancy, lactation, females and males of reproductive potential

Pregnancy

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

Risk summary

There are no adequate and well-controlled studies in pregnant females.

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

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

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

Reproductive studies in rats have demonstrated that Fingolimod induced teratogenicity starting at a dose corresponding to 2 times the exposure in humans at the recommended dose of 0.5 mg. Animal studies have shown reproductive toxicity including fetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect. Furthermore, the receptor affected by fingolimod (sphingosine-1-phosphate receptor) is known to be involved in vascular formation during embryogenesis.

Studies from USA, Canada, major EU countries and South American countries have shown that the risk of birth defects in multiple sclerosis (MS) population is similar to that in the general population. For spontaneous abortions and still births, the background risk in the MS population in the US appears to be similar to that in the general US population.

Clinical considerations

If Fingolimod is discontinued because of pregnancy or planned pregnancy see section 4.4 Special warnings and precautions for use - Return of disease activity (rebound) after Fingolimod

discontinuation and stopping therapy. For females planning to become pregnant, Fingolimod should be stopped 2 months before conception.

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

Human data
In more than 600 prospective pregnancies with live births, still births or termination of pregnancy due to fetal anomaly with maternal exposure to fingolimod during pregnancy that were reported in 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 malformation reported for Fingolimod is similar to that observed in the general population, wherein the common 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 Fingolimod.

Animal data
Fingolimod was teratogenic in rats when given at doses of 0.1 mg/kg or higher. A dose of 0.1 mg/kg in rats corresponds to 2 times the exposure in humans at the recommended dose of 0.5 mg. The most common fetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. An increase in post-implantation loss was observed in rats at 1 mg/kg and higher and a decrease in viable fetuses at 3 mg/kg. Fingolimod was not teratogenic in rabbits, however an increased embryo-fetal mortality was seen at doses of 1.5 mg/kg and higher, and a decrease in viable fetuses as well as fetal growth retardation at 5 mg/kg. A dose of 1.5 mg/kg in rabbits corresponds to similar exposure in humans at the recommended dose of 0.5mg.

Available data do not suggest that Fingolimod would be associated with an increased risk of male- mediated fetal toxicity.

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, behavior, and fertility were not affected by treatment with fingolimod.

Lactation
Risk summary
Fingolimod is transferred into the milk of treated animals during lactation at concentrations 2-3-fold higher than that found in maternal plasma (see section 5.3). There are no data on the effects of Fingolimod on the breastfed child or the effects of Fingolimod on milk production. Since many drugs are transferred into human milk and because of the potential for serious adverse reactions to fingolimod in nursing infants, females receiving Fingolimod should not breastfeed.

Females and males of reproductive potential

Pregnancy testing

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

Contraception

Before initiation of Fingolimod treatment, females of childbearing potential should be counselled regarding the potential for a serious risk to the foetus and the need for effective contraception during treatment with Fingolimod and for 2 months after stopping treatment. Since it takes approximately two months to eliminate fingolimod from the body after stopping treatment (see section 4.4), the potential risk to the foetus may persist and contraception should be continued during this period.

Infertility

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

4.7 Effects on ability to drive and use machines

Fingolimod capsule 0.5mg has no or negligible influence on the ability to drive and use machines.

However, dizziness or drowsiness may occasionally occur when initiating therapy with Fingolimod capsule 0.5mg. On initiation of Fingolimod capsule 0.5mg treatment it is recommended that patients be observed for a period of 6 hours (see section 4.4, Bradyarrhythmia).

4.8 Adverse drug reactions

Summary of the safety profile

The safety population of Fingolimod is derived from two Phase III placebo-controlled clinical trials and one Phase III active-controlled clinical trial in adult patients with relapsing remitting multiple sclerosis. It includes a total of 2,431 adult patients on Fingolimod (0.5 or 1.25 mg dose). Study D2301 (FREEDOMS) was a 2-year placebo-controlled clinical study in 854 multiple sclerosis adult patients treated with fingolimod (placebo: 418). Study D2309 (FREEDOMS II) was a 2 year placebo-controlled clinical study in 728 multiple sclerosis adult patients treated with fingolimod (placebo: 355). In the pooled data from these two studies the most serious adverse drug reactions (ADRs) for the 0.5 mg recommended therapeutic dose were infections, macular oedema and transient atrioventricular block at treatment initiation. The most frequent ADRs (incidence ≥10%) at the 0.5 mg were headache, hepatic enzyme increased, diarrhoea, cough, influenza, sinusitis, and back pain. The most frequent adverse event reported for Fingolimod 0.5 mg leading to treatment interruption was ALT elevations (2.2%).

The ADRs for fingolimod in Study D2302 (TRANSFORMS), a 1-year study in 849 adult patients treated with fingolimod which used interferon beta-1a as comparator, were generally

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

Tabulated summary of adverse drug reactions from clinical trials

Table 1 presents the frequency of ADRs reported in the pooled analysis of the placebo-controlled studies FREEDOMS and FREEDOMS II. The ADRs were defined based on a difference of incidence (1% higher in active group over placebo) and/or medical assessment of each event.

ADRs are listed according to MeDRA 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); not known (cannot be estimated from the available data).

Table 1 Percentage of patients with adverse drug reactions in clinical trials

Adverse drug reactions	**Fingolimod 0.5mg N=783 %**	**Placebo N=773 %**	**Frequency range for the 0.5 mg dose**
Infections and infestations			
Influenza	11.4	8.4	Very common
Sinusitis	10.9	8.3	Very common
Bronchitis	8.2	4.5	Common
Herpes zoster	2.0	0.9	Common
Tinea versicolor	1.8	0.4	Common
Pneumonia	0.9	0.1	Uncommon
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	1.8	0.6	Common
Melanoma	0.1	0.3	Uncommon**
Kaposi's sarcoma	0	0	Very rare**
Blood and lymphatic system disorders			
Lymphopenia	6.8	0.3	Common
Leucopenia	2.2	0.1	Common
Thrombocytopenia	0.5	0.0	Uncommon
Nervous system disorders			
Headache	24.5	22.6	Very common
Dizziness	8.8	8.4	Common
Migraine	5.7	3.6	Common
Seizure	0.9	0.3	Uncommon
Posterior reversible encephalopathy syndrome (PRES)	0.0	0.0	Rare*
Eye disorders			
Vision blurred	4.2	2.5	Common
Macular edema	0.5	0.4	Uncommon
Cardiac Disorders			
Bradycardia	2.6	0.9	Common
Vascular disorders			
Hypertension	8.0	3.6	Common
Respiratory, thoracic and mediastinal disorders			
Cough	12.3	11.3	Very common
Dyspnoea	9.1	7.0	Common
Gastrointestinal disorders			
Diarrhea	12.6	9.6	Very common
Skin and subcutaneous tissue disorders			
Eczema	2.7	1.9	Common
Pruritus	2.7	2.2	Common
Musculoskeletal and connective tissue disorders			
Back pain	10.0	8.9	Very common

General disorders and administration site conditions			
Asthenia	1.9	0.8	Common
Investigations			
Hepatic enzyme increased (increased ALT, GGT, AST)	15.2	4.1	Very common
Blood triglycerides increased	2.0	0.9	Common

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

**The frequency category and risk assessment were based on an estimated exposure of more than 24,000 patients to fingolimod 0.5 mg in all clinical trials.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known) The adverse drugs reactions as listed in Table 2 have been derived from post-marketing experience with Fingolimod via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes inMedDRA.

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

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

Description of selected adverse reactions

Infections

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

There have been very rare fatal cases of VZV infections in the context of prolonged concomitant corticosteroid use (more than 5 days) for treatment of multiple sclerosis relapses. Co-administration of a short course of corticosteroids (up to 5 days as per study protocols) did not increase the overall rate of infection in patients treated with fingolimod in the Phase III clinical trials, compared to placebo (see sections 4.4 and 4.5).

There have been very rare cases of other herpes viral infections with fatal outcome.

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

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

Macular edema
In multiple sclerosis clinical studies macular oedema occurred in 0.5% of patients treated with the recommended dose of 0.5 mg and 1.1% of patients treated with the higher dose of 1.25 mg. The majority of cases occurred within the first 3-4 months of therapy. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmic examination. The macular oedema generally improved or resolved spontaneously after discontinuation of Fingolimod. The risk of recurrence after re-challenge has not been evaluated.

Macular oedema incidence is increased in multiple sclerosis patients with a history of uveitis (17% with a history of uveitis vs. 0.6% without a history of uveitis). Fingolimod has not been studied in multiple sclerosis patients with diabetes mellitus, a disease which is associated with an increased risk for macular oedema (see section 4.4). In renal transplant clinical studies in which patients with diabetes mellitus were included, therapy with fingolimod 2.5 mg and 5 mg resulted in a 2-fold increase in the incidence of macular oedema.

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

In multiple sclerosis clinical studies first-degree atrioventricular block (prolonged PR interval onECG) was detected after treatment initiation in 4.7% of patients on fingolimod 0.5 mg, in 2.8% of patients on intramuscular interferon beta-1a, and in 1.6% of patients on placebo. Second-degree atrioventricular block was detected in less than 0.2% of adult patients on Fingolimod 0.5 mg. In the post-marketing setting, isolated reports of transient, spontaneously resolving complete AV block have been observed during the six hour monitoring period following first dose of Fingolimod. The patients recovered spontaneously. The conduction abnormalities observed both in clinical trials and post-marketing were typically transient, asymptomatic and resolved within the first 24 hours after treatment initiation. Although most patients did not require medical intervention, one patient on Fingolimod 0.5 mg received isoprenaline for asymptomatic second-degree Mobitz I atrioventricularblock.

In the post-marketing setting, isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These cases have been confounded by concomitant medicinal products and/or pre-existing disease. The relationship of such events to Fingolimod is uncertain.

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

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

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

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

Description of safety aspects of special interest

Vascular disorders
In Phase III clinical trials rare cases of peripheral arterial occlusive disease occurred in patients treated with Fingolimod at higher doses (1.25 mg). Rare cases of ischemic and hemorrhagic strokes have also been reported at the 0.5 mg dose in clinical trials and in the post-marketing setting although a causal relationship has not been established.

Respiratory system
Minor dose-dependent reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (DLCO) were observed with Fingolimod treatment starting at Month 1 and remaining stable thereafter. At Month 24, the reduction from baseline values in percentage of predicted FEV_1 was 2.7% for fingolimod 0.5 mg and 1.2% for placebo, a difference that resolved after treatment discontinuation. For DLCO the reductions at Month 24 were 3.3% for fingolimod 0.5 mg and 2.7% for placebo.

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

Special populations
Paediatric patients (10 years of age and above)
In the controlled paediatric trial, the safety profile in paediatric patients (10 to below 18 years of age) receiving Fingolimod 0.25 mg or 0.5 mg daily was similar to that seen in adult patients.

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

4.9 Overdose

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

Fingolimod can induce bradycardia upon treatment initiation. The decline in heart rate usually starts within one hour of the first dose, and is steepest within 6 hours. The negative chronotropic effect of Fingolimod capsule 0.5mg persists beyond 6 hours and progressively attenuates over subsequent days of treatment (see section 4.4 for details). There have been reports of slow atrioventricular conduction, with isolated reports of transient, spontaneously resolving complete AV block (see sections 4.4 and 4.8).

If the overdose constitutes first exposure to Fingolimod capsule 0.5mg, it is important to monitor patients with a continuous (real time) ECG and hourly measurement of heart rate and blood pressure, at least during the first 6 hours (see section 4.4).

The occurrence at any time of third degree AV block should also lead to extended monitoring including overnight monitoring.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressants, ATC code: L04AA27

Mechanism of action
Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolized by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptor 1 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptor 1 located on neural cells in the central nervous system (CNS). By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to

egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. This redistribution reduces the infiltration of pathogenic lymphocytes, including pro-inflammatory Th17 cells into the CNS, where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and *in vitro* experiments indicate that fingolimod may also act via interaction with S1P receptors on neural cells. Fingolimod penetrates the CNS, in both humans and animals, and has been shown to reduce astrogliosis, demyelination and neuronal loss. Further, fingolimod treatment increases the levels of brain derived neurotropic factor (BDNF) in the cortex, hippocampus and striatum of the brain to support neuronal survival and improve motor functions.

Pharmacodynamic effects

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

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

Fingolimod treatment with single or multiple doses of 0.5 and 1.25 mg for two weeks is not associated with a detectable increase in airway resistance as measured by FEV1 and forced expiratory flow rate (FEF) 25-75. However, single fingolimod doses ≥5 mg (10-fold the recommended dose) are associated with a dose- dependent increase in airway resistance. Fingolimod treatment with multiple doses of 0.5, 1.25, or 5 mg is not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Subjects on fingolimod treatment have a normal bronchodilator response to inhaled beta-agonists.

Clinical efficacy and safety

The efficacy of Fingolimod has been demonstrated in two studies that evaluated once-daily doses of fingolimod 0.5 mg and 1.25 mg in adult patients with relapsing-remitting multiple

sclerosis (RRMS). Both studies included patients who had experienced ≥2 relapses in the prior 2 years or ≥1 relapse during the prior year. Expanded Disability Status Score (EDSS) was between 0 and 5.5. A third study targeting the same patient population was completed after registration of Fingolimod.

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

Study D2301 (FREEDOMS)

Study D2301 (FREEDOMS) was a 2-year randomised, double-blind, placebo-controlled Phase III study of 1,272 patients (n=425 on 0.5 mg, 429 on 1.25 mg, 418 on placebo). Median values for baseline characteristics were: age 37 years, disease duration 6.7 years, and EDSS score 2.0. Outcome results are shown in Table 3 and Figures 1 and 2. There were no significant differences between the 0.5 mg and the 1.25 mg doses as regards either endpoint.

Table 3 Clinical and MRI results of Study FREEDOMS

	Fingolimod 0.5 mg	**Fingolimod 1.25 mg**	**Placebo**
Clinical endpoints	N=425	N=429	N=418
Annualized relapse rate (primary endpoint)	0.18 (p<0.001*)	0.16 (p<0.001*)	0.40
Relative reduction (percentage)	54	60	
Percent of patients remaining relapse-free at 24 months	70.4 (p<0.001*)	74.7 (p<0.001*)	45.6
Risk of disability progression			
Hazard ratio (95% CI) (3-month confirmed)	0.70 (0.52, 0.96) (p=0.024*)	0.68 (0.50, 0.93) (p=0.017*)	
Hazard ratio (95% CI) (6-month confirmed)	*0.63 (0.44, 0.90) (p=0.012*)*	*0.60 (0.41, 0.86) (p=0.006*)*	
MRI endpoints			
Number of new or newly enlarging T2 lesions	n=370	n=337	n=339
Median (mean) number over 24 months	0.0 (2.5) (p<0.001*)	0.0 (2.5) (p<0.001*)	5.0 (9.8)
Number of Gd-enhancing lesions	n=369 (Month 24)	n=343 (Month 24)	n=332 (Month 24)
Median (mean) number at			
Month 6	0.0 (0.2)	0.0 (0.3)	0.0 (1.3)
Month 12	0.0 (0.2)	0.0 (0.3)	0.0 (1.1)
Month 24	0.0 (0.2) (p<0.001* at each timepoint)	0.0 (0.2) (p<0.001* at each timepoint)	0.0 (1.1)
Percent change in T2 lesion total volume	n=368	n= 343	n=339
Median (mean) % change over 24 months	-1.7 (10.6) (p<0.001*)	-3.1 (1.6) (p<0.001*)	8.6 (33.8)
Change in T1 hypointense lesion volume	n=346	n=317	n=305
Median (mean) % change over 24 months	0.0 (8.8) (p=0.012*)	-0.2 (12.2) (p=0.015*)	1.6 (50.7)
Percent change in brain volume	n=357	n=334	n=331
Median (mean) % change over 24 months	-0.7 (-0.8) (p<0.001*)	-0.7 (-0.9) (p<0.001*)	-1.0 (-1.3)

All analyses of clinical endpoints were intent-to treat. MRI analyses used the evaluable dataset.

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

Determination of p-values: aggregate ARR by negative binomial regression adjusting for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS; percentage of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapses in previous 2 years, and baseline EDSS; time to 3-month/6-month confirmed disability progression by Cox's proportional hazards model adjusted for treatment, pooled country, baseline EDSS, and age; new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment and pooled country; Gd-enhancing lesions by rank ANCOVA adjusted for treatment, pooled country, and baseline number of Gd-enhancing lesions; and % change in lesion and brain volume by rank ANCOVA adjusted for treatment, pooled country, and corresponding baseline value.

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

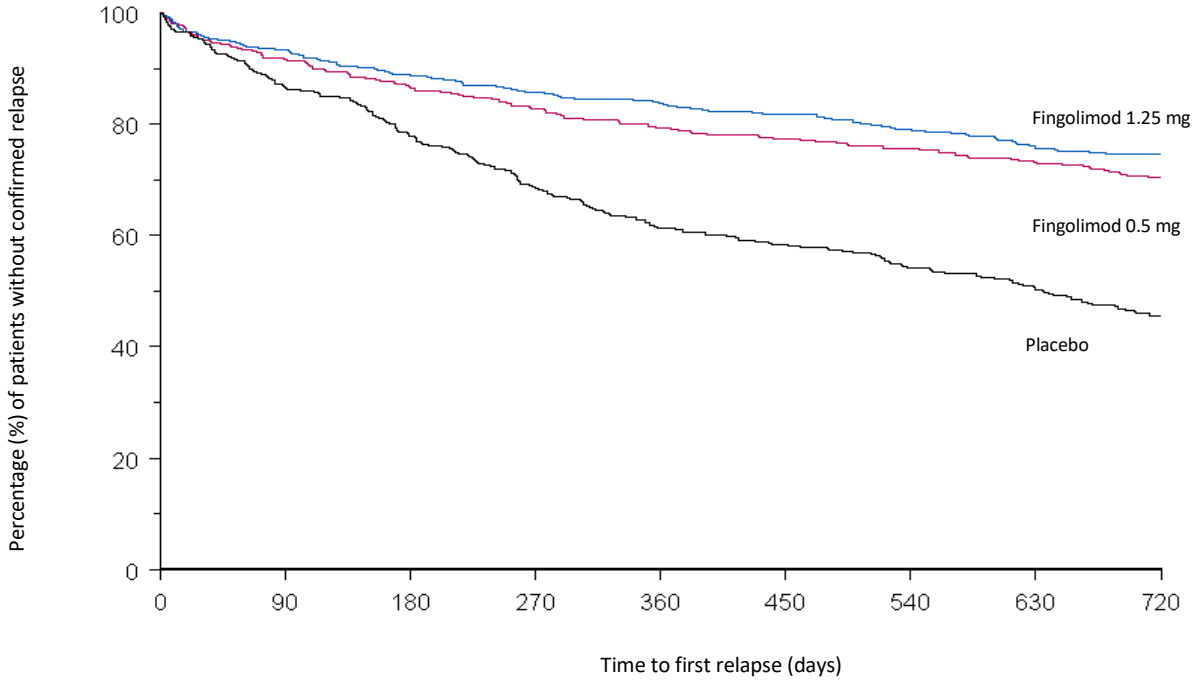
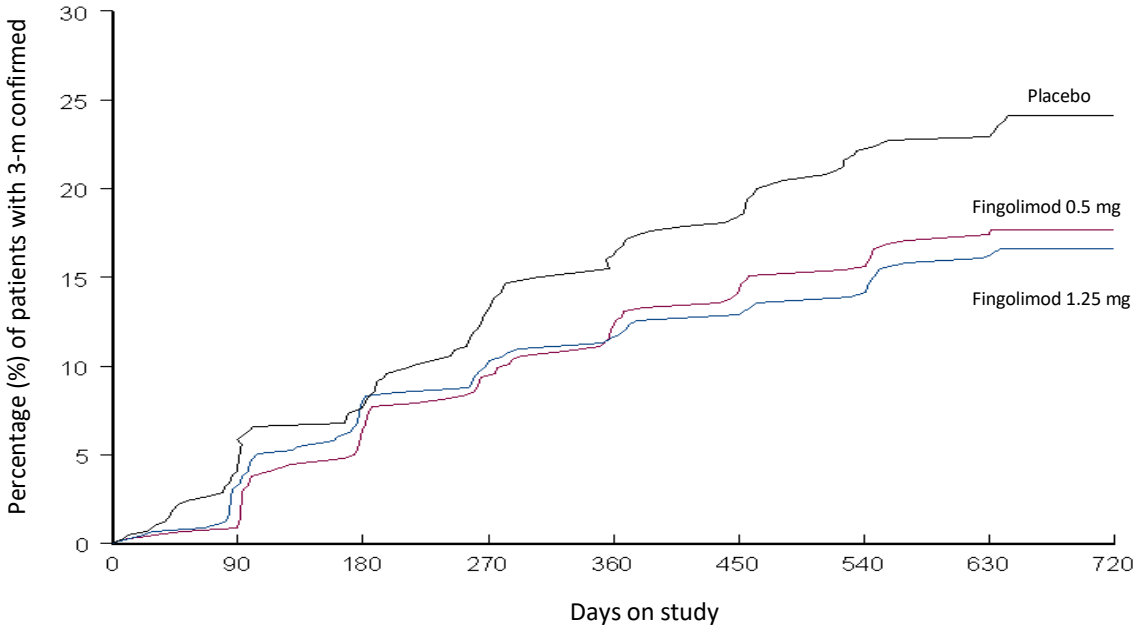


Figure 2 Cumulative plot of time to 3-month confirmed disability progression – Study FREEDOMS (ITT population)



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

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

Study D2309 (FREEDOMS II)

Study D2309 (FREEDOMS II) had a design similar to that of Study D2301 (FREEDOMS): it was a 2- year randomized, double-blind, placebo-controlled Phase III study in patients with relapsing- remitting multiple sclerosis who had not received any interferon-beta or glatiramer acetate for at least the previous 3 months and had not received any natalizumab for at least the previous 6 months. Neurological evaluations were performed at screening, every 3 months and at time of suspected relapse. MRI evaluations were performed at screening, Month 6, Month 12 and Month 24. The primary endpoint was the annualized relapse rate (ARR).

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

Median time on study drug was 719 days on 0.5 mg and 719 days on placebo. Patients

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

The annualized relapse rate was significantly lower in patients treated with Fingolimod than in patients who received placebo. The first key secondary endpoint was change from baseline in brain volume. Loss of brain volume was significantly less with Fingolimod treatment compared to placebo. The other key secondary endpoint was the time to 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for patients with baseline EDSS of 5.5) sustained for 3 months. The risk of disability progression for Fingolimod and placebo groups was not statistically different.

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

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

Table 4 Clinical and MRI results of Study FREEDOMS II

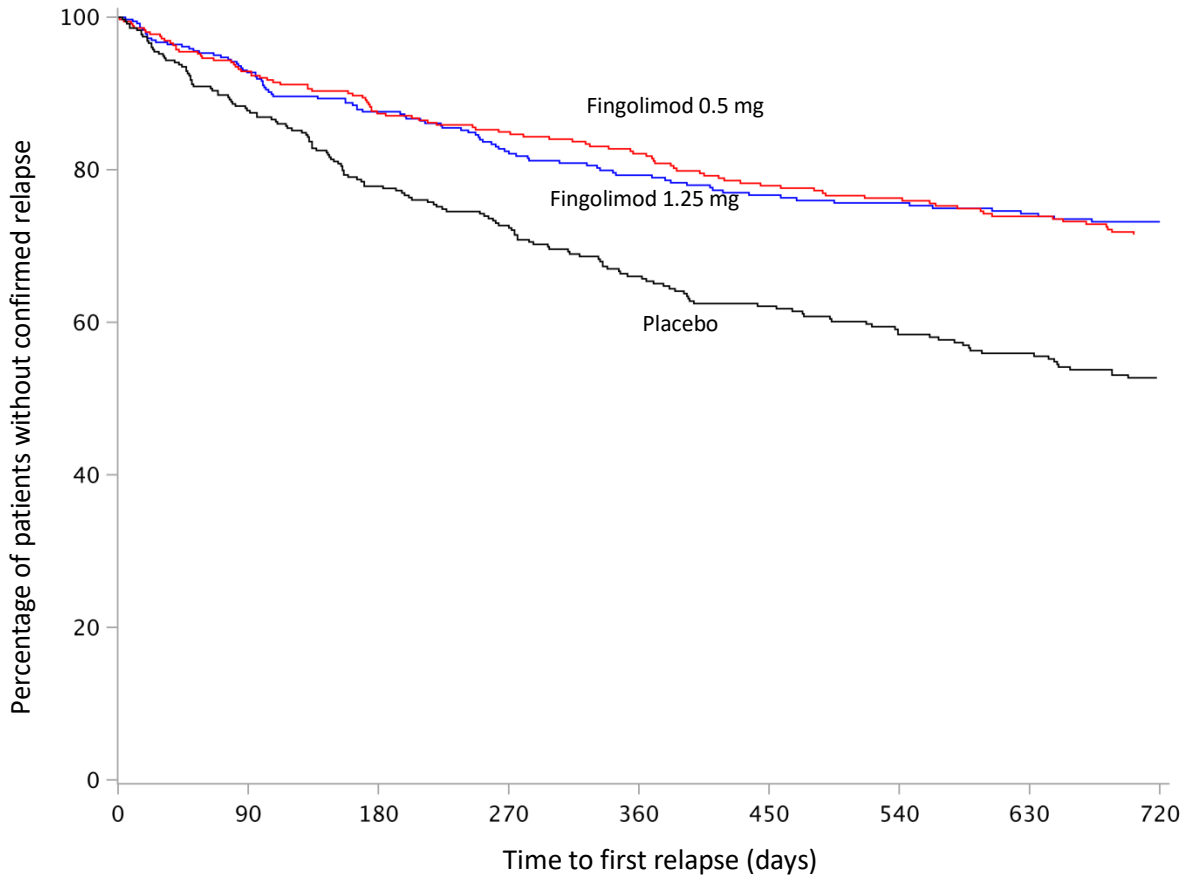
	Fingolimod 0.5 mg	**Fingolimod 1.25 mg**	**Placebo**
Clinical endpoints	N=358	N=370	N=355
Annualized relapse rate (primary endpoint)	0.21 (p<0.001*)	0.20 (p<0.001*)	0.40
Relative reduction (percentage)	48	50	
Percent of patients remaining relapse-free at 24 months	71.5 (p<0.001*)	73.2 (p<0.001*)	52.7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

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

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

Determination of p-values: aggregate ARR by negative binomial regression adjusted for treatment, pooled country, number of relapses in previous 2 years and baseline EDSS; percentage of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapses in previous 2 years, and baseline EDSS; time to 3-month/6-month confirmed disability progression by Cox's proportional hazards model adjusted for treatment, pooled country, baseline EDSS, and age; new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment and pooled country; Gd-enhancing lesions by rank ANCOVA adjusted for treatment, pooled country, and baseline number of Gd-enhancing lesions; and % change in lesion and brain volume by rank ANCOVA adjusted for treatment, pooled country, and corresponding baseline value.
† Additional analyses revealed that results in the overall population were not significant due to false positive progressions in the subgroup of patients with baseline EDSS=0 (n=62, 8.7% of study population). In patients with EDSS>0 (n=651; 91.3% of study population), fingolimod 0.5 mg demonstrated a statistically significant reduction compared to placebo (HR= 0.70; CI (0.50, 0.98); p=0.040) for the 3-month disability progression, consistent with study FREEDOMS

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



Study D2302 (TRANSFORMS)

Study D2302 (TRANSFORMS) was a 1-year randomised, double-blind, double-dummy, active- controlled (interferon beta-1a) Phase III study of 1,280 patients (n=429 on 0.5 mg, 420 on 1.25 mg, 431 on interferon beta-1a, 30 µg by intramuscular injection once weekly). Median values for baseline characteristics were: age 36 years, disease duration 5.9 years, and EDSS score 2.0. Outcome results are shown in Table 5 and Figure 4. There were no significant differences between the Fingolimod 0.5 mg and the
1.25 mg doses as regards study endpoints.

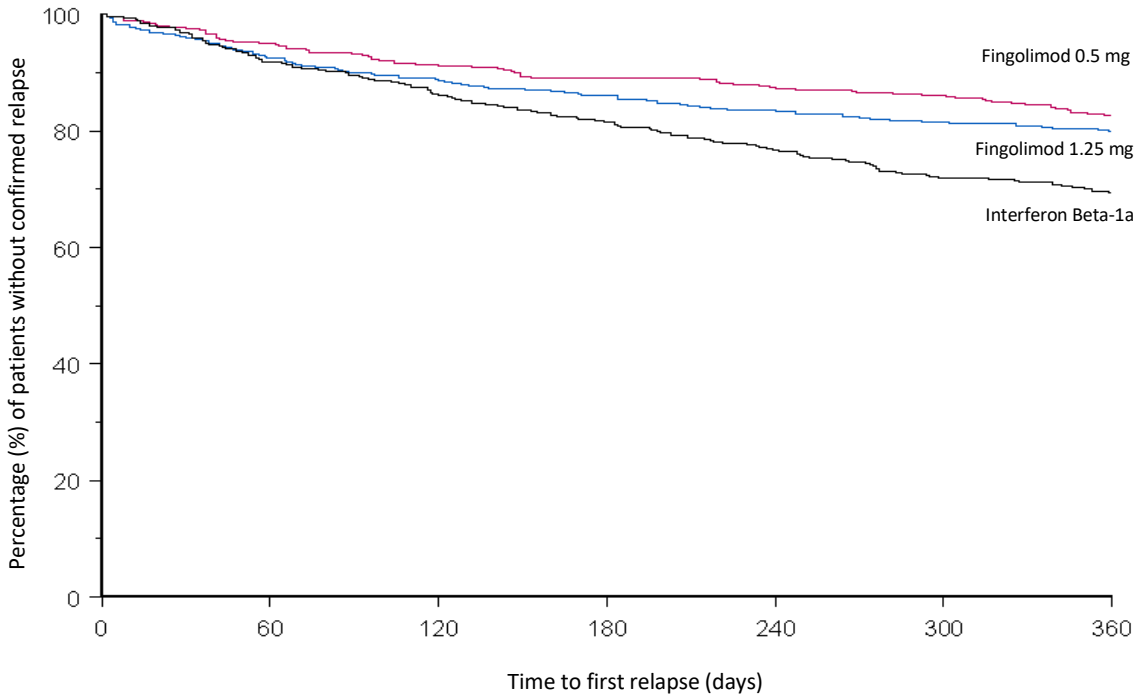
Table 5 Clinical and MRI results of Study TRANSFORMS

Clinical endpoints	**Fingolimod 0.5 mg** N=429	**Fingolimod 1.25 mg** N=420	**Interferon beta-1a IM, 30 mcg,** N=431
Annualized relapse rate (primary endpoint)	0.16 (p<0.001*)	0.20 (p<0.001*)	0.33
Relative reduction (percent)	52	38	
Percent of patients remaining relapse-free at 12 months	82.5 (p<0.001*)	80.5 (p<0.001*)	70.1
Risk of disability progression			
Hazard ratio (95% CI) (3-month confirmed)	0.71 (0.42, 1.21) (p=0.209)	0.85 (0.51, 1.42) (p=0.543)	
MRI endpoints			
Number of new or newly enlarging T2 lesions	n=380	n=356	n=365
Median (mean) number over 12 months	0.0 (1.7) (p=0.004*)	1.0 (1.5) (p<0.001*)	1.0 (2.6)
Number of Gd-enhancing lesions	n=374	n=352	n=354
Median (mean) number at 12 months	0.0 (0.2) (p<0.001*)	0.0 (0.1) (p<0.001*)	0.0 (0.5)
Percent change in brain volume	n=368	n=345	n=359
Median (mean) % change over 12 months	-0.2 (-0.3) (p<0.001*)	-0.2 (-0.3) (p<0.001*)	-0.4 (-0.5)

All analyses of clinical endpoints were intent-to treat. MRI analyses used the evaluable dataset.
* Indicates statistical significance vs. Interferon beta-1a IM at two-sided 0.05 level.

Determination of p-values: aggregate ARR by negative binomial regression adjusting for treatment, country, number of relapses in previous 2 years and baseline EDSS; percentage of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapses in previous 2 years, and baseline EDSS; risk of disability progression by Cox's proportional hazards model adjusted for treatment, country, baseline EDSS, and age; new/newly enlarging T2 lesions by negative binomial regression adjusted for treatment, country, number of relapses in previous 2 years and baseline EDSS; Gd-enhancing lesions by rank ANCOVA adjusted for treatment, country, and baseline number of Gd-enhancing lesions; and % change in brain volume by Wilcoxon rank sum test.

Figure 4 Kaplan-Meier plot for time to first confirmed relapse up to Month 12 – Study TRANSFORMS (ITT population)



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

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

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

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

Study D2311 (PARADIGMS) in paediatric patients 10 years of age and above
Study D2311 (PARADIGMS) was a double-blind, randomized, active-controlled, parallel-group, multicenter study with flexible duration up to 24 months, to evaluate the efficacy and

safety of fingolimod compared to interferon beta-1a in paediatric patients with MS, aged 10 to <18 years old. Prior therapy with interferon-beta, dimethyl fumarate or glatiramer acetate up to the time of randomization was permitted. Neurological evaluations were performed at screening, every 3 months and at the time of suspected relapses. MRI evaluations were performed at screening, and every 6 months throughout the study. The primary endpoint was the annualized relapse rate.
Median age was 16 years, median disease duration since first symptom was 1.5 years and median EDSS score at baseline was 1.5. Patients were randomized to receive fingolimod or interferon beta-1a via the intramuscular route once weekly for up to 24 months. Median time on study drug was 634 days on fingolimod and 547 days on interferon beta-1a.

The primary endpoint, the annualized relapse rate, was significantly lower in patients treated with fingolimod than in patients who received interferon beta-1a (relative reduction in ARR of 81.9%). The key secondary endpoint, the annualized rate of the number of new or newly enlarged T2 lesions up to Month 24, was also significantly lower in patients treated with fingolimod than in patients who received interferon beta-1a, as was the number of Gd-enhancing T1 lesions per scan up to Month 24. Fingolimod also significantly reduced the annualized rate of brain atrophy from baseline up to Month 24. An additional post-hoc analysis confirmed that time to onset of 3-month confirmed disability progression was significantly delayed with fingolimod compared to interferon beta-1a.
The results for this study are shown in Table 6, Figure 5, and Figure 6.

Table 6 Clinical and MRI results of Study PARADIGMS

	Fingolimod 0.25 mg or 0.5 mg	**Interferon beta-1a IM 30 µg**
Clinical endpoints	N=107	N=107#
Annualized relapse rate (primary endpoint)	0.122 (p<0.001*)	0.675
Relative reduction (percent)	81.9	
Percent of patients remaining relapse-free at 24 months	85.7 (p<0.001*)	38.8
Risk of disability progression		
Hazard ratio (95% CI)	0.23 (0.08,0.66)	
	Fingolimod 0.25 mg or 0.5 mg	**Interferon beta-1a IM 30 µg**
(3-month confirmed)	(p=0.007*)	
MRI endpoints		
Annualized rate of the number of new or newly enlarging T2 lesions	n=106	n=101
Adjusted mean	4.393 (p<0.001*)	9.269
Relative Reduction (percent)	52.6	
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	
Annualized rate of brain atrophy 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 on full analysis set. MRI analyses used the evaluable dataset.
One patient was randomized to receive Interferon beta-1a IM, 30 µg weekly, but was unable to swallow the

double dummy medication and discontinued from 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.

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

Figure 5 Kaplan-Meier plot for time to first confirmed relapse up to Month 24 – Study PARADIGMS (Full analysis set)

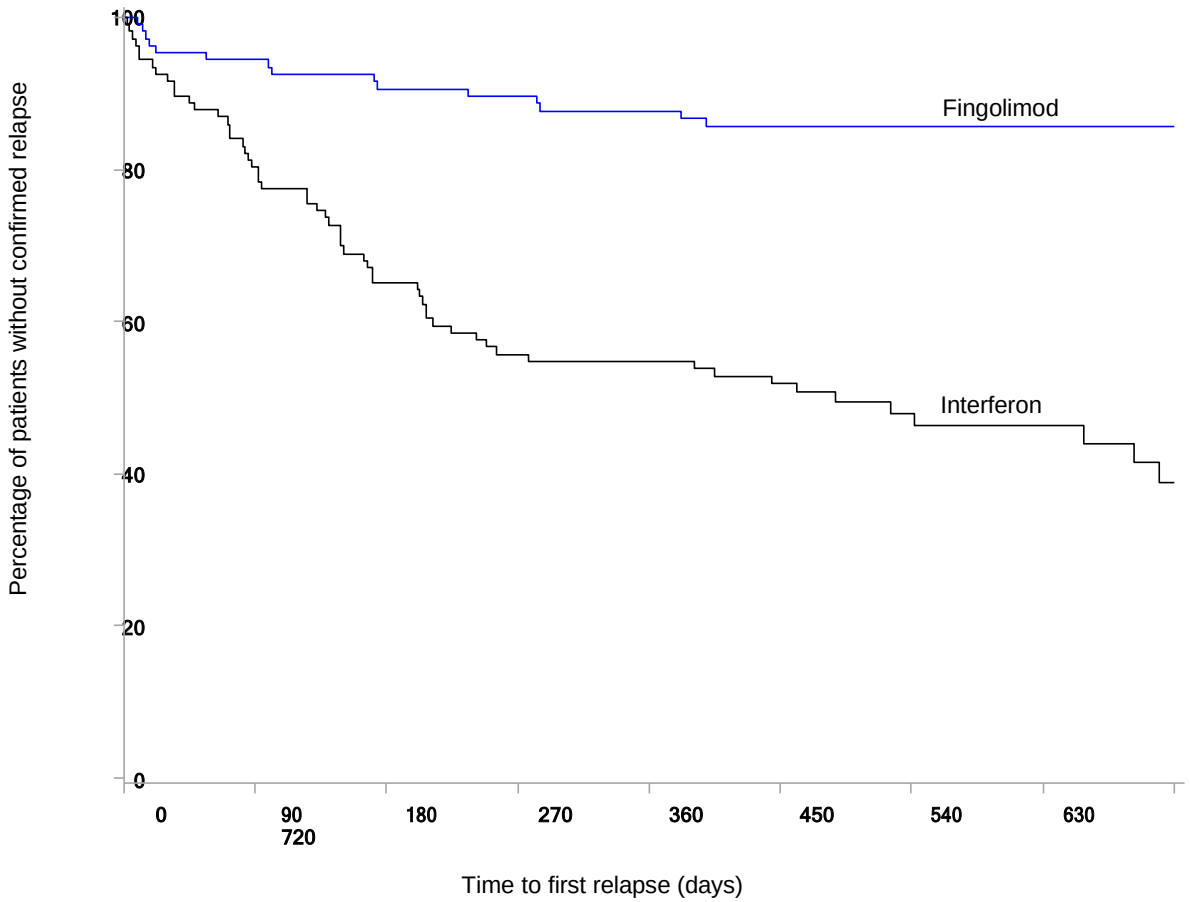
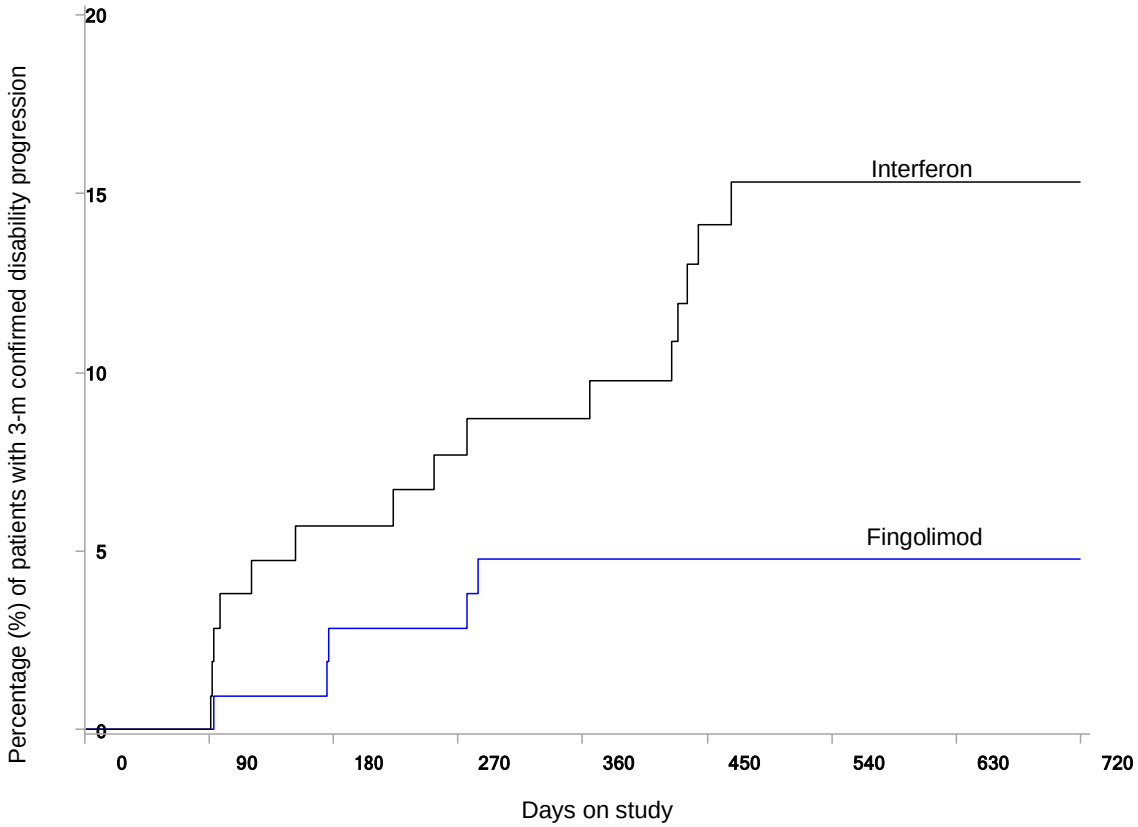


Figure 6 Kaplan-Meier plot of time to 3-month confirmed disability progression – Study PARADIGMS (Full analysis set)



5.2 Pharmacokinetic properties

Pharmacokinetic data were obtained in healthy volunteers, in renal transplant patients and in multiple sclerosis patients.
The pharmacologically active metabolite responsible for efficacy is fingolimod phosphate.

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

Food intake does not alter Cmax or exposure (AUC) of fingolimod. Fingolimod phosphate Cmax was slightly increased by 34% but AUC was unchanged. Therefore, Fingolimod capsule 0.5mg may be taken without regard to meals (see section 4.2).

Distribution
Fingolimod highly distributes in red blood cells, with the fraction in blood cells of 86%. Fingolimod phosphate has a smaller uptake in blood cells of <17%. Fingolimod and fingolimod phosphate are highly protein bound (>99%).

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1,200±260 litres. A study in four healthy subjects who received a single intravenous dose of radioiodolabeled fingolimod demonstrated that fingolimod penetrates into the brain. In a

study in 13 male multiple sclerosis patients who received Fingolimod capsule 0.5mg 0.5 mg/day at steady-state, the amount of fingolimod (and fingolimod- phosphate) in seminal ejaculate was more than 10,000 times lower than the dose administered (0.5 mg).

Biotransformation

Fingolimod is transformed in humans by reversible stereoselective phosphorylation to the pharmacologically active (S)-enantiomer of fingolimod phosphate. Fingolimod is eliminated by oxidative biotransformation catalyzed mainly by CYP4F2 and possibly other CYP4F isoenzymes and subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive non- polar ceramide analogues of fingolimod. The main enzyme involved in the metabolism of fingolimod is partially identified and may be either CYP4F2 or CYP3A4.

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

Elimination

Fingolimod blood clearance is 6.3±2.3 l/h, and the average apparent terminal elimination half-life ($t_{1/2}$) is 6-9 days. Blood levels of fingolimod and fingolimod phosphate decline in parallel in the terminal phase, leading to similar half-lives for both.

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

Linearity

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

In paediatric patients, fingolimod-phosphate concentrations increase in an apparent dose proportional manner after multiple once daily doses of fingolimod 0.5 mg.

Characteristics in specific groups of patients

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

In subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, and C), no change in fingolimod Cmax was observed, but fingolimod AUC was increased respectively by 12%, 44%, and 103%. In patients with severe hepatic impairment (Child-Pugh class C), fingolimod- phosphate Cmax was decreased by 22% and AUC increased by 38%. The pharmacokinetics of fingolimod-phosphate were not evaluated in patients with mild or moderate hepatic impairment. The apparent elimination half-life of fingolimod is unchanged in subjects with mild hepatic impairment, but is prolonged by about 50% in patients with moderate or severe hepatic impairment.

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

Clinical experience and pharmacokinetic information in patients aged above 65 years are limited. Fingolimod capsule 0.5mg should be used with caution in patients aged 65 years and over (see section 4.2).

Paediatric population
The median fingolimod-phosphate concentration in paediatric MS patients aged 10 to less than 18 years was 1.10 ng/mL, as compared to 1.35 ng/mL in adult MS patients.

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

5.3 Preclinical safety data

The preclinical safety profile of fingolimod was assessed in mice, rats, dogs and monkeys. The major target organs were the lymphoid system (lymphopenia and lymphoid atrophy), lungs (increased weight, smooth muscle hypertrophy at the bronchio-alveolar junction), and heart (negative chronotropic effect, increase in blood pressure, perivascular changes and myocardial degeneration) in several species; blood vessels (vasculopathy) in rats only at doses of 0.15 mg/kg and higher in a 2-year study, representing an approximate 4-fold margin based on the human systemic exposure (AUC) at a daily dose of 0.5 mg.

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

Fingolimod was neither mutagenic nor clastogenic in animal studies.

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

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
In a study in which fingolimod (0.3, 1.5, or 7.5 mg/kg/day) was orally administered to young rats from weaning through sexual maturity, changes in bone mineral density and persistent neurobehavioral impairment (altered auditory startle) were observed at all doses. Delayed sexual maturation was noted in females at the highest dose tested and in males at all doses. The bone changes observed in fingolimod-treated juvenile rats are consistent with a reported role of S1P in the regulation of bone mineral homeostasis. When fingolimod (0.5 or 5 mg/kg/day)

was orally administered to rats from the neonatal period through sexual maturity, a marked decrease in T-cell dependent antibody response was observed at both doses. This effect had not fully recovered by 6-8 weeks after the end of treatment. Overall, the no observed adverse effect levels (NOAELs) in juvenile animals were mainly driven by unspecific effects on body weight or food consumption.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill
Pregelatinised starch, Magnesium stearate

Capsule shell
Gelatin, Water, Titanium Dioxide, Iron Oxide Yellow

Printing ink
Shellac, Dehydrated Alcohol, Isopropyl Alcohol, Butyl Alcohol, Propylene Glycol, Strong Ammonia Solution, Iron Oxide Yellow, Iron Oxide Black, Potassium Hydroxide, Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Fingolimod capsules 0.5mg are packed in the PVC/PVDC-Alu blister pack of 14 capsules. Each carton contains such two blisters. (2 x 14Caps)

6.6 Special precautions for disposal

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

7. NAME AND ADDRESS OF PRODUCT REGISTRANT

Accord Healthcare Private Limited

6 Shenton Way, OUE Downtown #38-01
Singapore, 068809

8. MANUFACTURER

Manufactured by:
Intas Pharmaceuticals Limited
Plot No. 457-458, Village-Matoda, Bavla Road,
And Plot No: 191/218P, Village: Chacharwadi,
Ta: Sanand, Dist.-Ahmedabad, Gujarat, India.

8. DATE OF REVISION OF THE TEXT

April 2022