SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE HUMAN MEDICINAL PRODUCT

GILOMID 0.5 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Fingolimod hydrochloride 0.56 mg (equivalent to 0.5 mg fingolimod)

Excipients with known effect:
Tartrazine- FD&C Yellow 5 0.071 mg
Sunset yellow FCF- FD&C Yellow 6 0.008 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule
No. 3 hard gelatin capsule, containing white or off-white powder, with an opaque yellow cap and an opaque white body.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

GILOMID is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (MS) for the following groups of adult patients and pediatric patients aged 10 years and older:

1. Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see sections 4.4 and 5.1) or
2. Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

4.2. Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in MS.

Posology

The recommended dose of GILOMID in adults and children aged 10 years and over and weighing more than 40 kg is one 0.5 mg capsule that can be taken orally once a day, with or without food.

When switching from a 0.25 mg to a 0.5 mg daily dose, it is recommended to repeat the same first dose monitoring as for treatment initiation.

Capsules should always be swallowed whole, unopened.
Because of the risk of bradyarrhythmia and atrioventricular (AV) block, patients should be observed when initiating treatment with GILOMID (see section 4.4).

Restarting treatment after discontinuation:
The effects on heart rate and AV conduction may reappear with reintroduction of GILOMID and therefore the precautions at the first dose administration (see section 4.4) remain the same. Initial dose monitoring should be repeated in the following situations:

- If treatment is interrupted for one or more days during the first 2 weeks of treatment
- If treatment is interrupted for more than 7 days during the third and fourth weeks of treatment
- If treatment is interrupted for more than 14 days after one month of treatment

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

Patients can be switched directly from beta-interferon or glatiramer acetate to GILOMID, as long as there is no associated therapy-related abnormality such as neutropenia; no washout period is required.

Frequency and duration of administration
The recommended dose is one 0.5 mg capsule taken orally once a day on an empty or full stomach.

Method of administration
This medicinal product is for oral use.

Additional information on special populations
Renal impairment
It has not been studied in patients with renal impairment. Based on clinical pharmacology studies, no dose adjustment of GILOMID is necessary (see section 5.2).

Hepatic impairment
No dose adjustment of GILOMID is required in patients with mild or moderate hepatic impairment. GILOMID should not be used in patients with severe hepatic impairment (Child-Pugh class C) (see sections 4.3 and 5.2).

Pediatric population
The safety and efficacy of GILOMID in children aged below 10 years have not yet been established. No data are available. There are very limited data available in children between 10-12 years old (see sections 4.4, 4.8 and 5.1).

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

Ethnicity
No dose adjustment of GILOMID is required based on ethnic origin (see section 5.2).

Gender

No dose adjustment of GILOMID is required based on gender (see section 5.2).

4.3. Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1,
- 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),
- Active malignancies,
- Severe liver impairment (Child-Pugh class C),
- Patients who in the previous 6 months had myocardial infarction (MI), unstable angina pectoris, stroke/transient ischemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure (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 wear a pacemaker (see section 4.4),
- Patients with a baseline QTc interval ≥ 500 msec (see section 4.4),
- During pregnancy and in women of childbearing potential not using effective contraception (see sections 4.4 and 4.6),
- Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia or class III anti-arrhythmic medicinal products (see section 4.4).

4.4. Special warnings and precautions for use

Bradyarrhythmia

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

After the first dose, the decline in heart rate starts within one hour, and is maximal within 6 hours. This post-dose effect persists over the following days, although usually to a milder extent, and usually abates over the next weeks. With continued administration, the average heart rate returns towards baseline within one month. However individual patients may not return to baseline heart rate by the end of the first month. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. If necessary, the decrease in heart rate induced by fingolimod can be reversed by parenteral doses of atropine or isoprenaline.

All patients should have an ECG and blood pressure measurement performed prior to and 6 hours after the first dose of GILOMID. All patients should be monitored for a period of 6 hours for signs and symptoms of bradycardia with hourly heartrate and blood pressure measurement. Continuous (real time) ECG monitoring during this 6 hour period is recommended. At the end of the observation period, all patients should have their electrocardiograms taken.

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

Should post-dose bradyarrhythmia-related symptoms occur, appropriate clinical management should be initiated and monitoring should be continued until the symptoms have resolved. Should a patient require pharmacological intervention during the first-dose monitoring, overnight monitoring in a

medical facility should be instituted and the first-dose monitoring should be repeated after the second dose of GILOMID.
If the heart rate at 6 hours is the lowest since the first dose was administered (suggesting that the maximum pharmacodynamic effect on the heart may not yet be manifest), monitoring should be extended by at least 2 hours and until heart rate increases again. Additionally, if after 6 hours, the heart rate is <45 bpm in adults, <55 bpm in pediatric patients aged 12 years and above, or <60 bpm in pediatric 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).

The effects on heart rate and atrioventricular conduction may recur on re-introduction of fingolimod treatment depending on duration of the interruption and time since start of treatment. The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted (see section 4.2).

Very rare cases of T-wave inversion have been reported in patients treated with fingolimod. In case of T-wave inversion, the prescriber should ensure that there are no associated myocardial ischemia signs or symptoms. If myocardial ischemia is suspected, it is recommended to seek advice from a cardiologist.

Due to the risk of serious rhythm disturbances or significant bradycardia, GILOMID should not be used in patients with sino-atrial heart block, a history of symptomatic bradycardia, recurrent syncope or cardiac arrest, or in patients with significant QT prolongation (QTc>470 msec [adult female], QTc >460 msec [pediatric female] or >450 msec [adult and pediatric male]), uncontrolled hypertension or severe sleep apnea (see also section 4.3). In such patients, treatment with GILOMID should be considered only if the anticipated benefits outweigh the potential risks, and advice from a cardiologist sought prior to initiation of treatment in order to determine the most appropriate monitoring. At least overnight extended monitoring is recommended for treatment initiation (see also section 4.5).

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 which 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, concomitant use of these substances during treatment initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with GILOMID should not be initiated in patients who are concurrently treated with these substances (see also section 4.5 Interaction with other medicinal products and other forms of interaction). In such patients, treatment with GILOMID should be considered only if the anticipated benefits outweigh the potential risks. If treatment is being 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 treatment cannot be stopped, cardiologist's advice should be sought to determine appropriate first dose monitoring, at least overnight extended monitoring is recommended (see also section 4.5).

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).

QT interval
In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTcI, with the upper limit of the 90% CI (confidence interval) ≤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, hypokalemia 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, and increases the risk of developing lymphomas and other malignancies, particularly those of the skin. 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 (see also section 4.4 “Infections” and “Cutaneous neoplasms” and section 4.8“Lymphomas”).

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 GILOMID, a recent complete blood count (CBC) (i.e. performed within the last 6 months) should be available. Assessments of CBC are also recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte count<0.2x109/l, if confirmed, should lead to treatment interruption until recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count <0.2x109/l.

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

The immune system effects of GILOMID may increase the risk of infections, including opportunistic infections (see section 4.8). Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. When evaluating a patient with a suspected infection that could be serious, referral to a physician experienced in treating infections should be considered. During treatment, patients should be instructed to report promptly symptoms of infection to their physician.

Suspension of GILOMID should be considered if a patient develops a serious infection and

consideration of benefit-risk should be undertaken prior to re-initiation of therapy.

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

Herpes viral infection
Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex and varicella zoster viruses have occurred with fingolimod at any time during treatment. If herpes encephalitis, meningitis or meningoencephalitis occur, GILOMID should be discontinued and appropriate treatment for the respective infection should be administered.

Patients need to be assessed for their immunity to varicella (chickenpox) prior to GILOMID 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 GILOMID (see section 4.8). Initiation of treatment with fingolimod should be postponed for 1 month to allow full effect of vaccination to occur.

Cryptococcal meningitis
Cases of cryptococcal meningitis (a fungal infection), sometimes fatal, 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 4.8). Patients with symptoms and signs consistent with cryptococcal meningitis (e.g. headache accompanied by mental changes such as confusion, hallucinations, and/or personality changes) should undergo prompt diagnostic evaluation. If cryptococcal meningitis is diagnosed, fingolimod should be suspended and appropriate treatment should be initiated. A multidisciplinary consultation (i.e. infectious disease specialist) should be undertaken if re-initiation of fingolimod is warranted.

Progressive multifocal leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML) has been reported under fingolimod treatment since marketing authorization (see section 4.8). PML is an opportunistic infection caused by John Cunningham virus (JCV), which maybe fatal or result in severe disability. Cases of PML have occurred after approximately 2-3 years of monotherapy treatment without previous exposure to natalizumab. Although the estimated risk appears to increase with cumulative exposure over time, an exact relationship with the duration of treatment is unknown. Additional PML cases have occurred in patients who had been treated previously with natalizumab, which has a known association with PML. PML can only occur in the presence of a JCV infection. If JCV testing is undertaken, it should be considered that the influence of lymphopenia on the accuracy of anti-JCV antibody testing has not been studied in fingolimod-treated patients. It should also be noted that a negative anti-JCV antibody test does not preclude the possibility of subsequent JCV infection. Before initiating treatment with fingolimod, a baseline MRI should be available (usually within 3 months) as a reference. MRI findings may be apparent before clinical signs or symptoms. During routine MRI (in accordance with national and local recommendations), physicians should pay attention to PML suggestive lesions. MRI may be considered as part of increased vigilance in patients considered at increased risk of PML. Cases of asymptomatic PML based on MRI findings and positive JCV DNA in the cerebrospinal fluid have been reported in patients treated with fingolimod. If PML is suspected, MRI should be

performed immediately for diagnostic purposes and treatment with fingolimod should be suspended until PML has been excluded.

Human papilloma virus infection

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. 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 smear test, is recommended as per standard of care.

Macular edema

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

Patients with history of uveitis and patients with diabetes mellitus are at increased risk of macular edema (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 ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy.

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

Liver injury

Increased hepatic enzymes, in particular alanine aminotransaminase (ALT) but also gamma glutamyltransferase (GGT) and aspartate transaminase (AST) have been reported in multiple sclerosis patients treated with fingolimod. Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have also been reported. 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. In clinical trials, elevations 3-fold the upper limit of normal (ULN) or greater in ALT occurred in 8.0% of adult patients treated with fingolimod 0.5 mg compared to 1.9% of placebo patients. Elevations 5-fold the ULN occurred in 1.8% of patients on fingolimod and 0.9% of patients on placebo. In clinical trials, fingolimod was discontinued if the elevation exceeded 5 times the ULN. Recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to fingolimod. In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of fingolimod.

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. In the absence of clinical symptoms, liver transaminases and serum bilirubin should be monitored at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter until 2 months after GILOMID discontinuation. In the absence of clinical symptoms, if liver transaminases are greater than 3 but less than 5 times the ULN without increase in serum bilirubin, more frequent monitoring including serum bilirubin and alkaline phosphatase (ALP) measurement should be instituted to determine if further increases occur and in order to discern if an alternative aetiology of hepatic dysfunction is present. If liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin, GILOMID should be discontinued. Hepatic monitoring should be continued. If serum levels return to normal (including if an alternative cause of the hepatic dysfunction is discovered), GILOMID may be restarted based on a careful benefit-risk assessment of the patient.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have liver enzymes and bilirubin checked promptly and treatment should be discontinued if significant liver injury is confirmed. Treatment should not be resumed unless a plausible alternative aetiology for the signs and symptoms of liver injury can be established.

Although there are no data to establish that patients with pre-existing liver disease are at increased risk of developing elevated liver function tests when taking fingolimod, caution in the use of GILOMID should be exercised in patients with a history of significant liver disease.

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 GILOMID.

In MS clinical trials, patients treated with fingolimod 0.5 mg had an average increase of approximately 3 mmHg in systolic pressure, and approximately 1 mmHg in diastolic pressure, first detected approximately 1 month after treatment initiation, and persisting with continued treatment. In the two-year placebo-controlled study, hypertension was reported as an adverse event in 6.5% of patients on fingolimod 0.5 mg and in 3.3% of patients on placebo. Therefore, blood pressure should be regularly monitored during treatment with GILOMID.

Respiratory effects

Minor dose-dependent reductions in values for forced expiratory volume (FEV1) and diffusion capacity for carbonmonoxide (DLCO) were observed with fingolimod treatment starting at month 1 and remaining stable thereafter. GILOMID should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease (see section 4.8).

Posterior reversible encephalopathy syndrome

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

is suspected, GILOMID should be discontinued.

Prior treatment with immunosuppressive or immunomodulatory therapies
There have been no studies performed to evaluate the efficacy and safety of fingolimod when switching patients from teriflunomide, dimethyl fumarate or alemtuzumab treatment to fingolimod. When switching patients from another disease modifying therapy to GILOMID, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimizing the risk of disease reactivation. A CBC is recommended prior to initiating GILOMID to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.

GILOMID can generally be started immediately after discontinuation of interferon or glatiramer acetate.

For dimethyl fumarate, the washout period should be sufficient for CBC to recover before treatment with GILOMID is started.

Due to the long half-life of natalizumab, elimination usually takes up to 2-3 months following discontinuation. Teriflunomide is also eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide summary of product characteristics is recommended or alternatively washout period should not be shorter than 3.5 months. Caution regarding potential concomitant immune effects is required when switching patients from natalizumab or teriflunomide to GILOMID.

Alemtuzumab has profound and prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with GILOMID after alemtuzumab is not recommended unless the benefits of such treatment clearly outweigh the risks for the individual patient.

A decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration.

Co-administration with potent CYP450 inducers
The combination of fingolimod with potent CYP450 inducers should be used with caution. Concomitant administration with St John's Wort is not recommended.

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). 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 are detected.

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 (see section 4.8). 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. A fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma has also been observed. If lymphoma is suspected, treatment should be discontinued.

Women of childbearing potential
Due to risk to the fetus, fingolimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the fetus, must have a negative pregnancy test and must use effective contraception during treatment and for 2 months after treatment discontinuation (see sections 4.3 and 4.6 and the information contained in the Physician Information Pack).

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 treatment should be considered by the physician on a case-by-case basis taking into account individual benefits and risks.

Return of disease activity (rebound) after fingolimod discontinuation
In the post-marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping fingolimod. This has generally been observed within 12 weeks after stopping fingolimod, but has also been reported up to 24 weeks after fingolimod discontinuation. Caution is therefore indicated when stopping fingolimod therapy. If discontinuation of fingolimod is deemed necessary, the possibility of recurrence of exceptionally high disease activity should be considered and patients should be monitored for relevant signs and symptoms and appropriate treatment initiated as required (see “Stopping therapy” below).

Stopping therapy
If a decision is made to stop treatment with GILOMID a 6 week interval without therapy is needed, based on half-life, to clear fingolimod from the circulation (see section 5.2). Lymphocyte counts progressively return to normal range within 1-2 months of stopping therapy in most patients (see section 5.1) although full recovery can take significantly longer in some patients. Starting other therapies during this interval will result in concomitant exposure to fingolimod. Use of immunosuppressants soon after the discontinuation of GILOMID may lead to an additive effect on the immune system and caution is therefore indicated.
Caution is also indicated when stopping fingolimod therapy due to the risk of a rebound (see “Return of disease activity (rebound) after fingolimod discontinuation” above). If discontinuation of GILOMID is deemed necessary, patients should be monitored during this time for relevant signs of a possible rebound.

Interference with serological testing
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 GILOMID. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes.

Pediatric population

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

- Precautions should be followed at the time of the first dose (see "Bradyarrhythmia" above). The same precautions as for the first dose are recommended when patients are switched from the 0.25 mg to the 0.5 mg daily dose.
- In the controlled pediatric trial D2311, cases of seizures, anxiety, depressed mood and depression have been reported with a higher incidence in patients treated with fingolimod compared to patients treated with interferon beta-1a. Caution is required in this subgroup population (see "Pediatric population" in section 4.8).
- Mild isolated bilirubin increases have been noted in pediatric patients on GILOMID.
- It is recommended that pediatric patients complete all immunizations in accordance with current immunization guidelines before starting GILOMID therapy (see "Infections" above).
- There are very limited data available in children between 10-12 years old, less than 40 kg or at Tanner stage <2 (see sections 4.8 and 5.1). Caution is required in these subgroups due to very limited knowledge available from the clinical study.
- Long-term safety data in the pediatric population are not available.

The tartrazine- FD&C Yellow 5 and sunset yellow FCF- FD&C Yellow 6 contained in GILOMID may cause allergic reactions.

4.5. Interaction with other medicinal products and other forms of interaction

Anti-neoplastic, immunomodulatory or immunosuppressive therapies

Anti-neoplastic, immunomodulatory or immunosuppressive (including corticosteroids) therapies should not be co-administered due to the risk of additive immune system effects (see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).
Caution should also be exercised when switching patients from long-acting therapies with immune effects such as natalizumab, teriflunomide or mitoxantrone (see section 4.4 Prior treatment with immunosuppressants). In multiple sclerosis clinical studies, concomitant administration of a short course of corticosteroids did not increase the overall infection rate.

Vaccination

During and for up to two months after treatment with GILOMID vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided (see sections 4.4 and 4.8).

Bradycardia-inducing substances

Fingolimod has been studied in combination with atenolol and diltiazem. When fingolimod was used with atenolol in an interaction study in healthy volunteers, there was an additional 15% reduction of heart rate at fingolimod treatment initiation, an effect not seen with diltiazem. Treatment with GILOMID 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), ivabradine, digoxin, anticholinesteratic agents or pilocarpine because of the potential additive effects on heart rate (see sections 4.4 and 4.8). If treatment with GILOMID 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

Pharmacokinetic interactions of other substances on fingolimod
Fingolimod is metabolized mainly by CYP4F2. Other enzymes like CYP3A4 may also contribute to its metabolism, notably in the case of strong induction of CYP3A4. Potent inhibitors of transporter proteins are not expected to influence fingolimod disposition. Co-administration of fingolimod with ketoconazole resulted in a 1.7-fold increase in fingolimod and fingolimod phosphate exposure (AUC) by inhibition of CYP4F2. Caution should be exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, and some macrolides such as clarithromycin or telithromycin).

Co-administration of carbamazepine 600 mg twice daily at steady-state and a single dose of fingolimod 2 mg reduced the AUC of fingolimod and its metabolite by approximately 40%. Other strong CYP3A4 enzyme inducers, for example rifampicin, phenobarbital, phenytoin, efavirenz and St. John's Wort, may reduce the AUC of fingolimod and its metabolite at least to this extent. As this could potentially impair the efficacy, their co-administration should be used with caution. Concomitant administration with St. John's Wort is however not recommended.

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

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

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

Additional information on special populations
Renal impairment
No interaction studies have been conducted in patients with renal impairment.

Hepatic impairment
No interaction studies have been conducted in patients with hepatic impairment.

Pediatric population
No interaction studies have been conducted in pediatric patients.

4.6. Fertility, pregnancy and lactation
General recommendation
Pregnancy category is C.

Women of childbearing potential / Contraception in females
Fingolimod is contraindicated in women of childbearing potential not using effective contraception (see section 4.3). Therefore, before initiation of treatment in women of childbearing potential, a negative pregnancy test result must be available and counselling should be provided regarding the serious risk to the fetus. Women of childbearing potential must use effective contraception during treatment and for 2 months after discontinuation of GILOMID, since fingolimod takes approximately

2 months to eliminate from the body after treatment discontinuation (see section 4.4).
Specific measures are also included in the Physician Information Pack. These measures must be implemented before fingolimod is prescribed to female patients and during treatment.
When stopping fingolimod therapy for planning a pregnancy the possible return of disease activity should be considered (see section 4.4).

Pregnancy
Post-marketing data suggest that use of fingolimod is associated with a 2-fold increased risk of major congenital malformations when administered during pregnancy compared with the rate observed in the general population (2-3%; EUROCAT).

The following major malformations were most frequently reported:
- Congenital heart disease such as atrial and ventricular septal defects, tetralogy of Fallot
- Renal abnormalities
- Musculoskeletal abnormalities

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

Animal studies have shown reproductive toxicity including fetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect (see section 5.3). Furthermore, the receptor affected by fingolimod (sphingosine1-phosphate receptor) is known to be involved in vascular formation during embryogenesis.

Consequently, fingolimod is contraindicated during pregnancy (see section 4.3). Fingolimod should be stopped 2 months before planning a pregnancy (see section 4.4). If a woman becomes pregnant during treatment, fingolimod must be discontinued. Medical advice should be given regarding the risk of harmful effects to the fetus associated with treatment and ultrasonography examinations should be performed.

Lactation
Fingolimod is excreted in milk of treated animals during lactation (see section 5.3). Due to the potential for serious adverse reactions to fingolimod in nursing infants, women receiving GILOMID should not breastfeed.

Fertility
Data from preclinical studies do not suggest that fingolimod would be associated with an increased risk of reduced fertility.

4.7. Effects on ability to drive and use machines
GILOMID has no or negligible influence on the ability to drive and use machines.

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

4.8. Undesirable effects
The most frequent adverse reactions (incidence ≥10%) at the 0.5 mg dose were headache (24.5%), hepatic enzyme increased (15.2%), diarrhea (12.6%), cough (12.3%), influenza (11.4%), sinusitis (10.9%) and back pain (10.0%).

Adverse reactions derived from post-marketing experience with fingolimod have also been reported via spontaneous case reports or literature cases.

Undesirable effects are listed by MedDRA system organ class. Frequencies were defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Infections and infestations	
Very common:	Influenza Sinusitis
Common:	Bronchitis Herpes viral infections Tinea versicolor
Uncommon:	Pneumonia
Not known**:	Progressive multifocal leukoencephalopathy (PML)** Cryptococcal infections**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common:	Basal cell carcinoma
Uncommon****:	Malignant melanoma****
Rare***:	Lymphoma*** Squamous cell carcinoma****
Very rare****:	Kaposi's sarcoma****
Not known***:	Merkel cell carcinoma***
Blood and lymphatic system disorders	
Common:	Leucopenia Lymphopenia
Uncommon:	Thrombocytopenia
Not known***:	Autoimmune hemolytic anemia*** Peripheral edema***
Immune system disorders	
Not known***:	Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation***
Psychiatric disorders	
Common:	Depression
Uncommon:	Depressed mood
Nervous system disorders	
Very common:	Headache
Common:	Dizziness Migraine
Uncommon:	Seizure
Rare*:	Posterior reversible encephalopathy syndrome (PRES)*
Not known***:	Severe exacerbation of disease after fingolimod discontinuation***

Eye disorders	
Common:	Vision blurred
Uncommon:	Macular edema
Cardiac disorders	
Common:	Bradycardia Atrioventricular block
Very rare***:	T-wave inversion***
Vascular disorders	
Common:	Hypertension
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough
Common:	Dyspnea
Gastrointestinal disorders	
Very common:	Diarrhea
Uncommon***:	Nausea***
Hepatobiliary disorders	
Not known***:	Acute hepatic failure***
Skin and subcutaneous tissue disorders	
Common:	Eczema Alopecia Pruritus
Musculoskeletal and connective tissue disorders	
Very common:	Back pain
Common:	Myalgia Arthralgia
General disorders and administration site conditions	
Common:	Asthenia
Investigations	
Very common:	Hepatic enzyme increased (increased ALT, GGT and AST)
Common:	Weight decreased*** Blood triglycerides increased
Uncommon:	Neutrophil count decreased

* The frequency category was based on an estimated exposure of approximately 10,000 patients to fingolimod in all clinical trials.
** PML and cryptococcal infections (including cases of cryptococcal meningitis) have been reported in the post-marketing setting (see section 4.4).
*** Adverse reactions from spontaneous reports and literature
**** 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 studies the overall rate of infections (65.1%) at the 0.5 mg dose was similar to placebo. However, lower respiratory tract infections, primarily bronchitis and to a lesser

extent herpes infection and pneumonia were more common in fingolimod-treated patients.

Some cases of disseminated herpes infection, including fatal cases, have been reported even at the 0.5 mg dose.
In the post-marketing setting, cases of infections with opportunistic pathogens, such as viral (e.g. varicella zoster virus [VZV], John Cunningham virus [JCV] causing Progressive Multifocal Leukoencephalopathy, herpes simplex virus [HSV]), fungal (e.g. cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported, some of which have been fatal (see section 4.4).

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. 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.

Macular edema
In multiple sclerosis clinical studies macular edema occurred in 0.5% of patients treated with the recommended dose of 0.5 mg and 1.1% of patients treated with the higher dose of 1.25 mg.

The majority of cases occurred within the first 3-4 months of therapy. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmological examination. The macular edema generally improved or resolved spontaneously after discontinuation of treatment. The risk of recurrence after re-challenge has not been evaluated.

Macular edema 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 edema (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 edema.

Bradyarrhythmia
Initiation of treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays.

In multiple sclerosis clinical studies the maximal decline in heart rate was seen within 6 hours after treatment initiation, with declines in mean heart rate of 12-13 beats per minute for fingolimod 0.5 mg. Heart rate below 40 beats per minute in adults, and below 50 beats per minute in pediatric patients, was rarely observed in patients on fingolimod 0.5 mg. The average heart rate returned towards baseline within 1 month of chronic treatment. Bradycardia was generally asymptomatic but some patients experienced mild to moderate symptoms, including hypotension, dizziness, fatigue and/or palpitations, which resolved within the first 24 hours after treatment initiation.

In multiple sclerosis clinical studies first-degree atrioventricular block (prolonged PR interval on ECG) was detected after treatment initiation in adult and pediatric patients. In adult clinical trials it occurred 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% 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 the 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 atrioventricular block.

In the post-marketing setting, isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These cases have been confounded by concomitant medicinal products and/or pre-existing disease. The relationship of such events to 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 have been reported in adult and pediatric 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 and ≥5x ULN, respectively. Recurrence of liver transaminase elevations has occurred upon re-challenge in some patients, supporting a relationship to fingolimod. In clinical studies, transaminase elevations occurred at any time during treatment although the majority occurred within the first 12 months. ALT levels returned to normal within approximately 2 months after discontinuation of treatment. In a small number of patients (N=10 on 1.25 mg, N=2 on 0.5 mg) who experienced ALT elevations ≥5x ULN and who continued on fingolimod therapy, the ALT levels returned to normal within approximately 5 months (see also section 4.4, Liver function).

Nervous system disorders
In clinical studies, rare events involving the nervous system occurred in patients treated with fingolimod at higher doses (1.25 or 5.0 mg) including ischemic and hemorrhagic strokes and neurological atypical disorders, such as acute disseminated encephalomyelitis (ADEM)-like events.

Cases of seizures, including status epilepticus, have been reported with the use of fingolimod in clinical studies and in the post-marketing setting.

Vascular disorders
Rare cases of peripheral arterial occlusive disease occurred in patients treated with fingolimod at higher doses (1.25 mg).

Respiratory system

Minor dose-dependent reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (DLCO) were observed with 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 (see also section 4.4, Respiratory effects).

Lymphomas
There have been cases of lymphoma of different varieties, in both clinical studies and the post-marketing setting, including a fatal case of Epstein-Barr virus (EBV) positive B-cell lymphoma. The incidence of lymphoma (B-cell and T-cell) cases was higher in clinical trials than expected in the general population. Some T-cell lymphoma cases were also reported in the post-marketing setting, including cases of cutaneous T-cell lymphoma (mycosis fungoides) (see also section 4.4, Malignancies).

Hemophagocytic syndrome
Very rare cases of hemophagocytic syndrome (HPS) with fatal outcome have been reported in patients treated with fingolimod in the context of an infection. HPS has been described in association with infections, immunosuppression and a variety of autoimmune diseases.

Pediatric population
In the controlled pediatric trial D2311 (see section 5.1), the safety profile in pediatric patients (10 to below 18 years of age) receiving fingolimod 0.25 mg or 0.5 mg daily was overall similar to that seen in adult patients. There were, nevertheless, more neurological and psychiatric disorders observed in the study. Caution is needed in this subgroup due to very limited knowledge available from the clinical study.

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

Depression and anxiety are known to occur with increased frequency in the multiple sclerosis population. Depression and anxiety have also been reported in pediatric patients treated with fingolimod.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9. Overdose
Single doses up to 80 times the recommended dose (0.5 mg) were tolerated in healthy volunteers. At 40 mg, 5 of 6 subjects reported mild chest tightness or discomfort which was clinically consistent with small airway (bronchioles with inner diameter <2 mm) reactivity.

Fingolimod can induce bradycardia upon treatment initiation. The decline in heart rate starts within one hour of the first dose, and is steepest within 6 hours. The negative chronotropic effect of

fingolimod 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, it is important to monitor patients with a continuous (real time) ECG and hourly measurement of heart rate and blood pressure, at least during the first 6 hours (see section 4.4).

Additionally, if after 6 hours the heart rate is <45 bpm in adults, <55 bpm in pediatric patients aged 12 years and above, or <60 bpm in pediatric patients aged 10 years to below 12 years, or if the ECG at 6 hours after the first dose shows second degree or higher AV block, or if it shows a QTc interval ≥500 msec, monitoring should be extended at least for overnight and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring including overnight monitoring.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, 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. Animal studies have shown that this redistribution reduces the infiltration of pathogenic lymphocytes, including pro-inflammatory Th17 cells, into the CNS, where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and *in vitro* experiments indicate that fingolimod may also act beneficial effects on multiple sclerosis and via interaction with S1P receptors on neural cells.

Pharmacodynamic effects

Effects on the immune cell count in the blood: Within 4-6 hours after the first dose of fingolimod 0.5 mg, 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 minimal count of approximately 500 cells/microliter or approximately 30% of baseline. Eighteen percent of patients reached a minimal count below 200 cells/microliter 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). Heart rate gradually increases after the first day, returning to baseline levels 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 or 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 parenteral doses of atropine, isoprenaline or salmeterol.

S1P4 could partially contribute to the effect but was not the main receptor responsible for the lymphoid depletion. The mechanism of action of bradycardia and vasoconstriction were also studied *in vitro* in guinea pigs and isolated rabbit aorta and coronary artery. It was concluded that bradycardia could be mediated primarily by activation of inward-rectifying potassium channel or G-protein activated inwardly rectifying K^+ channel (IKACh/GIRK) and that vasoconstriction seems to be mediated by a Rho kinase and calcium dependent mechanism.

Fingolimod treatment with single or multiple doses of 0.5 and 1.25 mg for two weeks is not associated with a detectable increase in airway resistance as measured by FEV_1 and forced expiratory flow rate (FEF) 25-75. However, single fingolimod doses ≥5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance. Fingolimod treatment with multiple doses of 0.5, 1.25, or 5 mg is not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Subjects on fingolimod treatment have a normal bronchodilator response to inhaled beta-agonists.

Clinical efficacy and safety

The efficacy of fingolimod has been demonstrated in two studies which 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 adult patients who had experienced ≥2 relapses in the prior 2 years or ≥1 relapse during the prior year. Expanded Disability Status Score (EDSS) was between 0 and 5.5.

Study D2301 (FREEDOMS) was a 2-year randomized, 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) with relapsing-remitting multiple sclerosis who had not used any interferon-beta or glatiramer acetate in at least the previous 3 months and had not received any dose of natalizumab in at least the previous 6 months. Median values for baseline characteristics were: age 37 years, disease duration 6.7 years, and EDSS score 2.0. There were no significant differences between the 0.5 mg and the 1.25 mg doses. Outcome results are shown in Table 1.

Table 1: Study D2301 (FREEDOMS): main results

	Fingolimod 0.5 mg	**Placebo**
Clinical endpoints		
Annualized relapse rate (primary endpoint)	0.18**	0.40
Percentage of patients remaining relapse-free at 24 months	70%**	46%
Proportion with 3-month Confirmed Disability Progression†	17%	24%
Hazard ratio (95% CI)	0.70 (0.52, 0.96)*	

MRI endpoints		
Median (mean) number of new or enlarging T2 lesions over 24 months	0 (2.5)**	5 (9.8)
Median (mean) number of Gd-enhancing lesions at month 24	0 (0.2)**	0 (1.1)
Median (mean) % change in brain volume over 24 months	-0.7 (-0.8)**	-1 (-1.3)

† Disability progression defined as 1-point increase in EDSS confirmed 3 months later
** p<0.001, *p<0.05 compared to placebo
All analyses of clinical endpoints were intent-to-treat. MRI analyses used evaluable dataset.

Patients who completed the 24-month core FREEDOMS study could enter a dose-blinded extension study (D2301E1) and receive fingolimod. In total, 920 patients entered (n=331 continued on 0.5 mg, 289 continued on 1.25 mg, 155 switched from placebo to 0.5 mg and 145 switched from placebo to 1.25 mg). After 12 months (month 36), 856 patients (93%) were still enrolled. Between months 24 and 36, the annualized relapse rate (ARR) for patients on fingolimod 0.5 mg in the core study who remained on 0.5 mg was 0.17 (0.21 in the core study). The ARR for patients who switched from placebo to fingolimod 0.5 mg was 0.22 (0.42 in the core study).

Study D2309 (FREEDOMS II) [194] has a similar design to Study D2301 (FREEDOMS): Comparable results were shown in a replicate 2-year randomized, double-blind, placebo-controlled Phase III study on fingolimod in 1,083 patients (n=358 on 0.5 mg, 370 on 1.25 mg, 355 on placebo) with relapsing remitting multiple sclerosis who had not used interferon-beta or glatiramer acetate for at least 3 months and had not used natalizumab for at least the previous 6 months. Median values for baseline characteristics were: age 41 years, disease duration 8.9 years, EDSS score 2.5. Outcome results are shown in Table 2.

Table 2: Clinical and MRI Results from Study D2309 (FREEDOMS II)

	Fingolimod 0.5 mg	**Placebo**
Clinical endpoints		
Annualized relapse rate (primary endpoint)	0.21**	0.4
Percentage of patients remaining relapse-free at 24 months	71.5%**	52.7%
Proportion with 3-month Confirmed Disability Progression†	25%	29%
Hazard ratio (95% CI)	0.83 (0.61, 1.12)	
MRI endpoints		
Median (mean) number of new or enlarging T2 lesions over 24 months	0 (2.3)**	4 (8.9)
Median (mean) number of Gd-enhancing lesions at month 24	0 (0.4)**	0 (1.2)
Median (mean) % change in brain volume over 24 months	-0.71 (-0.86)**	-1.02 (-1.28)

† Disability progression defined as 1-point increase in EDSS confirmed 3 months later
** p<0.001 compared to placebo
All analyses of clinical endpoints were intent-to-treat. MRI analyses used evaluable dataset.

Study D2302 (TRANSFORMS) was a 1-year randomized, double-blind, double-dummy, active (interferon beta-1a)-controlled Phase III study of 1,280 patients (n=429 on 0.5 mg, 420 on 1.25 mg, 431 on interferon beta-1a, 30 mcg by intramuscular injection once weekly) with RRMS who had not used natalizumab in the previous 6 months. Median values for baseline characteristics were: age 36 years, disease duration 5.9 years, and EDSS score 2.0. Outcome results are shown in Table 3. There were no significant differences between the 0.5 mg and the 1.25 mg doses as regards study

endpoints.

Table 3: Study D2302 (TRANSFORMS): main results

	Fingolimod 0.5 mg	Interferon beta-1a, 30 mcg
Clinical endpoints		
Annualized relapse rate (primary endpoint)	0.16**	0.33
Percentage of patients remaining relapse-free at 12 months	83%**	71%
Proportion with 3-month Confirmed Disability Progression†	6%	8%
Hazard ratio (95% CI)	0.71 (0.42, 1.21)	
MRI endpoints		
Median (mean) number of new or enlarging T2 lesions over 12 months	0 (1.7)*	1 (2.6)
Median (mean) number of Gd-enhancing lesions at 12 months	0 (0.2)**	0 (0.5)
Median (mean) % change in brain volume over 12 months	-0.2 (-0.3)**	-0.4 (-0.5)

† Disability progression defined as 1-point increase in EDSS confirmed 3 months later.
* p<0.01,** p<0.001, compared to interferon beta-1a
All analyses of clinical endpoints were intent-to-treat. MRI analyses used evaluable dataset.

Patients who completed the 12-month core TRANSFORMS study could enter a dose-blinded extension (D2302E1) and receive fingolimod. In total, 1,030 patients entered, however, 3 of these patients did not receive treatment (n=356 continued on 0.5 mg, 330 continued on 1.25 mg, 167 switched from interferon beta-1a to 0.5 mg and 174 from interferon beta-1a to 1.25 mg). After 12 months (month 24), 882 patients (86%) were still enrolled. Between months 12 and 24, the ARR for patients on fingolimod 0.5 mg in the core study who remained on 0.5 mg was 0.20 (0.19 in the core study). The ARR for patients who switched from interferon beta-1a to fingolimod 0.5 mg was 0.33 (0.48 in the core study).

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

Pediatric population

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 pediatric patients aged 10 to <18 years with relapsing-remitting multiple sclerosis.

Study D2311 (PARADIGMS) was a double-blind, double-dummy, active-controlled study with flexible duration up to 24 months, with 215 patients 10 to <18 years old (n=107 on fingolimod, 108 on interferon beta-1a 30 mcg by intramuscular injection once weekly).

Median values for baseline characteristics were: age 16 years, median disease duration 1.5 years and EDSS score 1.5. The majority of patients were Tanner stage 2 or higher (94.4%) and were >40 kg

(95.3%). Overall, 180 (84%) of patients completed the core phase on study drug (n=99 [92.5%] on fingolimod, 81 [75%] on interferon beta-1a). Outcome results are shown in Table 4.

Table 4: Study D2311 (PARADIGMS): main results

	Fingolimod 0.25 mg or 0.5 mg	**Interferon beta-1a 30 mcg**
Clinical endpoints	N=107	N=107#
Annualized relapse rate (primary endpoint)	0.122**	0.675
Percentage of relative decline	81.9	
Percentage of patients remaining relapse-free at 24 months	85.7**	38.8
Risk of disability progression† Hazard ratio (95% CI) (3 months verified)	0.23 (0.08, 0.66)**	
MRI endpoints		
Annualized rate of the median number of new or newly enlarging T2 lesions	n=106	n=102
Adjusted mean	4.393**	9.269
Percentage of relative decline	52.6	
Median (mean) number of Gd-enhancing lesions at 24 months	n=105	n=95
Adjusted mean	0.436**	1.282
Percentage of relative decline	66.0	
Annualized rate of brain atrophy from baseline up to month 24	n=96	n=89

†If baseline is 0, disability progression defined as 1.5-point increase in EDSS;
If baseline is 1-5 included, 1-point increase in EDSS;
If baseline is ≥5.5, defined as 0.5-point increase in EDSS, confirmed 3 months later.
One patient randomized to receive interferon beta-1a by intramuscular injection was unable to swallow the double-dummy medication and discontinued from study. The patient was excluded from the full analysis and safety set.
* p<0.05, **p<0.01, *** p<0.001, compared to interferon beta-1a.
All analyses of clinical endpoints were on the full analysis set.

5.2. Pharmacokinetic properties

General particulars

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

The pharmacologically active metabolite responsible for efficacy is fingolimod phosphate.

Absorption

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

Food intake does not alter C_{max} or exposure (AUC) of fingolimod. Fingolimod phosphate C_{max} was decreased by 34% but AUC was unchanged. Therefore, GILOMID may be taken without regard to meals (see section 4.2 Posology and method of 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%). Protein binding of fingolimod and fingolimod-phosphate is not altered by renal or hepatic impairment.

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1,200±260 liters. A study in four healthy subjects who received a single intravenous dose of a radioiodo-labelled analogue of fingolimod demonstrated that fingolimod penetrates into the brain. In a study in 13 male multiple sclerosis patients who received fingolimod 0.5 mg/day, the mean amount of fingolimod (and fingolimod phosphate) in seminal ejaculate, at steady-state, was approximately 10,000 times lower than the oral dose administered (0.5 mg).

Biotransformation

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

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

Elimination

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

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

Linearity/non-linearity

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

Characteristics in patients

Gender, ethnicity, and renal impairment

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.

Hepatic impairment
In subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, and C), the pharmacokinetics of single dose fingolimod (1 or 5 mg) showed no change in fingolimod C_{max}, but fingolimod AUC was increased respectively by 12%, 44%, and 103%. 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. In patients with severe hepatic impairment (Child-Pugh class C), fingolimod-phosphate C_{max} was decreased by 22% and AUC was increased by 38%. The pharmacokinetics of fingolimod-phosphate were not evaluated in patients with mild or moderate hepatic impairment. Although hepatic impairment resulted in changes in the breakdown of fingolimod and fingolimod-phosphate, the extent of these changes suggests that no adjustment of the fingolimod dose in patients with mild to moderate hepatic impairment (Child-Pugh class A, B) is required. However, caution should be exercised. Fingolimod should not be used in patients with severe hepatic impairment (Child-Pugh class C).

Pediatric population
In pediatric patients (10 years of age and above), fingolimod-phosphate concentrations increase in an apparent dose proportional manner between 0.25 mg and 0.5 mg.

Fingolimod-phosphate concentration at steady state is approximately 25% lower in pediatric patients (10 years of age and above) following daily administration of 0.25 mg or 0.5 mg fingolimod compared to the concentration in adult patients treated with fingolimod 0.5 mg once daily.

There are no data available for pediatric patients below 10 years old.

Geriatric population
Clinical experience and pharmacokinetic information in patients aged above 65 years are limited. GILOMID should be used with caution in patients aged 65 years and over (see section 4.2).

Ethnicity
The effects of ethnicity on the pharmacokinetics of fingolimod and fingolimod phosphate are not clinically relevant.

Gender
Gender has no effect on the pharmacokinetics of fingolimod and fingolimod-phosphate.

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); blood vessels (vasculopathy) only in rats, and the pituitary gland, anterior stomach, liver, adrenal glands, gastrointestinal tract and nervous system (often associated with general signs of toxicity) in several species only at high doses.

No evidence of carcinogenicity was seen in a 2-year bioassay in rats at oral doses of fingolimod up to the maximally tolerated dose of 2.5 mg/kg, representing an approximate 50-fold margin based on

human systemic exposure (AUC) at the 0.5 mg dose. However, in a 2-year mouse study, an increased incidence of malignant lymphoma was seen at doses of 0.25 mg/kg and higher, representing an approximate 6-fold margin based on the human systemic exposure (AUC) at a daily dose of 0.5 mg.

Fingolimod was not mutagenic in an Ames assay and L5178Y mouse lymphoma cell line *in vitro*. No clastogenic effects were seen *in vitro* in V79 Chinese hamster lung cells. In V79 cells, fingolimod induced numerical (polyploidy) chromosomal abnormalities at concentrations of 3.7 mcg/mL and above. Fingolimod was not clastogenic in the *in vivo* micronucleus test in mice and rats.

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

Fingolimod was teratogenic when given at doses of 0.1 mg/kg or higher. The most common fetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. An increase in post-implantation loss was observed at doses of 1 mg/kg and higher in rats and a decrease in viable fetuses at 3 mg/kg. Fingolimod was not teratogenic in rabbits where an increased embryo-fetal mortality occurred at doses of 1.5 mg/kg and higher, and a decrease in fetal growth as well as viable fetus at 5 mg/kg.

In rats, F1 generation pup survival was decreased in the early postpartum period at doses that did not cause maternal toxicity. However, F1 body weights, development, behavior, and fertility were not affected by treatment with fingolimod. In a toxicity study in juvenile rats, no additional target organ toxicity was observed compared to adult rats. Repeated stimulations with Keyhole Limpet Hemocyanin (KLH) demonstrated a moderately reduced response during the treatment period but fully functional immune reactions at the end of the 8-week recovery period.

Fingolimod was excreted in milk of treated animals during lactation. Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

Juvenile animal studies
Results from two toxicity studies in juvenile rats showed slight effects on bone mineral density, neurobehavioral response, delayed sexual maturation and a decreased immune response to repeated stimulations with keyhole limpet hemocyanin (KLH), which were not considered adverse. Overall, the treatment-related effects of fingolimod in juvenile animals were comparable to those seen in adult rats at similar dose levels, with the exception of changes in bone mineral density and neurobehavioral impairment (reduced auditory startle response) observed at doses of 1.5 mg/kg and higher in juvenile animals and the absence of smooth muscle hypertrophy in the lungs of the juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Carmellose calcium
Sodium stearyl fumarate

Hard gelatin capsule:
Gelatin (bovine gelatin)
Titanium Dioxide
Tartrazine- FD&C Yellow 5

Sunset yellow FCF- FD&C Yellow 6

6.2. Incompatibilities
Not applicable.

6.3. Shelf life
24 months

6.4. Special precautions for storage
Store at room temperature below 25°C protected from moisture.

6.5. Nature and contents of container
Transparent PVC/PE/PVDC-Alu blisters packed in cardboard boxes.
Presented in blister packs of 7 or 28 hard gelatin capsules in a box, together with a patient leaflet.

6.6. Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.:1
34303 Küçükçekmece - ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER

2018/467

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 31.08.2018
Date of last renewal :

10. DATE OF REVISION OF THE SPC