

1 PRODUCT NAME

Pharmacor Fingolimod 500 micrograms capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 560 micrograms Fingolimod hydrochloride (equivalent to 500 micrograms fingolimod).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

PHARMACOR FINGOLIMOD 500 micrograms: White to off- white powder filled in size 4 hard gelatin capsules, with a white opaque body with two radial band imprinted with yellow ink and bright yellow cap imprinted with FIG 500 micrograms with black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pharmacor Fingolimod is indicated as a disease modifying therapy for the treatment of patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

4.2 Dose and method of administration

Posology

The recommended dose of Pharmacor Fingolimod is one 500 micrograms capsule taken orally once daily, which can be taken with or without food. If a dose is missed treatment should be continued with the next dose as planned.

On initiation of Pharmacor Fingolimod treatment, after the first dose, it is recommended that all patients be observed, with hourly pulse and blood pressure measurement, for a period of 6 hours for signs and symptoms of bradycardia. All patients should have an electrocardiogram performed prior to dosing and at the end of the 6-hour monitoring period (see section 4.4 special warnings and precautions, Bradyarrhythmia).

For recommendations related to switching patients from other disease modifying therapies to Pharmacor Fingolimod (see section 4.4 special warnings and precautions: Prior treatment with immunosuppressants).

Special populations

Children

Pharmacor Fingolimod is not indicated for use in paediatric patients. (See section 5 PHARMACOLOGICAL PROPERTIES).

The Elderly (≥ 65 years)

Pharmacor Fingolimod should be used with caution in patients aged 65 years and over (see section 5 PHARMACOLOGICAL PROPERTIES).

Patients with Renal Impairment

No Pharmacor Fingolimod dose adjustments are needed in patients with renal impairment (see section 5 PHARMACOLOGICAL PROPERTIES).

Patients with Hepatic Impairment

No Pharmacor Fingolimod dose adjustments are needed in patients with mild or moderate hepatic impairment. Pharmacor Fingolimod should be used with caution in patients with severe hepatic impairment (Child-Pugh class C) (see section 5 PHARMACOLOGICAL PROPERTIES).

Ethnicity

No Pharmacor Fingolimod dose adjustments are needed based on ethnic origin (see section 5 PHARMACOLOGICAL PROPERTIES).

Gender

No Pharmacor Fingolimod dose adjustments are needed based on gender (see section 5 PHARMACOLOGICAL PROPERTIES).

Diabetic Patients

Pharmacor Fingolimod should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular oedema (see section 4.4 Special warnings and precautions for use).

4.3 Contraindications

- 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 with severe cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs (see section 4.4 Special warnings and precautions for use).
- 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 Special warnings and precautions for use).
- Patients with a baseline QTc interval ≥ 500 msec (see section 4.4 Special warnings and precautions for use).

Further, Pharmacor Fingolimod should not be administered to patients with known hypersensitivity to fingolimod or any of the excipients.

4.4 Special warnings and precautions for use

Infections

Fingolimod causes a dose-dependent reduction in peripheral lymphocyte count to 20 – 30 % of baseline values because of reversible sequestration of lymphocytes in lymphoid tissues (see section 5 Pharmacological properties). Fingolimod may therefore increase the risk of infections, including opportunistic infections, some serious in nature. Before initiating treatment with fingolimod (for switching patients from other disease modifying therapies see section 4.4 Special warnings and precautions for use - Prior treatment with immunosuppressive or immune-modulating therapies), a recent complete blood count (CBC) should be available.

Because the elimination of fingolimod after discontinuation can take up to two months, continue monitoring for infections throughout this period.

Anti-neoplastic, immune modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution due to the risk of additive immune system effects. Specific decisions as to the dosage and duration of treatment with corticosteroids should be based on clinical judgment (see section 4.8 Adverse effects (undesirable effects) and section 4.5 Interactions with other medicines and other forms of interactions).

Instruct patients receiving fingolimod to report symptoms of infections to a physician. Suspension of treatment with fingolimod if a patient develops a serious infection, and consideration of the benefit-risk should be undertaken.

Cases of cryptococcal infections, including cryptococcal meningitis, have been reported in the post-marketing setting after approximately 2-3 years of treatment, although the exact relationship between the risk of cryptococcal infections and the duration of treatment is unknown (see section 4.8 Adverse effects (undesirable effects)). Cryptococcal meningitis may be fatal. For this reason, patients with symptoms and signs consistent with cryptococcal infections should undergo prompt diagnostic evaluation. If a cryptococcal infection is diagnosed, appropriate treatment should be initiated.

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in patients treated with fingolimod in the post-marketing setting (see section 4.8 Adverse effects (undesirable effects)). 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 is recommended as per standard of care.

Progressive Multifocal Leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in the post-marketing setting, (see section 4.8 Undesirable effects). 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 between the risk of PML and the duration of treatment is unknown. The incidence rate for PML appears to be higher for patients in Japan; the reasons are currently unknown. Cases of PML cases have occurred in patients who had not been treated previously with natalizumab, which has a known association with PML, and who were not taking any concomitant immunosuppressive or immunomodulatory medications, and who had no other ongoing systemic medical conditions resulting in compromised immune system function.

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. Early diagnosis and stopping therapy are important factors in management of PML in patients on fingolimod. Delay in diagnosis and treatment worsen prognosis which can result in permanent neurological sequelae or death. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

For diagnosis, an evaluation that includes neurological assessment and a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain is recommended. 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. Many of these patients subsequently became symptomatic with PML. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if

present.

Patients with active acute or chronic infections should not start treatment until the infection(s) is resolved. Appropriate diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. In multiple sclerosis clinical trials, the overall rate of infections (65.1%) at the 500 micrograms dose was similar to placebo. However, bronchitis, herpes zoster and pneumonia, were more common in fingolimod treated patients. Serious infections occurred at a rate of 1.6% in the fingolimod 500 micrograms group versus 1.4% in the placebo group.

Vaccination

Vaccination may be less effective during and for up to two months after stopping treatment with fingolimod (see section 4.4 Special warnings and precautions for use - Stopping fingolimod therapy). The use of live attenuated vaccines should be avoided.

As could be considered for any immune modulating drug, before initiating therapy, patients need to be assessed for their immunity to varicella (chickenpox) prior to fingolimod therapy. It is recommended that patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating fingolimod therapy. A full course of VZV vaccination of antibody-negative patients should be considered prior to commencing treatment with fingolimod, following which initiation of treatment with fingolimod should be postponed for 1 month to allow full effect of vaccination to occur.

For paediatric patients, please also refer to subsection 'Paediatric patients'.

Macular Oedema

Macular oedema (see section 4.8 Undesirable effects) with or without visual symptoms. An ophthalmologic evaluation should be performed before starting fingolimod and at 3-4 months after treatment initiation. Monitor visual acuity at baseline and during routine evaluations of patients.

Patients with diabetes mellitus or history of uveitis are at increased risk of macular oedema (see section 4.8 Adverse effects (Undesirable effects)). 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 fingolimod therapy and should have regular follow-up ophthalmologic evaluations.

If patients report visual disturbances at any time while on fingolimod therapy, evaluation of the fundus, including the macula, should be carried out.

Continuation of fingolimod in patients with macular oedema has not been evaluated. A decision on whether or not fingolimod therapy should be discontinued needs to take into account the potential benefits and risks for the individual patient.

Bradyarrhythmia

Initiation of fingolimod treatment results in a transient decrease in heart rate. After the first dose, the heart rate decrease starts within an hour and the Day 1 decline is maximal within 6 hours. (see section 5 Pharmacological properties [Pharmacodynamics - Heart rate and rhythm]). In patients receiving fingolimod 500 micrograms, this decrease in heart rate, as measured by pulse, averages approximately 8 beats per minute (bpm) (see section 4.8 Adverse effects (undesirable effects)). Some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue, and/or palpitations.

Initiation of fingolimod treatment has been associated with atrioventricular conduction delays, usually first-degree atrioventricular blocks (prolonged PR interval on electrocardiogram). Second-degree atrioventricular blocks, usually Mobitz type I (Wenckebach) have been observed in less than 0.2% of patients receiving fingolimod 500 micrograms in clinical trials. The conduction abnormalities typically were transient, asymptomatic, usually did not require treatment and resolved within the first 24 hours on treatment. Isolated cases of transient, spontaneously resolving complete AV block have been reported during post-marketing use of fingolimod (see section 4.8 Undesirable effects).

First dose monitoring

Therefore on initiation of fingolimod treatment, it is recommended that all patients be observed, with hourly pulse and blood pressure measurements, for a period of 6 hours for signs and symptoms of bradycardia. All patients should have an electrocardiogram performed prior to dosing and at the end of the 6-hour monitoring period. Should post-dose bradyarrhythmia-related symptoms occur, appropriate management should be initiated as necessary and the patient should be observed until the symptoms have resolved. Should a patient require pharmacologic intervention during the first dose observation, overnight monitoring in a medical facility should be instituted and the first dose monitoring strategy should be repeated after the second dose of fingolimod.

Additional observation until the finding has resolved is also required:

- if the heart rate at 6 hours post-dose is <45 bpm or is the lowest value post-dose (suggesting that the maximum pharmacodynamic effect on the heart is not yet manifest) or
- If the ECG at 6 hours after the first dose shows new onset second degree or higher AV block.
- If the ECG at 6 hours after the first dose shows a QTc interval ≥ 500 msec patients should be monitored overnight.

Due to the risk of serious cardiac rhythm disturbances, fingolimod is contraindicated in patients with second degree Mobitz type II or higher AV block, or sick-sinus syndrome unless the patient has a functioning pacemaker (see section 4.3 Contraindications) and should not be used in patients with sino-atrial heart block, a history of recurrent syncope or symptomatic bradycardia. Since initiation of fingolimod treatment results in decreased heart rate and therefore a prolongation of the QT interval, fingolimod must not be used in patients with a baseline QTc interval ≥ 500 msec (see section 4.3 Contraindications) and should be used with caution in patients with significant QT prolongation (QTc >470 msec (females) or >450 msec (males)). Fingolimod is best avoided in patients with relevant risk factors for QT prolongation, (for example, hypokalaemia, hypomagnesemia or congenital QT prolongation) or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin). Since significant bradycardia may be poorly tolerated in patients with known ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnea period, fingolimod should not be used in these patients. 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, which should last overnight.

Fingolimod has not been studied in patients with arrhythmias requiring treatment with Class Ia (e.g. quinidine, procainamide) or Class III anti-arrhythmic drugs (e.g. amiodarone, sotalol). Class Ia and Class III anti-arrhythmic drugs have been associated with cases of Torsades de Pointes in patients with bradycardia. Since initiation of fingolimod treatment results in decreased heart rate, fingolimod must not be used concomitantly with these drugs during fingolimod initiation (see section 4.3 Contraindications).

Experience with fingolimod is limited in patients receiving concurrent therapy with beta blockers, heart- rate lowering calcium channel blockers (such as verapamil or diltiazem), or other substances

that may decrease heart rate (e.g. digoxin or ivabradine). Since the initiation of fingolimod treatment is also associated with slowing of the heart rate (see section 4.8 Adverse effects (undesirable effects)), (see “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 generally not be initiated in patients who are concurrently treated with these substances. If treatment with fingolimod is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering drugs or appropriate monitoring for treatment initiation (should last overnight).

If fingolimod 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 reintroduction 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.

Liver Function

Increased liver enzymes, mostly alanine aminotransaminase (ALT) elevation, have been reported in multiple sclerosis patients treated with fingolimod. During clinical trials, a 3-fold or greater elevation in liver transaminases occurred in 8.5% of patients treated with fingolimod 500 micrograms and the drug was discontinued if the elevation exceeded a 5 fold increase. Recurrence of liver transaminase elevations occurred upon re-challenge in some patients, supporting a relationship to the drug. In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within 6-9 months. Serum transaminase levels returned to normal within approximately two months after discontinuation of fingolimod.

Clinically significant liver injury has been reported in patients treated with fingolimod in the post-market setting including cases of acute liver failure requiring liver transplant.

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with fingolimod. Patients should be monitored periodically while on treatment and until two months after fingolimod discontinuation.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine during treatment, should have liver enzymes and bilirubin checked and fingolimod should be discontinued if significant liver injury is confirmed (see section 4.8 Adverse effects (undesirable effects), Liver Transaminase).

Although there are no data to establish that patients with pre-existing liver disease are at increased risk to develop 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.

Fingolimod has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and is not recommended for use in these patients.

Posterior reversible encephalopathy syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported at 500 micrograms dose in clinical trials and in the post-marketing setting (see section 4.8 Undesirable effects). Symptoms reported included sudden onset of severe headache, nausea, vomiting, altered mental status, visual disturbances and seizure. Symptoms may evolve into ischemic stroke or cerebral haemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, fingolimod should be discontinued.

Prior treatment with immunosuppressive and immunomodulating 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 additive immune effects, whilst at the same time, minimizing the 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, glatiramer acetate or dimethyl fumarate

Fingolimod can generally be started immediately after discontinuation of beta interferon, 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 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 following discontinuation.

Teriflunomide is also eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take several months to up to 2-years. An accelerated elimination procedure is described in the teriflunomide product information.

Alemtuzumab

Due to the characteristics and duration of alemtuzumab immune suppressive effects described in its product information, initiating treatment with fingolimod after alemtuzumab is not recommended unless the benefits of fingolimod treatment clearly outweigh the risks for the individual patient.

Malignancies

Skin Cancers

Skin cancers including basal cell carcinoma (BCC), malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma, have been reported in patients receiving fingolimod (see section 4.8 Adverse effects (undesirable effects) - Post-marketing experience).

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.

Periodic skin examination is recommended for all patients. Vigilance for cutaneous neoplasms is recommended in patients receiving fingolimod. Healthcare professionals and patients are advised to monitor for suspicious skin lesions before initiating treatment and regularly during treatment with fingolimod. If a suspicious skin lesion is observed, it should be promptly evaluated.

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 Undesirable effects).

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 Fingolimod Therapy

If a decision is made to stop treatment with fingolimod, the physician needs to be aware that fingolimod remains in the blood and has pharmacodynamic effects, such as decreased lymphocyte counts, for up to two months following the last dose. Lymphocyte counts typically return to the normal range within 1-2 months of stopping therapy (see section 5 PHARMACOLOGICAL PROPERTIES). Starting other therapies during this interval will result in a concomitant exposure to fingolimod. Use of immunosuppressants soon after the discontinuation of fingolimod may lead to an additive effect on the immune system and therefore caution should be applied.

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

Use in hepatic impairment

Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function tests (LFTs) when taking fingolimod, caution in the use of fingolimod should be exercised in patients with a history of significant liver disease.

Use in the elderly

Fingolimod should be used with caution in patients aged 65 years and over (see section 5 Pharmacological properties).

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 on 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 Use in Pregnancy and section 4.4 Special warnings and precautions for use. Return of disease activity (rebound) after fingolimod discontinuation.)

Effects on laboratory tests

Since fingolimod reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilized to evaluate the lymphocyte subset status of a patient treated with fingolimod.

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions:

Anti-neoplastic, immune-modulating, or immunosuppressive therapies (including corticosteroids) should be co-administered with caution due to the risk of additive immune system effects (see section 4.4 Special warnings and precautions for use - Prior treatment with immunosuppressive or immune-modulating therapies). Specific decisions as to the dosage and duration of concomitant treatment with corticosteroids should be based on clinical judgment. (see section 4.4 Special warnings and precautions for use and section 4.8 Adverse effects (undesirable effects)).

Caution should also be applied when switching patients from long-acting therapies with immune effects such as natalizumab, teriflunomide, or mitoxantrone (see section 4.4 Special warnings and precautions for use - Prior treatment with immunosuppressive or immune-modulating therapies). In multiple sclerosis clinical trials the concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection.

When fingolimod is used with atenolol, there is an additional 15% reduction in heart rate upon fingolimod initiation, an effect not seen with diltiazem.

Treatment with fingolimod should not be initiated in patients receiving beta blockers, heart rate lowering calcium channel blockers (such as verapamil or diltiazem), or other substances which may decrease heart rate (e.g. digoxin or ivabradine) because of the potential additive effects on heart rate. If treatment with fingolimod is considered, advice from a cardiologist should be sought regarding the switch to non-heart-rate lowering medicinal products or appropriate monitoring for treatment initiation (should last overnight) (see section 4.4 Special warnings and precautions for use).

During and for up to two months after treatment with fingolimod, vaccination may be less effective. The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided (see section 4.8 Undesirable effects and section 4.4 Special warnings and precautions for use).

Pharmacokinetic interactions:

Fingolimod is primarily cleared via cytochrome P450 4F2 (CYP4F2) and possibly other CYP4F isoenzymes. In vitro studies with human hepatocytes indicated that CYP3A4 may contribute to fingolimod metabolism in the case of strong induction of CYP3A4.

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

In vitro inhibition studies using 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 drugs that are mainly cleared through metabolism by the major CYP isoenzymes.

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

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2, and ABCB1 (P-glycoprotein) 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 CYP enzymes and ABCB1 with respect to the vehicle control. Therefore no clinically relevant induction by fingolimod of the tested CYP450 enzymes or ABCB1 is expected at therapeutic concentrations. In vitro experiments with primary human hepatocytes did not provide an indication of CYP induction by fingolimod-phosphate at clinically relevant concentrations.

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

Based on in vitro data, fingolimod as well as fingolimod-phosphate are not expected to inhibit the uptake of co-medications and/or biologics transported by the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1, OATP1B3) or the sodium taurocholate co-transporting polypeptide (NTCP). Similarly, they are not expected to inhibit the efflux of co-medications and/or biologics transported by the breast cancer resistance protein (BCRP), the bile salt export pump (BSEP), the multidrug resistance-associated protein 2 (MRP2) or P-gp at therapeutic concentrations.

Cyclosporine:

The pharmacokinetics of single-dose fingolimod were not altered during co-administration with cyclosporine at steady-state, nor were cyclosporine steady-state pharmacokinetics altered by single-dose, or multi-dose (28 days) fingolimod administration. These data indicate that fingolimod is unlikely to reduce, or increase the clearance of drugs mainly cleared by CYP3A4 and that inhibition of CYP3A4 is unlikely to reduce the clearance of fingolimod. Potent inhibition of transporters P-gp, MRP2 and OATP1B1 does not influence fingolimod disposition.

Ketoconazole:

The co-administration of oral ketoconazole 200 mg twice daily at steady-state and a single dose of fingolimod 5 mg led to a modest increase in the AUC of fingolimod and fingolimod-phosphate (1.7-fold increase) by inhibition of CYP4F2. Patients who use fingolimod and systemic ketoconazole concomitantly should be closely monitored, as the risk of adverse reactions is greater.

Isoproterenol, atropine, atenolol, and diltiazem:

Single-dose fingolimod and fingolimod-phosphate exposure was not altered by co-administered isoproterenol, or atropine. Likewise, the single-dose pharmacokinetics of fingolimod and fingolimod-phosphate and the steady-state pharmacokinetics of both atenolol and diltiazem were unchanged during the co-administration of the latter two drugs with fingolimod.

Carbamazepine

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.

Population pharmacokinetics analysis of potential drug-drug interactions:

A population pharmacokinetics evaluation, performed in multiple sclerosis patients, did not provide evidence for a significant effect of fluoxetine and paroxetine (strong CYP2D6 inhibitors) and carbamazepine (potent enzyme inducer) on fingolimod or fingolimod-phosphate concentrations. In addition, the following, commonly prescribed substances had no clinically relevant effect ($\leq 20\%$) on fingolimod or fingolimod-phosphate concentrations: baclofen, gabapentin, oxybutynin, amantadine,

modafinil, amitriptyline, pregabalin, corticosteroids and oral contraceptives.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

There are no human data on the effects of fingolimod on male or female fertility. Fingolimod had no effect on fertility in rats up to the highest dose tested of 10 mg/kg/day (estimated systemic exposure more than 100 times the anticipated clinical exposure) in a study in which both male and female animals were treated and mated. There was no apparent effect on sperm counts. Data from animals do not suggest that fingolimod would be associated with an increased risk of reduced fertility.

Use in Pregnancy (Category D)

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

For females planning to become pregnant, fingolimod should be stopped 2 months before conception (see section 4.4 Special warnings and precautions for use – Pregnancy, fetal risk and contraception). It will take approximately 2 months to eliminate the compound from the body upon 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.

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). If fingolimod is discontinued because of pregnancy or planned pregnancy, the possibility of severe exacerbation of disease should be considered, see section 4.4 Special warnings and precautions for use - Return of disease activity (rebound) after fingolimod discontinuation and Stopping therapy.

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 studies have shown reproductive toxicity, including fetal loss. Fingolimod and/or its metabolites crossed the placental barrier in pregnant rats and rabbits. When administered during organogenesis, fingolimod was teratogenic in the rat at oral doses of 0.1 mg/kg/day or higher (similar to the clinical dose on a body surface area basis). The most common malformations were persistent truncus arteriosus and ventricular septal defect. At a lower dose (0.03 mg/kg/day), an increased incidence of left umbilical artery was the only finding. A pharmacological mechanism may be responsible as the sphingosine 1-phosphate receptor is involved in vascular formation during embryogenesis. Rabbits showed an increase in skeletal variations at exposures similar to clinical

exposure. An increase in post-implantation loss and/or abortion was observed in rat (0.5 mg/kg/day or higher) and rabbit (5 mg/kg/day or higher) studies. Reduced perinatal survival was seen in offspring from rats treated orally from early gestation to weaning with 0.05 mg/kg/day or higher (similar to the clinical dose on a body surface area basis); a no effect dose was not established.

Women of Childbearing Potential

Pregnancy testing

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

Contraception

Before initiation of Pharmacor Fingolimod treatment, females of childbearing potential should be counselled on the potential for a serious risk to the foetus and the need for effective contraception during treatment with Pharmacor Fingolimod and for 2 months after stopping treatment. Since it takes approximately 2 months to eliminate the compound from the body after stopping treatment (see section 4.4 Special warnings and precautions for use - Stopping Pharmacor Fingolimod Therapy) the potential to the foetus may persist and contraception should be pursued during this period.

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

Labour and Delivery

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

Use in Lactation

Fingolimod and/or its metabolites was excreted in the milk of treated rats during lactation. There were no effects on body weight, development, behaviour, or fertility in rat pups from dams treated with oral fingolimod from early gestation to weaning. Reduced immunocompetence was evident in juvenile rats following oral administration.

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 excreted in human milk and because of the potential for serious adverse drug reactions from fingolimod in nursing infants, females receiving fingolimod should not breast feed.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration

4.8 Adverse effects (Undesirable effects)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://pophealth.my.site.com/carmreportnz/s/>

The safety population of fingolimod is derived from two Phase III placebo-controlled clinical trials

and one Phase III active-controlled clinical trial in patients with relapsing remitting multiple sclerosis. It includes a total of 2431 patients on fingolimod (500 micrograms or 1.25 mg dose) In the pooled data from the two placebo controlled studies (D2301, FREEDOMS and D2309, FREEDOMS II) the most serious adverse drug reactions (ADRs) for the 500 micrograms recommended therapeutic dose were infections, macular edema and transient atrio-ventricular blocks on treatment initiation. The most frequent ADRs (incidence $\geq 10\%$) at the 500 micrograms dose were headache, hepatic enzyme increased, diarrhoea, cough, influenza, sinusitis and back pain. The most frequent adverse event reported for fingolimod 500 micrograms at an incidence greater than 1% leading to treatment interruption was ALT elevations (2.2%).

The ADRs for fingolimod in Study D2302 (TRANSFORMS), a 1-year controlled study using interferon beta-1a as comparator in 849 patients with multiple sclerosis treated with fingolimod), were generally similar to Study D2301, taking into account the differences in study duration.

Table 1 presents the frequency of ADRs reported in the pooled analysis of the placebo-controlled studies. ADRs are listed according to MedDRA system organ class. Frequencies were defined as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); rare ($\geq 1/10,000$ to $<1/1,000$); very rare ($<1/10,000$). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 ADRs occurring in $\geq 1\%$ of patients in Studies D2301 and D2309

Primary system organ class Preferred Term	Placebo N=773 %	Fingolimod 500 micrograms N=783 %
Infections and infestations		
Influenza	65 (8.4)	89 (11.4)
Sinusitis	64 (8.3)	85 (10.9)
Bronchitis	35 (4.5)	64 (8.2)
Herpes zoster	7 (0.9)	16 (2.0)
Tinea versicolor	3 (0.4)	14 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Basal cell carcinoma	5 (0.6)	14 (1.8)
Blood and lymphatic system disorders		
Lymphopenia	2 (0.3)	53 (6.8)
Leucopenia	1 (0.1)	17 (2.2)
Thrombocytopenia*	0 (0.0)	5 (0.3)
Nervous system disorders		
Headache	175 (22.6)	192 (24.5)
Dizziness	65 (8.4)	69 (8.8)
Migraine	28 (3.6)	45 (5.7)
Eye disorders		
Vision blurred	19 (2.5)	33 (4.2)
Cardiac Disorders		
Bradycardia	0.9	2.6
Vascular disorders		
Hypertension	28 (3.6)	63 (8.0)
Respiratory, thoracic and mediastinal disorders		
Cough	87 (11.3)	96 (12.3)

Dyspnoea	54 (7.0)	71 (9.1)
Gastrointestinal disorders		
Diarrhea	74 (9.6)	99 (12.6)
Skin and subcutaneous tissue disorders		
Eczema	15 (1.9)	21 (2.7)
Pruritus	17 (2.2)	21 (2.7)
Musculoskeletal and connective tissue disorders		
Back pain	69 (8.9)	78 (10.0)
General disorders and administration site conditions		
Asthenia	6 (0.8)	15 (1.9)
Investigations		
Hepatic enzyme increased (increased ALT, GGT, AST)	32 (4.1)	119 (15.2)
Blood triglycerides increased	7 (0.9)	16 (2.0)

* n=1709, based on retrospective review of the pivotal clinical studies

Other adverse reactions reported in clinical trials:

Uncommon: pneumonia, macular oedema, melanoma* and seizure

Very rare: Kaposi's sarcoma*

*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

Infections

In multiple sclerosis clinical trials, the overall rate of infections (65.1%) at the 500 micrograms dose was similar to placebo. However, bronchitis, herpes zoster and pneumonia, were more common in fingolimod treated patients. Serious infections occurred at a rate of 1.6% in the fingolimod 500 micrograms 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 section 4.4 Special warnings and precautions for use and section 4.5 Interactions with other medicines and other forms of interactions).

There have been very rare cases of other herpes viral infections with fatal outcome. Two serious cases of disseminated herpes infection which were fatal have occurred on the 1.25 mg dose; a case of herpes encephalitis in a patient in whom initiation of acyclovir therapy was delayed by one week and a case of a primary disseminated varicella zoster infection in a patient not previously exposed to varicella receiving concomitant high-dose steroid therapy for a multiple sclerosis relapse.

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 Special warnings and precautions for use).

Cases of opportunistic infections, have been reported in the post-marketing setting, some of which have been fatal. These cases included viral infections such as JCV causing Progressive Multifocal Leukoencephalopathy (PML), herpes simplex or varicella zoster virus which may lead to encephalitis/meningitis, fungal infections including cryptococcal meningitis and atypical mycobacterial skin and lung infections (see section 4.4 Special warnings and precautions for use).

Macular Oedema

In clinical trials, macular oedema occurred in 0.4 % of patients treated with the recommended fingolimod dose of 500 micrograms and in 1.1 % of patients treated with the higher 1.25 mg dose. The majority of cases in multiple sclerosis clinical trials 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 ophthalmologic examination. The macular oedema generally improved or resolved spontaneously after drug discontinuation. 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 (approximately 20% with a history of uveitis vs 0.6% without a history of uveitis).

Fingolimod has not been tested in multiple sclerosis patients with diabetes mellitus. In renal transplant clinical studies where 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. Multiple sclerosis patients with diabetes mellitus are therefore expected to be at a higher risk for macular oedema (see section 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 atrio-ventricular conduction delays (see section 4.4 Special warnings and precautions for use).

In multiple sclerosis clinical trials the mean maximal decrease in heart rate after the first dose intake was seen 4 - 5 hours post-dose, with declines in mean heart rate, as measured by pulse, of 8 beats per minute for fingolimod 500 micrograms. The second dose may result in a slight further decrease. Heart rates below 40 beats per minute (bpm) in adults, and below 50 bpm in paediatric patients were rarely observed in patients on fingolimod 500 micrograms. Heart rate returned to baseline within 1 month of chronic dosing.

In the multiple sclerosis clinical program first-degree atrio-ventricular block (prolonged PR interval on electrocardiogram) was detected following drug initiation in 4.7% of patients on fingolimod 500 micrograms, in 2.8% of patients on intramuscular interferon beta-1a and in 1.5% of patients on placebo. Second-degree atrioventricular block were detected in less than 0.5 % patients on fingolimod 500 micrograms.

The conduction abnormalities were typically transient, asymptomatic and resolved within 24 hours on treatment. Although most patients did not require medical intervention, in clinical trials one patient on the 500 micrograms dose received isoprenaline for an asymptomatic second degree Mobitz I atrio-ventricular block.

Blood Pressure

In multiple sclerosis clinical trials fingolimod 500 micrograms was associated with a mild increase of approximately 1 mmHg on average in mean arterial pressure manifesting after approximately 2 months of treatment initiation. This increase persisted with continued treatment. Hypertension was reported in 6.1% of patients on fingolimod 500 micrograms and in 3.8 % of patients on placebo.

Liver Transaminases

Increased hepatic enzymes (mostly ALT elevation) have been reported in multiple sclerosis patients treated with fingolimod (see section 4.4 Special warnings and precautions for use). In multiple sclerosis clinical trials, 8.5% and 1.9% of patients treated with fingolimod 500 micrograms experienced asymptomatic elevation in serum levels of hepatic transaminases $\geq 3 \times$ ULN and $\geq 5 \times$ ULN, respectively. The majority of elevations occurred within 6-9 months. Serum transaminase levels

returned to normal after discontinuation of fingolimod within approximately 2 months. In a small number of patients, 10 patients on fingolimod 1.25 mg and 2 patients on fingolimod 500 micrograms, who experienced liver transaminase elevations $\geq 5 \times$ ULN and who continued on fingolimod therapy, the elevations returned to normal within approximately 5 months (see section 4.4 Special warnings and precautions for use).

Respiratory System

Minor dose-dependent reductions in FEV1 and diffusion capacity of the lung for carbon monoxide (DLCO) values were observed with fingolimod treatment starting at month 1 and remaining stable thereafter. At month 24, the reduction from baseline values in percent of predicted FEV1 was 3.1% for fingolimod 500 micrograms and 2.0% for placebo. For DLCO the reductions at Month 24 were 3.8% for fingolimod 500 micrograms and 2.7% for placebo. The changes in FEV1 were reversible following treatment discontinuation.

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.

Vascular Events

In phase III clinical trials, rare cases of peripheral arterial occlusive disease occurred in patients treated with fingolimod at higher doses (1.25 or 5.0 mg). Rare cases of ischemic and haemorrhagic strokes have also been reported at 500 micrograms dose in clinical trials and in the post-marketing setting although a causal relationship has not been established.

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.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions 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.

Table 2: Adverse drug reactions from spontaneous reports and literature cases (frequency not known) or from pooled clinical trials

Nervous system disorders	
Rare	Posterior reversible encephalopathy syndrome (PRES)*
Not known***	Severe exacerbation of disease after discontinuation (see section 4.4 Special warnings and precautions for use)
Neoplasms benign, malignant and unsuspected (incl cysts and polyps)	
Uncommon	Malignant melanoma**
Rare	Lymphoma
Very rare	Kaposi's sarcoma**

Not known***	Squamous cell carcinoma of the skin, Merkel cell carcinoma
Immune system disorders	
Not known***	Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation, autoimmune haemolytic anaemia
Gastrointestinal disorders	
Not known***	Nausea
Blood and lymphatic system disorders	
Not known***	Thrombocytopenia
Musculoskeletal and connective tissue disorders	
Not known***	Myalgia, arthralgia
Investigations	
Not known***	Weight decreased
Hepatobiliary disorders	
Not known***	Liver injury

* 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 500 micrograms in all clinical trials.

***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 categorised as not known. Adverse drug reactions are listed according to system organ classes.

Bradyarrhythmia

Isolated events of transient, spontaneously resolving complete AV block have been observed during the six hour observation period following the first dose of fingolimod. The patients recovered spontaneously. 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 medications and/or pre-existing disease. The relationship of such events to fingolimod is uncertain.

4.9 Overdose

No cases of overdosage have been reported. However, single doses up to 80-fold the recommended dose (500 micrograms) were well tolerated in healthy adult volunteers. At 40mg, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with small airway reactivity.

Fingolimod can induce bradycardia (see section 5 Pharmacological properties, Heart rate and rhythm). Some patients experience mild to moderate symptoms, including hypotension, dizziness, fatigue, and/or palpitations. There have been reports of slow atrioventricular conduction with isolated reports of transient, spontaneously resolving complete AV block (see section 4.4 Special warnings and precautions for use and section 4.8 Adverse effects (undesirable effects)).

If the overdose constitutes first exposure to fingolimod it is important to observe for signs and symptoms of bradycardia, which could include overnight monitoring. Regular measurements of pulse rate and blood pressure are required and electrocardiograms should be performed (see DOSAGE AND ADMINISTRATION and section 4.4 Special warnings and precautions for use).

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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) receptors 1, 3, and 4 located on lymphocytes, and readily crosses the blood brain barrier to bind to S1P receptors 1, 3, and 5 located 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 lymphocyte cells into the central nervous system where they would be involved in nerve inflammation and nervous tissue damage.

Animal studies and *in vitro* experiments indicate that fingolimod may also exert beneficial effects in multiple sclerosis via interaction with S1P receptors on neural cells.

Pharmacodynamic effects

Immune system:

Effects on immune cell numbers in the blood:

Within 4-6 hours after the first dose of fingolimod 500 micrograms, the lymphocyte count decreases to approximately 75 % of baseline. With continued daily dosing, the lymphocyte count continues to decrease over a two week period, reaching a nadir count of approximately 500 cells/ μ L or approximately 30 % of baseline. Eighteen percent of patients reached a nadir of < 200 cells/ μ L 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.

Heart rate and rhythm:

Fingolimod causes a transient reduction in heart rate and atrioventricular conduction upon treatment initiation (see section 4.4 Special warnings and precautions for use - Bradyarrhythmia and section 4.8 Undesirable effects). The maximum decline in heart rate is seen in the first 4-5 hours post-dose, with 70% of the negative chronotropic effect achieved on the first day. Heart rate progressively returns to baseline values within one month of chronic treatment.

Autonomic responses of the heart, including diurnal variation of heart rate and response to exercise are not affected by fingolimod treatment.

With initiation of fingolimod treatment there is an increase in atrial premature contractions, but there is no increased rate of atrial fibrillation/flutter, ventricular arrhythmias or ectopy. Fingolimod treatment is not associated with a decrease in 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 a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTcI, with the upper boundary of the 90 % CI ≤ 13.0 msec. 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. In the multiple sclerosis studies, there was no clinically relevant prolongation of the QT interval.

Pulmonary function:

Fingolimod treatment with single or multiple doses of 500 micrograms and 1.25 mg for two weeks is not associated with a detectable increase in airway resistance as measured by forced expiratory volume in 1 second (FEV1) and forced expiratory flow during expiration of 25 to 75 % of the forced vital capacity (FEF25-75). 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 500 micrograms, 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 β -agonists.

Clinical efficacy and safety

The efficacy of fingolimod has been demonstrated in two studies that evaluated once-daily doses of fingolimod 500 micrograms and 1.25 mg in patients with relapsing remitting multiple sclerosis. Both studies included patients who had experienced at least 2 clinical relapses during the 2 years prior to randomization, or at least 1 clinical relapse during the 1 year prior to randomisation, and had an Expanded Disability Status Scale (EDSS) between 0 to 5.5. A third study targeting the same patient population was completed after registration of fingolimod.

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 any interferon-beta or glatiramer acetate for at least the previous 3 months and had not received 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 37 years, median disease duration was 6.7 years and median EDSS score at baseline was 2.0. Patients were randomized to receive fingolimod 500 micrograms (n=425), fingolimod 1.25 mg (n=429), or placebo (n=418) for up to 24 months. Median time on study drug was 717 days on 0.5 mg, 715 days on 1.25 mg and 718.5 days on placebo.

The annualised relapse rate was significantly lower in patients treated with fingolimod than in patients who received placebo. 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 (0.5 point increase for patients with baseline EDSS of 5.5) sustained for 3 months. Time to onset of 3-month confirmed disability progression was significantly delayed with fingolimod treatment compared to placebo. There were no significant differences between the 500 micrograms and the 1.25 mg doses on either endpoint.

The results for this study are shown in Table 3 and Figures 1 and 2.

Table 3 Clinical and MRI results of FREEDOMS Study (D2301)

	Fingolimod 500 micrograms	Fingolimod 1.25 mg	Placebo
Clinical Endpoints	N=425	N=429	N=418
Annualised 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 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 relapse 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 for time to first confirmed relapse up to Month 24 – FREEDOMS Study (D2301) (ITT population)

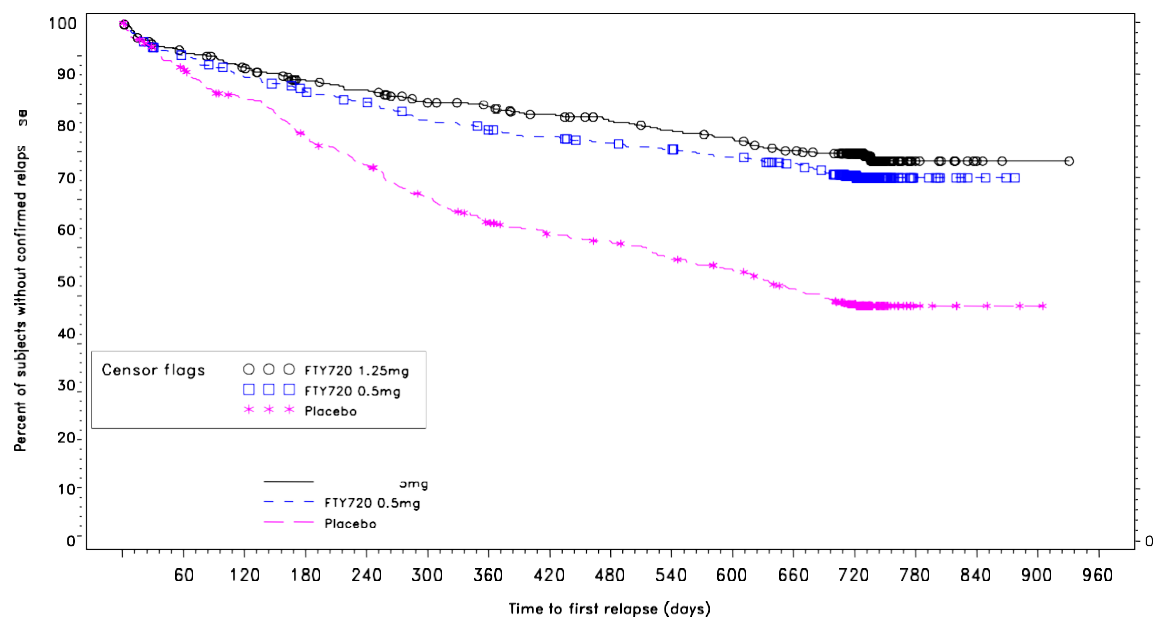
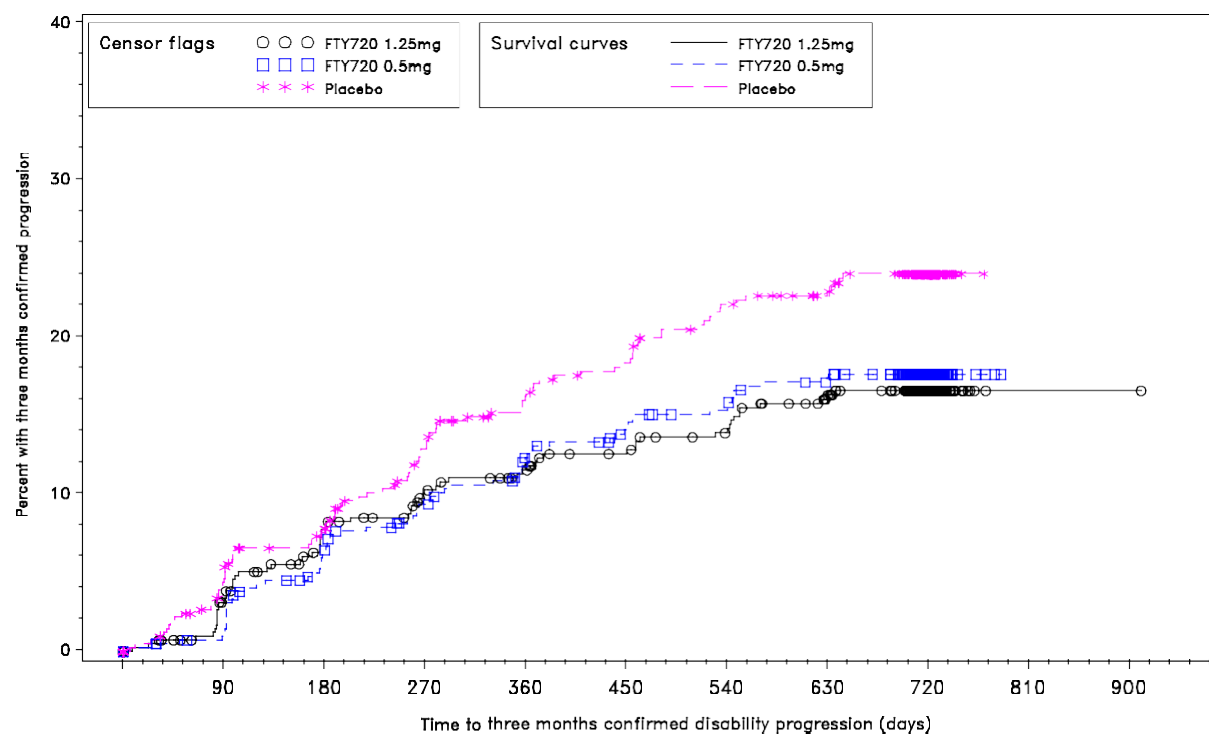


Figure 2 Cumulative plot of time to 3-month confirmed disability progression – FREEDOMS Study (D2301) (ITT population)



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 500 micrograms, 289 continued on 1.25 mg, 155 switched from placebo to 500 micrograms 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 500 micrograms (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 500 micrograms (ARR ratio 0.45, 95% CI 0.32 to 0.62, $p < 0.001$). The ARR for patients who were treated with fingolimod 500 micrograms 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 500 micrograms (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 500 micrograms and 719 days on placebo. Patients randomized to the fingolimod 1.25 mg dose arm were switched in a blinded manner to receive fingolimod 500 micrograms

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 500 micrograms.

The annualised 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 500 micrograms 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 D2302

	Fingolimod 500 micrograms	Fingolimod 1.25 mg	Placebo
Clinical Endpoints	N=358	N=370	N=355
Annualised relapse rate	0.21	0.20	0.40

New Zealand Data sheet

(primary endpoint)	(p<0.001*)	(p<0.001*)	
Relative reduction (percent)	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)	0.83 (0.61, 1.12)	0.72 (0.53, 0.99)	
3-month confirmed)	(p=0.227)	(p=0.041*)	
Hazard ratio (95% CI)	0.72 (0.48, 1.07)	0.72 (0.48, 1.08)	
(6-month confirmed)	(p=0.113)	(p=0.101)	
MRI Endpoints			
Percentage change in brain volume	n=266	n=247	n=249
Median (mean) % change over 24 months	-0.7 (-0.9) (p<0.001*)	-0.6 (-0.9) (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) (p<0.001* at each time point)	0.0 (0.2) (p<0.001* at each time point)	0.0 (1.2)
Percentage 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 evaluable dataset.

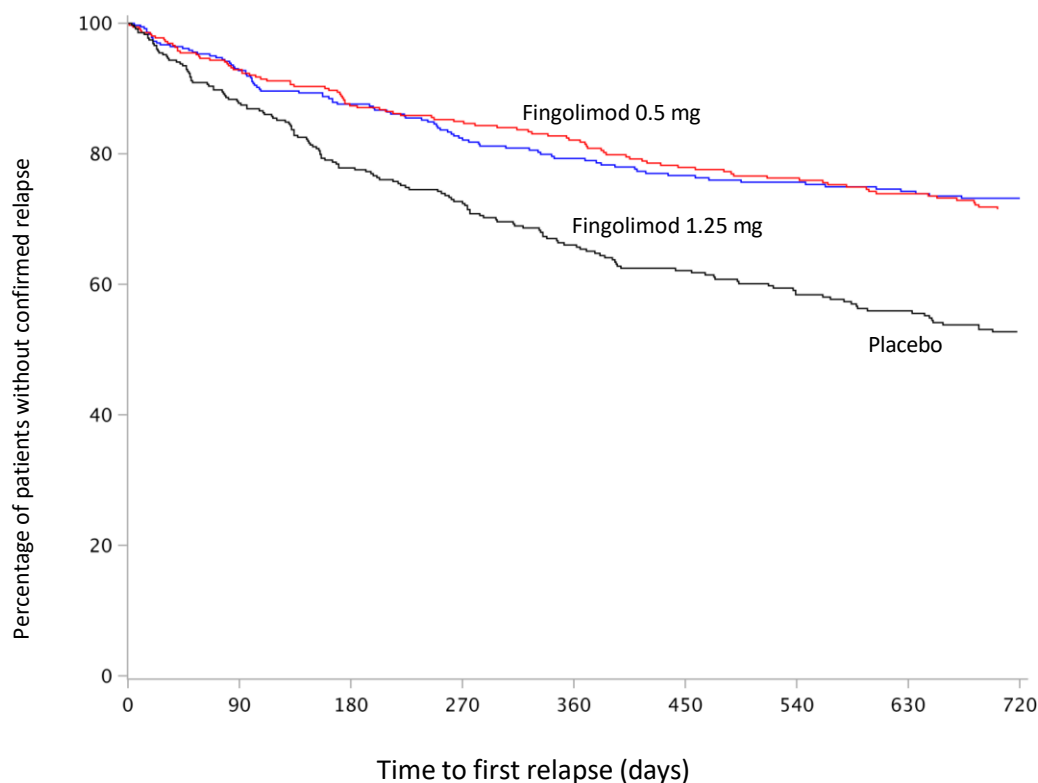
* Indicates statistical significance vs. Interferon beta-1a at two-sided 0.05 level.

Determination of p-values: aggregate ARR by negative binomial regression adjusting for treatment, country, number of relapses in previous 2 years and baseline EDSS; percent of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapse 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.

† 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 500 micrograms

demonstrated a clinically relevant and statistically significant reduction compared to placebo (HR= 0.70; CI (0.50, 0.98); p=0.040), consistent with study FREEDOMS.

Figure 3 Kaplan-Meier plot of time to first confirmed relapse up to Month 24 –FREEDOMS II Study (D2309) (ITT population)



Study D2302 (TRANSFORMS)

Study D2302 (TRANSFORMS) was a 1-year randomised, double-blind, double-dummy, active-controlled (interferon beta-1a 30 micrograms, intramuscular, once weekly) Phase III study in patients with relapsing-remitting multiple sclerosis who had not received natalizumab in the previous 6 months. Prior therapy with interferon-beta or glatiramer acetate up to the time of randomisation 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 at Month 12. The primary endpoint was the annualized relapse rate.

Median age was 36 years, median disease duration was 5.9 years and median EDSS score at baseline was 2.0. Patients were randomized to receive fingolimod 500 micrograms (n=431) or 1.25 mg (n=426) or interferon beta-1a 30 micrograms via the intramuscular route once weekly (n=435) for up to 12 months. Median time on study drug was 365 days on fingolimod 500 micrograms, 354 days on fingolimod 1.25 mg and 361 days on interferon beta-1a IM.

The annualised relapse rate was significantly lower in patients treated with fingolimod than in patients who received interferon beta-1a IM. There was no significant difference between the fingolimod 500 micrograms and 1.25 mg doses. The key secondary endpoints were number of new or newly enlarging T2 lesions and time to onset of 3-month confirmed disability progression as measured by at least a 1-point increase from baseline in EDSS (0.5 point increase for those with baseline EDSS of 5.5) sustained for 3 months. The number of new or newly enlarging T2 lesions was significantly lower in patients treated with fingolimod than in patients who received interferon beta-1a IM. There was no significant

difference in the time to 3-month confirmed disability progression between fingolimod and interferon beta-1a- treated patients at 1 year. There were no significant differences between the 500 micrograms and 1.25 mg doses for either endpoint.

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

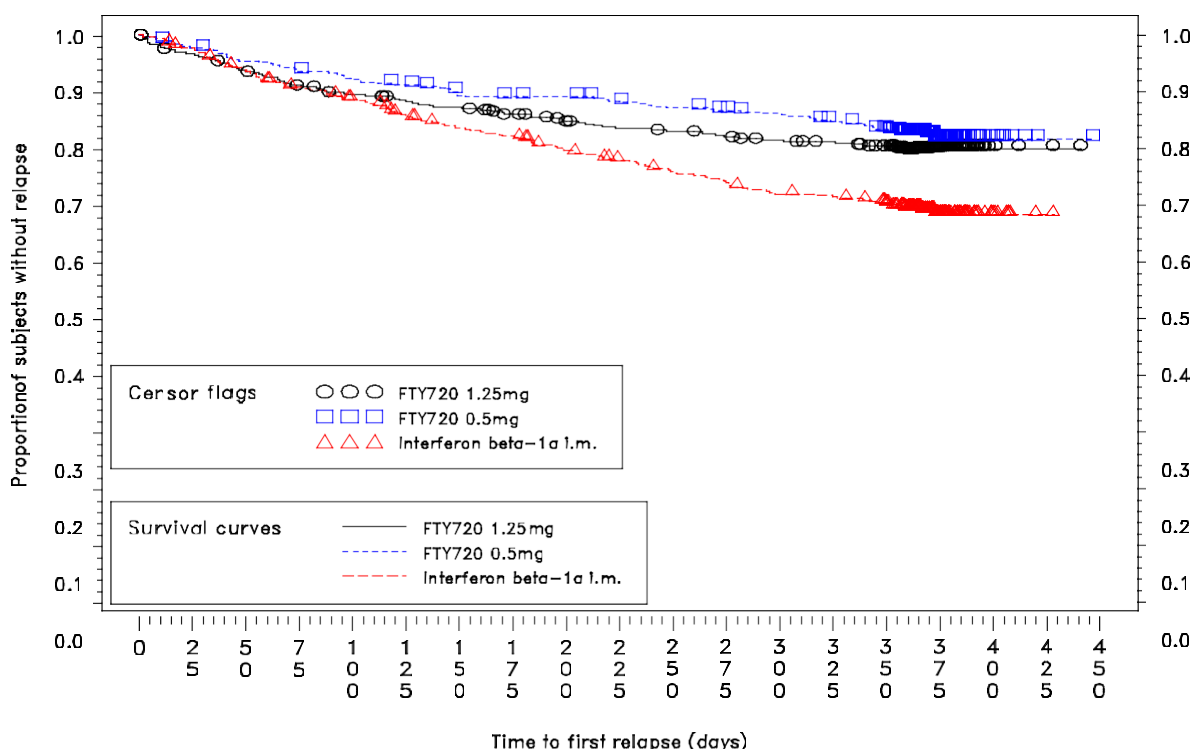
Table 5 Clinical and MRI results of TRANSFORMS Study (D2302)

	Fingolimod 500 micrograms	Fingolimod 1.25 mg	Interferon beta-1a IM 30 µg
Clinical endpoints	N=429	N=420	N=431
Annualised 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)
Percentage 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 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; percent of patients maintaining relapse-free logistic regression adjusted for treatment, country, number of relapse 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 – TRANSFORMS Study (D2302) (ITT population)

Patients who completed Study TRANSFORMS (D2302) had the option to enter a dose-blinded extension study. 1,030 patients from the core study entered the extension (Study D2302E1) and were treated with fingolimod (n=357 continued on 500 micrograms, 330 continued on 1.25 mg, 167 switched from interferon beta-1a to 500 micrograms 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 500 micrograms (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 500 micrograms (ARR ratio=0.70, p=0.06). The ARR for patients who were treated with fingolimod 500 micrograms in the core study was low during the combined core and extension study (ARR of 0.18 up to Month 24).

The pooled results of studies D2301 (FREEDOMS) and D2302 (TRANSFORMS) showed a consistent reduction in the 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.

5.2 Pharmacokinetic properties

Absorption:

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

Food intake does not alter C_{max} or exposure (AUC) of fingolimod or fingolimod-phosphate. Therefore fingolimod may be taken without regard to meals (see DOSAGE AND ADMINISTRATION).

Steady-state-blood concentrations are reached within 1 to 2 months following once-daily administration, and steady-state levels are approximately 10-fold greater than with the initial dose.

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 (>99.7%). 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.

Metabolism:

The biotransformation of fingolimod in humans occurs by three main pathways; by reversible stereoselective phosphorylation to the pharmacologically active (S)-enantiomer of fingolimod-phosphate, 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 analogs of fingolimod.

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 816 hours post-dose of total radiolabeled components, 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 %)).

Excretion:

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-phosphate decline in parallel with fingolimod in the terminal phase yielding 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 apparent dose proportional manner after multiple once daily doses of fingolimod 500 micrograms or 1.25 mg.

In paediatric patients, fingolimod-phosphate concentrations increase in an apparent dose proportional manner after multiple once daily doses of fingolimod 0.25 mg or 500 micrograms.

Pharmacokinetics in special patient groups:

Pharmacokinetics in children:

Safety and efficacy of fingolimod in paediatric patients below the age of 18 have not been studied. Fingolimod is not indicated for use in paediatric patients.

Pharmacokinetics in the elderly:

The mechanism for elimination and results from population pharmacokinetics suggest that dose

adjustment would not be necessary in elderly patients. However, clinical experience in patients aged above 65 years is limited.

Pharmacokinetics in patients with impaired renal or hepatic function:

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. In severe renal impairment C_{max} and AUC for M3, an inactive metabolite, were increased by 805 % and 1356 % respectively. No fingolimod dose adjustments are needed in patients with renal impairment.

The pharmacokinetics of single-dose fingolimod (1 or 5 mg), when assessed in subjects with mild, moderate and severe hepatic impairments, (Child-Pugh class A, B, and C), showed no change on fingolimod C_{max}, but an increase in AUC 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 %. The pharmacokinetics of fingolimod-phosphate was not evaluated in patients with mild or moderate hepatic impairment. Although hepatic impairment elicited changes in the disposition of fingolimod and fingolimod-phosphate, the magnitude of these changes suggests that the fingolimod dose does not need to be adjusted in mild or moderate hepatic impaired patients (Child-Pugh class A and B). Fingolimod should be used with caution in patients with severe hepatic impairment (Child-Pugh class C).

Ethnicity:

The effects of ethnic origin on fingolimod and fingolimod phosphate pharmacokinetics are not of clinical relevance.

Gender:

Gender has no influence on fingolimod and fingolimod-phosphate pharmacokinetics.

5.3 Preclinical safety data

Genotoxicity

Fingolimod induced numerical chromosomal aberrations (polyploidy) in Chinese hamster cells at concentrations more than three orders of magnitude greater than the clinical steady-state plasma levels, but not in human lymphocytes when tested at similar concentrations. Fingolimod was not clastogenic in the in vivo micronucleus tests in mice and rats at exposures at least 500 times that expected clinically.

Carcinogenicity

In a 2-year mouse study, an increased incidence of malignant lymphoma was seen at oral doses of fingolimod of 0.25 mg/kg/day and higher, with exposure (plasma AUC) 5-fold the human systemic exposure at a daily dose of 500 micrograms. Exposure at the NOEL (0.025 mg/kg/day) was 0.6-fold human exposure. 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/day, representing a 50-fold margin based on the human systemic exposure (AUC) at the 500 micrograms dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core:

Magnesium stearate

Calcium hydrogen phosphate

Capsule shell:

Iron oxide yellow

Titanium dioxide

Gelatin

Printing ink:

TekPrint SW-9008 Black Ink (ARTG PI No: 2328):

- Shellac
- Dehydrated alcohol
- Isopropyl alcohol
- Butyl alcohol
- Propylene Glycol
- Strong ammonia solution
- Potassium hydroxide
- Black Iron oxide

Tekprint SB-3002 Gold Ink (ARTG PI No: 3426):

- Shellac
- Dehydrated alcohol
- Isopropyl alcohol
- Butyl alcohol
- Propylene Glycol
- Strong ammonia solution
- Yellow Iron oxide

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

36 months. The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25 degrees Celsius.

6.5 Nature and contents of container

PVC/ACLAR-Al blister packs of 28 or 84 capsules. Not all presentations might be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription only medicine (S4)

8 SPONSOR

Pharmacor Limited
c/- Wynn Williams
Level 25, Vero Centre
48 Shortland Street
Auckland Central
AUCKLAND 1010
New Zealand
Ph: +64 800 172 553
Or 0800 172 553

9 DATE OF FIRST APPROVAL

27/03/2025

10 DATE OF REVISION OF THE TEXT

DD/MM/YYYY

SUMMARY TABLE OF CHANGES

Section	Summary of changes