Package insert

1. NAME OF THE MEDICINAL PRODUCT

Fincord (Fingolimod capsules 0.5 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

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

2.2 Qualitative and quantitative composition

Each hard gelatin capsule contains: Fingolimod Hydrochloride Ph.Eur. 0.56mg eq. to Fingolimod 0.5mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fincord is indicated for the treatment of adult patients and pediatric patients of 10 years of age and above with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

4.2 Posology and method of administration

Assessment Prior to Initiating Fincord

Cardiac Evaluation

Obtain a cardiac evaluation in patients with certain preexisting conditions.

Prior to starting treatment, determine whether patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction

Complete Blood Count (CBC)

Review results of a recent CBC

Serum transaminases (ALT and AST) and Total Bilirubin Levels

Prior to starting treatment with Fincord (i.e., within 6 months), obtain serum transaminases (ALT and AST) and total bilirubin levels.

Prior Medications

If patients are taking antineoplastic, immunosuppressive, or immune-modulating therapies, or if there is a history of prior use of these drugs, consider possible unintended additive immunosuppressive effects before initiating treatment with Fincord.

Vaccinations

Test patients for antibodies to varicella zoster virus (VZV) before initiating Fincord; VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with Fincord. It is recommended that pediatric patients if possible, complete all immunizations in accordance with current immunization guidelines prior to initiating Fincord therapy.

Recommended Dosage In adults and pediatric patients 10 years of age and older weighing more than 40 kg, the recommended dosage of Fincord is 0.5 mg orally once daily.

In pediatric patients 10 years of age and older weighing less than or equal to 40 kg, the recommended dosage of Fincord is 0.25 mg orally once daily.

Fingolimod doses higher than 0.5 mg are associated with a greater incidence of adverse reactions without additional benefit.

First-Dose Monitoring Initiation of Fincord treatment results in a decrease in heart rate, for which monitoring is recommended. Prior to dosing and at the end of the observation period, obtain an electrocardiogram (ECG) in all patients.

First 6-Hour Monitoring

Administer the first dose of Fincord in a setting in which resources to appropriately manage symptomatic bradycardia are available. Monitor all patients for 6 hours after the first dose for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement.

Additional Monitoring after 6-Hour Monitoring

Continue monitoring until the abnormality resolves if any of the following is present (even in the absence of symptoms) after 6 hours:

- The heart rate 6 hours postdose is less than 45 bpm in adults, less than 55 bpm in pediatric patients 12 years of age and older, or less than 60 bpm in pediatric patients 10 or 11 years of age
- The heart rate 6 hours postdose is at the lowest value postdose suggesting that the maximum pharmacodynamic effect on the heart may not have occurred
- The ECG 6 hours postdose shows new onset second degree or higher AV block

If postdose symptomatic bradycardia occurs, initiate appropriate management, begin continuous ECG monitoring, and continue monitoring until the symptoms have resolved if no pharmacological treatment is required. If pharmacological treatment is required, continue monitoring overnight and repeat 6-hour monitoring after the second dose.

Overnight Monitoring

Continuous overnight ECG monitoring in a medical facility should be instituted:

- in patients that require pharmacologic intervention for symptomatic bradycardia. In these patients, the first-dose monitoring strategy should be repeated after the second dose of Fincord.
- in patients with some preexisting heart and cerebrovascular conditions
- in patients with a prolonged QTc interval before dosing or during 6-hour observation, or at additional risk for QT prolongation, or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes
- in patients receiving concurrent therapy with drugs that slow heart rate or AV conduction

Monitoring After Reinitiation of Therapy Following Discontinuation

When restarting Fincord after discontinuation for more than 14 days after the first month of treatment, perform first- dose monitoring, because effects on heart rate and AV conduction may recur on reintroduction of Fincord treatment. The same precautions (first-dose monitoring) as for initial dosing are applicable. Within the first 2 weeks of treatment, first-dose procedures are recommended after interruption of 1 day or more; during weeks 3 and 4 of treatment first-dose procedures are recommended after treatment interruption of more than 7 days.

Note: FINCORD is not able to deliver all approved dose regimens of Fingolimod. Therefore, other approved strengths of Fingolimod capsules should be used in such cases.

Method of administration

Patients who initiate Fincord and those who reinitiate treatment after discontinuation for longer than 14 days require first-dose monitoring. This monitoring is also recommended when the dose is increased in pediatric patients.

Fincord capsules should always be swallowed intact, without opening them. Fingolimod can be taken with or without food.

4.3 Contraindications

Fingolimod is contraindicated in patients who have:

- in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization or Class III/IV heart failure.
- a history or presence of Mobitz Type II second-degree or third-degree AV block or sick sinus syndrome, unless patient has a functioning pacemaker.
- a baseline QTc interval ≥ 500 msec

- cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs
- during pregnancy and in women of childbearing potential not using effective contraception
- had a hypersensitivity reaction to fingolimod or any of the excipients in Fincord. Observed reactions include rash, urticaria and angioedema upon treatment initiation.

4.4 Special warnings and precautions for use

Bradyarrhythmia and Atrioventricular Blocks

Because of a risk for bradyarrhythmia and AV blocks, patients should be monitored during Fingolimod treatment initiation.

Reduction in Heart Rate

After the first dose of Fingolimod, the heart rate decrease starts within an hour. On Day 1, the maximum decline in heart rate generally occurs within 6 hours and recovers, although not to baseline levels, by 8 to 10 hours postdose. Because of physiological diurnal variation, there is a second period of heart rate decrease within 24 hours after the first dose. In some patients, heart rate decrease during the second period is more pronounced than the decrease observed in the first 6 hours. Heart rates below 40 beats per minute (bpm) in adults, and below 50 bpm in pediatric patients occurred rarely. In controlled clinical trials, in adult patients, adverse reactions of symptomatic bradycardia following the first dose were reported in 0.6% of patients receiving Fingolimod 0.5 mg and in 0.1% of patients on placebo. Patients who experienced bradycardia were generally asymptomatic, but some patients experienced hypotension, dizziness, fatigue, palpitations, and/or chest pain that usually resolved within the first 24 hours on treatment.

Patients with some preexisting conditions (e.g., ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, history of symptomatic bradycardia, history of recurrent syncope, severe untreated sleep apnea, AV block, sinoatrial heart block) may poorly tolerate the Fingolimod-induced bradycardia, or experience serious rhythm disturbances after the first dose of Fingolimod. Prior to treatment with Fingolimod, these patients should have a cardiac evaluation by a physician appropriately trained to conduct such evaluation, and, if treated with Fingolimod, should be monitored overnight with continuous ECG in a medical facility after the first dose.

Since initiation of Fingolimod treatment, results in decreased heart rate and may prolong the QT interval, patients with a prolonged QTc interval (> 450 msec adult and pediatric males, > 470 msec adult females, or > 460 msec pediatric females) before dosing or during 6 hour observation, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome), or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility.

Following the second dose, a further decrease in heart rate may occur when compared to the heart rate prior to the second dose, but this change is of a smaller magnitude than that observed following the first dose. With continued dosing, the heart rate returns to baseline within 1 month of chronic treatment. Clinical data indicate effects of Fingolimod on heart rate are maximal after

the first dose although milder effects on heart rate may persist for, on average, 2 to 4 weeks after initiation of therapy at which time heart rate generally returns to baseline. Physicians should continue to be alert to patient reports of cardiac symptoms.

Atrioventricular Blocks

Initiation of Fingolimod treatment has resulted in transient AV conduction delays. In adult patients, first-degree AV block after the first dose occurred in 4.7% of patients receiving Fingolimod and 1.6% of patients on placebo. In a study of 697 patients with available 24-hour Holter monitoring data after their first dose (N=351 receiving Fingolimod and N=346 on placebo), second-degree AV blocks (Mobitz Type I [Wenckebach] or 2:1 AV blocks) occurred in 4% (N=14) of patients receiving Fingolimod and 2% (N=7) of patients on placebo. Of the 14 patients receiving Fingolimod, 7 patients had 2:1 AV block (5 patients within the first 6 hours postdose and 2 patients after 6 hours postdose). All second degree AV blocks on placebo were Mobitz Type I and occurred after the first 12 hours postdose. The conduction abnormalities were usually transient and asymptomatic, and resolved within the first 24 hours on treatment, but they occasionally required treatment with atropine or isoproterenol.

Postmarketing Experience

In the postmarketing setting, third-degree AV block and AV block with junctional escape have been observed during the first-dose 6-hour observation period with Fingolimod. Isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These events were confounded by concomitant medications and/or preexisting disease and the relationship to Fingolimod is uncertain. Cases of syncope were also reported after the first dose of Fingolimod.

Infections

Risk of 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. Fingolimod may therefore increase the risk of infections, some serious in nature. Life-threatening and fatal infections have occurred in association with Fingolimod.

Before initiating treatment with Fingolimod, a recent CBC (i.e. within 6 months or after discontinuation of prior therapy) should be available. Consider suspending treatment with Fingolimod if a patient develops a serious infection, and reassess the benefits and risks prior to reinitiation of therapy. Because the elimination of fingolimod after discontinuation may take up to 2 months, continue monitoring for infections throughout this period. Instruct patients receiving Fingolimod to report symptoms of infections to a physician. Patients with active acute or chronic infections should not start treatment until the infection(s) is resolved.

In MS placebo-controlled trials in adult patients, the overall rate of infections (72%) with Fingolimod was similar to placebo. However, bronchitis, herpes zoster, influenza, sinusitis, and pneumonia were more common in Fingolimod-treated patients. Serious infections occurred at a rate of 2.3% in the Fingolimod group versus 1.6% in the placebo group.

In the postmarketing setting, serious infections with opportunistic pathogens including viruses (e.g., John Cunningham virus (JCV), herpes simplex viruses 1 and 2, varicella-zoster virus), fungi

(e.g., cryptococci), and bacteria (e.g., atypical mycobacteria) have been reported with Fingolimod. Patients with symptoms and signs consistent with any of these infections should undergo prompt diagnostic evaluation and appropriate treatment.

Herpes Viral Infections

In placebo-controlled trials in adult patients, the rate of herpetic infections was 9% in patients receiving Fingolimod 0.5 mg and 7% on placebo.

Two patients died of herpetic infections during controlled trials. One death was due to disseminated primary herpes zoster and the other was to herpes simplex encephalitis. In both cases, the patients were taking a 1.25 mg dose of fingolimod (higher than the recommended 0.5 mg dose) and had received high-dose corticosteroid therapy to treat suspected MS relapses.

Serious, life-threatening events of disseminated varicella zoster and herpes simplex infections, including cases of encephalitis and multiorgan failure, have occurred with Fingolimod in the postmarketing setting. Include disseminated herpetic infections in the differential diagnosis of patients who are receiving Fingolimod and present with an atypical MS relapse or multiorgan failure.

Cases of Kaposi's sarcoma have been reported in the postmarketing setting. Kaposi's sarcoma is an angioproliferative disorder that is associated with infection with human herpes virus 8 (HHV-8). Patients with symptoms or signs consistent with Kaposi's sarcoma should be referred for prompt diagnostic evaluation and management.

Cryptococcal Infections

Cryptococcal infections, including cases of fatal cryptococcal meningitis and disseminated cryptococcal infections, have been reported with Fingolimod in the postmarketing setting. Cryptococcal infections have generally occurred after approximately 2 years of Fingolimod treatment, but may occur earlier. The relationship between the risk of cryptococcal infection and the duration of treatment is unknown. Patients with symptoms and signs consistent with a cryptococcal infection should undergo prompt diagnostic evaluation and treatment.

Prior and Concomitant Treatment with Antineoplastic, Immunosuppressive, or Immune-Modulating therapies

In clinical studies, patients who received Fingolimod did not receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of Fingolimod with any of these therapies, and also with corticosteroids, would be expected to increase the risk of immunosuppression (see DRUG INTERACTIONS).

When switching to Fingolimod from immune-modulating or immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.

Varicella Zoster Virus Antibody Testing/Vaccination

Patients without a healthcare professional confirmed history of chickenpox or without documentation of a full course of vaccination against VZV should be tested for antibodies to VZV

before initiating Fingolimod. VZV vaccination of antibody-negative patients is recommended prior to commencing treatment with Fingolimod, following which initiation of treatment with Fingolimod should be postponed for 1 month to allow the full effect of vaccination to occur (see DRUG INTERACTIONS).

Human Papilloma Virus (HPV) Infection

Human papilloma virus (HPV) infections, including papilloma, dysplasia, warts, and HPV-related cancer, have been reported in patients treated with FINGOLIMOD in the postmarketing setting. Vaccination against HPV should be considered prior to treatment initiation with FINGOLIMOD, taking into account vaccination recommendations. Cancer screening, including Papanicolaou (Pap) test, is recommended as per standard of care for patients using an immunosuppressive therapy.

Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients with MS who received Fingolimod in the postmarketing setting. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML has occurred in patients who had not been treated previously with natalizumab, which has a known association with PML, were not taking any other immunosuppressive or immunomodulatory medications concomitantly, and did not have any ongoing systemic medical conditions resulting in compromised immune system function The majority of cases have occurred in patients treated with Fingolimod for at least 2 years. The relationship between the risk of PML and the duration of treatment is unknown.

At the first sign or symptom suggestive of PML, withhold Fingolimod and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

MRI findings 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. Lower PML-related mortality and morbidity have been reported following discontinuation of another MS medication associated with PML in patients with PML who were initially asymptomatic compared to patients with PML who had characteristic clinical signs and symptoms at diagnosis. It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients.

Macular Edema

Fingolimod increases the risk of macular edema. Perform an examination of the fundus including the macula in all patients before starting treatment, again 3 to 4 months after starting treatment, and again at any time after a patient reports visual disturbances while on Fingolimod therapy.

A dose-dependent increase in the risk of macular edema occurred in the Fingolimod clinical development program.

In 2-year, double-blind, placebo-controlled studies in adult patients with multiple sclerosis, macular edema with or without visual symptoms occurred in 1.5% of patients (11/799) treated with fingolimod 1.25 mg, 0.5% of patients (4/783) treated with Fingolimod 0.5 mg and 0.4% of patients (3/773) treated with placebo. Macular edema occurred predominantly during the first 3 to 4 months of therapy. These clinical trials excluded patients with diabetes mellitus, a known risk factor for macular edema (see below *Macular Edema in Patients with History of Uveitis or Diabetes Mellitus).* Symptoms of macular edema included blurred vision and decreased visual acuity. Routine ophthalmological examination detected macular edema in some patients with no visual symptoms. Macular edema generally partially or completely resolved with or without treatment after drug discontinuation. Some patients had residual visual acuity loss even after resolution of macular edema. Macular edema has also been reported in patients taking Fingolimod in the postmarketing setting, usually within the first 6 months of treatment.

Continuation of Fingolimod in patients who develop macular edema has not been evaluated. A decision on whether or not to discontinue Fingolimod therapy should include an assessment of the potential benefits and risks for the individual patient. The risk of recurrence after rechallenge has not been evaluated.

Macular Edema in Patients with History of Uveitis or Diabetes Mellitus

Patients with a history of uveitis and patients with diabetes mellitus are at increased risk of macular edema during Fingolimod therapy. The incidence of macular edema is also increased in MS patients with a history of uveitis. In the combined clinical trial experience in adult patients with all doses of fingolimod, the rate of macular edema was approximately 20% in MS patients with a history of uveitis versus 0.6% in those without a history of uveitis. Fingolimod has not been tested in MS patients with diabetes mellitus. In addition to the examination of the fundus including the macula prior to treatment and at 3 to 4 months after starting treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

Liver Injury

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

In 2-year placebo-controlled clinical trials in adult patients, elevation of liver enzymes (ALT, AST and GGT) to 3-fold the upper limit of normal (ULN) or greater occurred in 14% of patients treated with FINGOLIMOD 0.5 mg and 3% of patients on placebo. Elevations 5-fold the ULN or greater occurred in 4.5% of patients on FINGOLIMOD and 1% of patients on placebo. The majority of elevations occurred within 6 to 9 months. In clinical trials, FINGOLIMOD was

discontinued if the elevation exceeded 5 times the ULN. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of FINGOLIMOD. Recurrence of liver transaminase elevations occurred with rechallenge in some patients.

Prior to starting treatment with FINGOLIMOD (within 6 months), obtain serum transaminases (ALT and AST) and total bilirubin levels. Obtain transaminase levels and total bilirubin levels periodically until two months after FINGOLIMOD discontinuation.

Patients should be monitored for signs and symptoms of any hepatic injury. Measure liver transaminase and bilirubin levels promptly in patients who report symptoms that may indicate liver injury, including new or worsening fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. In this clinical context, if the patient is found to have an alanine aminotransferase (ALT) greater than three times the reference range with serum total bilirubin greater than two times the reference range, treatment with FINGOLIMOD treatment should be interrupted. Treatment should not be resumed if a plausible alternative etiology for the signs and symptoms cannot be established, because these patients are at risk for severe drug-induced liver injury.

Because FINGOLIMOD exposure is doubled in patients with severe hepatic impairment, these patients should be closely monitored, as the risk of adverse reactions is greater.

Posterior Reversible Encephalopathy Syndrome

There have been rare cases of posterior reversible encephalopathy syndrome (PRES) reported in adult patients receiving Fingolimod. Symptoms reported included sudden onset of severe headache, altered mental status, visual disturbances, and seizure. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, Fingolimod should be discontinued.

Respiratory Effects

Dose-dependent reductions in forced expiratory volume over 1 second (FEV1) and diffusion lung capacity for carbon monoxide (DLCO) were observed in patients treated with Fingolimod as early as 1 month after treatment initiation. In 2-year placebo-controlled trials in adult patients, the reduction from baseline in the percent of predicted values for FEV1 at the time of last assessment on drug was 2.8% for Fingolimod 0.5 mg and 1.0% for placebo. For DLCO, the reduction from baseline in percent of predicted values at the time of last assessment on drug was 3.3% for Fingolimod 0.5 mg and 0.5% for placebo. The changes in FEV1 appear to be reversible after treatment discontinuation. There is insufficient information to determine the reversibility of the decrease of DLCO after drug discontinuation. In MS placebo-controlled trials in adult patients, dyspnea was reported in 9% of patients receiving Fingolimod 0.5 mg and 7% of patients receiving placebo. Several patients discontinued Fingolimod because of unexplained dyspnea during the extension (uncontrolled) studies. Fingolimod has not been tested in MS patients with compromised respiratory function.

Spirometric evaluation of respiratory function and evaluation of DLCO should be performed during therapy with Fingolimod if clinically indicated.

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.

Severe Increase in Disability After Stopping Fingolimod

Severe increase in disability accompanied by multiple new lesions on MRI has been reported after discontinuation of Fingolimod in the postmarketing setting. Patients in most of these reported cases did not return to the functional status they had before stopping Fingolimod. The increase in disability generally occurred within 12 weeks after stopping Fingolimod, but was reported up to 24 weeks after Fingolimod discontinuation.

Monitor patients for development of severe increase in disability following discontinuation of Fingolimod and begin appropriate treatment as needed.

Tumefactive Multiple Sclerosis

MS relapses with tumefactive demyelinating lesions on imaging have been observed during FINGOLIMOD therapy and after FINGOLIMOD discontinuation in the postmarketing setting. Most reported cases of tumefactive MS in patients receiving Fingolimod have occurred within the first 9 months after FINGOLIMOD initiation, but tumefactive MS may occur at any point during treatment. Cases of tumefactive MS have also been reported within the first 4 months after Fingolimod discontinuation. Tumefactive MS should be considered when a severe MS relapse occurs during FINGOLIMOD treatment, especially during initiation, or after discontinuation of FINGOLIMOD, prompting imaging evaluation and initiation of appropriate treatment.

Increased Blood Pressure

In adult MS controlled clinical trials, patients treated with Fingolimod 0.5 mg had an average increase over placebo of approximately 3 mmHg in systolic pressure, and approximately 2 mmHg in diastolic pressure, first detected after approximately 1 month of treatment initiation, and persisting with continued treatment. Hypertension was reported as an adverse reaction in 8% of patients on Fingolimod 0.5 mg and in 4% of patients on placebo. Blood pressure should be monitored during treatment with Fingolimod.

Malignancies

Cutaneous Malignancies

The risk of basal cell carcinoma (BCC) and melanoma is increased in patients treated with Fingolimod. In two-year placebo-controlled trials in adult patients, the incidence of BCC was 2% in patients on Fingolimod 0.5 mg and 1% in patients on placebo (see ADVERSE REACTIONS). Melanoma, squamous cell carcinoma and Merkel cell carcinoma have been reported with Fingolimod in the postmarketing setting. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Providers and patients are advised to monitor for suspicious skin lesions. If a suspicious skin lesion is observed, it should be promptly evaluated. As usual for patients with increased risk for skin cancer, exposure to sunlight and

ultraviolet light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Lymphoma

Cases of lymphoma, including both T-cell and B-cell types and CNS lymphoma, have occurred in patients receiving FINGOLIMOD. The reporting rate of non-Hodgkin lymphoma with FINGOLIMOD is greater than that expected in the general population adjusted by age, gender, and region. Cutaneous T-cell lymphoma (including mycosis fungoides) has also been reported with FINGOLIMOD in the postmarketing setting.

Immune System Effects Following Fingolimod Discontinuation

Fingolimod remains in the blood and has pharmacodynamic effects, including decreased lymphocyte counts, for up to 2 months following the last dose of Fingolimod. Lymphocyte counts generally return to the normal range within 1-2 months of stopping therapy. Because of the continuing pharmacodynamic effects of fingolimod, initiating other drugs during this period warrants the same considerations needed for concomitant administration (e.g., risk of additive immunosuppressant effects) (see DRUG INTERACTIONS).

Hypersensitivity Reactions

Hypersensitivity reactions, including rash, urticaria, and angioedema have been reported with Fingolimod in the postmarketing setting. Fingolimod is contraindicated in patients with history of hypersensitivity to fingolimod or any of its excipients.

Pediatrics Patients

Safety and effectiveness of FINGOLIMOD for the treatment of relapsing forms of multiple sclerosis in pediatric patients 10 to less than 18 years of age were established in one randomized, double-blind clinical study in 215 patients (FINGOLIMOD n = 107; intramuscular interferon (IFN) beta-1a n = 108).

In the controlled pediatric study, the safety profile in pediatric patients (10 to less than 18 years of age) receiving FINGOLIMOD 0.25 mg or 0.5 mg daily was similar to that seen in adult patients. 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.

It is recommended that pediatric patients if possible, complete all immunizations in accordance with current immunization guidelines prior to initiating FINGOLIMOD therapy.

Safety and effectiveness of FINGOLIMOD in pediatric patients below the age of 10 years have not been established.

Juvenile Animal Toxicity Data

In a study in which fingolimod (0.3, 1.5, or 7.5 mg/kg/day) was orally administered to young rats from weaning through sexual maturity, changes in bone mineral density and persistent neurobehavioral impairment (altered auditory startle) were observed at all doses. Delayed sexual maturation was noted in females at the highest dose tested and in males at all doses. The bone

changes observed in fingolimod-treated juvenile rats are consistent with a reported role of S1P in the regulation of bone mineral homeostasis.

When fingolimod (0.5 or 5 mg/kg/day) was orally administered to rats from the neonatal period through sexual maturity, a marked decrease in T-cell dependent antibody response was observed at both doses. This effect had not fully recovered by 6-8 weeks after the end of treatment.

Overall, a no-effect dose for adverse developmental effects in juvenile animals was not identified.

Geriatrics Use

Clinical MS studies of Fingolimod did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. Fingolimod should be used with caution in patients aged 65 years and over, reflecting the greater frequency of decreased hepatic, or renal, function and of concomitant disease or other drug therapy.

Hepatic Impairment

Because fingolimod, but not fingolimod-phosphate, exposure is doubled in patients with severe hepatic impairment, patients with severe hepatic impairment should be closely monitored, as the risk of adverse reactions may be greater.

No dose adjustment is needed in patients with mild or moderate hepatic impairment.

Renal Impairment

The blood level of some Fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment. The toxicity of these metabolites has not been fully explored. The blood level of these metabolites has not been assessed in patients with mild or moderate renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

QT Prolonging Drugs

Fingolimod has not been studied in patients treated with drugs that prolong the QT interval. Drugs that prolong the QT interval have been associated with cases of torsades de pointes in patients with bradycardia. Since initiation of Fingolimod treatment results in decreased heart rate and may prolong the QT interval, patients on QT prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility.

Ketoconazole

The blood levels of fingolimod and fingolimod-phosphate are increased by 1.7-fold when used concomitantly with ketoconazole. Patients who use Fingolimod and systemic ketoconazole concomitantly should be closely monitored, as the risk of adverse reactions is greater.

Vaccines

Fingolimod reduces the immune response to vaccination. Vaccination may be less effective during and for up to 2 months after discontinuation of treatment with Fingolimod. Avoid the use of live attenuated vaccines during and for 2 months after treatment with Fingolimod because of the risk of infection. It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Fingolimod therapy.

Antineoplastic, Immunosuppressive, or Immune-Modulating Therapies

Antineoplastic, immune-modulating or immunosuppressive therapies, (including corticosteroids) are expected to increase the risk of immunosuppression, and the risk of additive immune system effects must be considered if these therapies are coadministered with Fingolimod. When switching from drugs with prolonged immune effects, such as natalizumab, teriflunomide or mitoxantrone, the duration and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects when initiating Fingolimod.

Drugs That Slow Heart Rate or Atrioventricular Conduction (e.g., beta blockers or diltiazem)

Experience with Fingolimod in patients receiving concurrent therapy with drugs that slow the heart rate or AV conduction (e.g., beta blockers, digoxin, or heart-rate slowing calcium channel blockers such as diltiazem or verapamil) is limited. Because initiation of Fingolimod treatment may result in an additional decrease in heart rate, concomitant use of these drugs during Fingolimod initiation may be associated with severe bradycardia or heart block. Seek advice from the physician prescribing these drugs regarding the possibility to switch to drugs that do not slow the heart rate or atrioventricular conduction before initiating Fingolimod. Patients who cannot switch, should have overnight continuous ECG monitoring after the first dose.

Laboratory Test Interaction

Because Fingolimod reduces blood lymphocyte counts via redistribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilized to evaluate the lymphocyte subset status of a patient treated with Fingolimod. A recent CBC should be available before initiating treatment with Fingolimod.

4.6 Fertility, pregnancy and lactation

Women of Childbearing Potential / Contraception in Females

Fingolimod is contraindicated in women of childbearing potential not using effective contraception. 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 Fingolimod, since fingolimod takes approximately 2 months to eliminate from the body after treatment discontinuation.

When stopping fingolimod therapy for planning a pregnancy the possible return of disease activity should be considered.

Pregnancy

Based on human experience, 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 labour and delivery.

Animal studies have shown reproductive toxicity including fetal loss and organ defects, notably persistent truncus arteriosus and ventricular septal defect. Furthermore, the receptor affected by fingolimod (sphingosine 1-phosphate receptor) is known to be involved in vascular formation during embryogenesis.

Consequently, fingolimod is contraindicated during pregnancy. Fingolimod should be stopped 2 months before planning a pregnancy. 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.

Breast-feeding

Fingolimod is excreted in milk of treated animals during lactation. Due to the potential for serious adverse reactions to fingolimod in nursing infants, women receiving Fingolimod 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

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

However, dizziness or drowsiness may occasionally occur when initiating therapy with Fingolimod. On initiation of Fingolimod treatment it is recommended that patients be observed for a period of 6 hours.

4.8 Undesirable effects

The following serious adverse reactions are described elsewhere in labeling:

- Bradyarrhythmia and Atrioventricular Blocks
- Infections
- Progressive Multifocal Leukoencephalopathy
- Macular Edema

- Liver Injury
- Posterior Reversible Encephalopathy Syndrome
- Respiratory Effects
- Fetal Risk
- Severe Increase in Disability After Stopping Fingolimod
- Tumefactive Multiple Sclerosis
- Increased Blood Pressure
- Malignancies
- Immune System Effects Following Fingolimod Discontinuation
- Hypersensitivity Reactions

Vascular Events

Vascular events, including ischemic and hemorrhagic strokes and peripheral arterial occlusive disease were reported in premarketing clinical trials in patients who received Fingolimod doses (1.25-5 mg) higher than recommended for use in MS. Similar events have been reported with Fingolimod in the postmarketing setting although a causal relationship has not been established.

Seizure

Cases of seizures, including status epilepticus have been reported with the use of Fingolimod in clinical trials and in the postmarketing setting in adults (see ADVERSE REACTIONS). In adult clinical trials, the rate of seizures was 0.9% in Fingolimod-treated patients and 0.3% in placebo-treated patients. It is unknown whether these events were related to the effects of multiple sclerosis alone, to Fingolimod, or to a combination of both.

Pediatric Patients 10 Years of Age and Older

In the controlled pediatric trial (Study 4), the safety profile in pediatric patients receiving FINGOLIMOD 0.25 mg or 0.5 mg daily was similar to that seen in adult patients.

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.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Fingolimod. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Hemolytic anemia and thrombocytopenia

Hepatobiliary Disorders: Liver injury

Infections: infections including cryptococcal infections, human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, progressive multifocal leukoencephalopathy

Musculoskeletal and connective tissue disorders: arthralgia, myalgia

Nervous system disorders: posterior reversible encephalopathy syndrome, seizures, including status epilepticus

Neoplasms, benign, malignant, and unspecified (incl cysts and polyps): melanoma, Merkel cell carcinoma, and cutaneous T cell lymphoma (including mycosis fungoides)

Skin and subcutaneous tissue disorders: hypersensitivity

4.9 Overdose

Fingolimod can induce bradycardia as well as AV conduction blocks (including complete AV block). The decline in heart rate usually starts within 1 hour of the first dose and is maximal within 6 hours in most patients. In case of Fingolimod overdosage, observe patients overnight with continuous ECG monitoring in a medical facility, and obtain regular measurements of blood pressure.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Fingolimod is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate. Fingolimod-phosphate is a sphingosine 1-phosphate receptor modulator, and binds with high affinity to sphingosine 1-phosphate receptors 1, 3, 4, and 5. Fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which fingolimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the central nervous system.

Pharmacodynamics

Heart Rate and Rhythm

Fingolimod causes a transient reduction in heart rate and AV conduction at treatment initiation.

Heart rate progressively increases after the first day, returning to baseline values within 1 month of the start of chronic treatment.

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

Fingolimod treatment is not associated with a decrease in cardiac output.

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 QTc, with the upper boundary of the 90% confidence interval (CI) of 14.0 msec. There is no consistent signal of increased incidence of QTc outliers, either absolute or change

from baseline, associated with fingolimod treatment. In MS studies, there was no clinically relevant prolongation of the QT interval, but patients at risk for QT prolongation were not included in clinical studies.

Immune System

Effects on Immune Cell Numbers in the Blood

In a study in which 12 adult subjects received Fingolimod 0.5 mg daily, the lymphocyte count decreased to approximately 60% of baseline within 4 to 6 hours after the first dose. With continued daily dosing, the lymphocyte count continued to decrease over a 2-week period, reaching a nadir count of approximately 500 cells/mcL or approximately 30% of baseline. In a placebo-controlled study in 1272 MS patients (of whom 425 received fingolimod 0.5 mg daily and 418 received placebo), 18% (N=78) of patients on fingolimod 0.5 mg reached a nadir of <200 cells/mcL on at least 1 occasion. No patient on placebo reached a nadir of <200 cells/mcL. Low lymphocyte counts are maintained with chronic daily dosing of Fingolimod 0.5 mg daily.

Chronic fingolimod dosing leads to a mild decrease in the neutrophil count to approximately 80% of baseline. Monocytes are unaffected by fingolimod.

Peripheral lymphocyte count increases are evident within days of stopping fingolimod treatment and typically normal counts are reached within 1 to 2 months.

Effect on Antibody Response.

Fingolimod reduces the immune response to vaccination, as evaluated in 2 studies.

In the first study, the immunogenicity of keyhole limpet hemocyanin (KLH) and pneumococcal polysaccharide vaccine (PPV-23) immunization were assessed by IgM and IgG titers in a steady-state, randomized, placebo-controlled study in healthy adult volunteers. Compared to placebo, antigen-specific IgM titers were decreased by 91% and 25% in response to KLH and PPV-23, respectively, in subjects on Fingolimod 0.5 mg. Similarly, IgG titers were decreased by 45% and 50%, in response to KLH and PPV-23, respectively, in subjects on Fingolimod 0.5 mg daily compared to placebo. The responder rate for Fingolimod 0.5 mg as measured by the number of subjects with a >4-fold increase in KLH IgG was comparable to placebo and 25% lower for PPV-23 IgG, while the number of subjects with a >4 fold increase in KLH and PPV-23 IgM was 75% and 40% lower, respectively, compared to placebo. The capacity to mount a skin delayed-type hypersensitivity reaction to *Candida* and tetanus toxoid was decreased by approximately 30% in subjects on Fingolimod 0.5 mg daily, compared to placebo. Immunologic responses were further decreased with fingolimod 1.25 mg (a dose higher than recommended in MS).

In the second study, the immunogenicity of Northern hemisphere seasonal influenza and tetanus toxoid vaccination was assessed in a 12-week steady-state, randomized, placebo-controlled study of Fingolimod 0.5 mg in adult multiple sclerosis patients (n=136). The responder rate 3 weeks after vaccination, defined as seroconversion or a ≥4-fold increase in antibody directed against at least 1 of the 3 influenza strains, was 54% for Fingolimod 0.5 mg and 85% in the placebo group. The responder rate 3 weeks after vaccination, defined as seroconversion or a ≥4-fold increase in antibody directed against tetanus toxoid was 40% for Fingolimod 0.5 mg and 61% in the placebo group.

Pulmonary Function

Single fingolimod doses ≥5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance. In a 14-day study of 0.5, 1.25, or 5 mg/day, fingolimod was not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine. Subjects on fingolimod treatment had a normal bronchodilator response to inhaled beta-agonists.

In a 14-day placebo-controlled study of adult patients with moderate asthma, no effect was seen for Fingolimod 0.5 mg (recommended dose in MS). A 10% reduction in mean FEV1 at 6 hours after dosing was observed in adult patients receiving fingolimod 1.25 mg (a dose higher than recommended for use in MS) on Day 10 of treatment. Fingolimod 1.25 mg was associated with a 5-fold increase in the use of rescue short-acting beta-agonists.

5.2 Pharmacokinetic properties

Absorption

The T_{max} of fingolimod is 12-16 hours. The apparent absolute oral bioavailability is 93%.

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

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 (86%) distributes in red blood cells. Fingolimod-phosphate has a smaller uptake in blood cells of <17%. Fingolimod and fingolimod-phosphate are >99.7% protein bound. 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 3 main pathways: by reversible stereoselective phosphorylation to the pharmacologically active (*S*)-enantiomer of fingolimod-phosphate, by oxidative biotransformation catalyzed mainly by the cytochrome P450 4F2 (CYP4F2) and possibly other CYP4F isoenzymes with subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive non-polar ceramide analogs of fingolimod.

Inhibitors or inducers of CYP4F2 and possibly other CYP4F isozymes might alter the exposure of fingolimod or fingolimod-phosphate. In vitro studies in hepatocytes indicated that CYP3A4 may contribute to fingolimod metabolism in the case of strong induction of CYP3A4.

Following single oral administration of [^{14}C] fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the AUC up to 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%)].

Elimination

Fingolimod blood clearance is 6.3±2.3 L/h, and the average apparent terminal half-life ($t_{½}$) is 6 to 9 days. Blood levels of fingolimod-phosphate decline in parallel with those of 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 feces with amounts of each representing less than 2.5% of the dose.

Specific Populations

Pediatric Patients

The median fingolimod-phosphate (fingolimod-P) concentration in pediatric MS patients aged 10 to less than 18 years was 1.10 ng/mL, as compared to 1.35 ng/mL in adult MS patients.

Geriatric Patients

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.

Gender

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

Race

The effects of race on fingolimod and fingolimod-phosphate pharmacokinetics cannot be adequately assessed due to a low number of non-white patients in the clinical program.

Renal Impairment

In adult patients with severe renal impairment, fingolimod C_{max} and AUC are increased by 32% and 43%, respectively, and fingolimod-phosphate C_{max} and AUC are increased by 25% and 14%, respectively, with no change in apparent elimination half-life. Based on these findings, the Fingolimod 0.5 mg dose is appropriate for use in adult patients with renal impairment. Fingolimod 0.25 mg and 0.5 mg are appropriate for use in pediatric patients with renal impairment. The systemic exposure of 2 metabolites (M2 and M3) is increased by 3- and 13-fold, respectively. The toxicity of these metabolites has not been fully characterized.

A study in patients with mild or moderate renal impairment has not been conducted.

Hepatic Impairment

In subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, and C), no change in fingolimod C_{max} was observed, but fingolimod $AUC_{0-\infty}$ was increased respectively by

12%, 44%, and 103%. In patients with severe hepatic impairment (Child-Pugh class C), fingolimod-phosphate C_{max} was decreased by 22% and $AUC_{0\text{-}96\ hours}$ was decreased by 29%. The pharmacokinetics of fingolimod-phosphate was not evaluated in patients with mild or moderate hepatic impairment. The apparent elimination half-life of fingolimod is unchanged in subjects with mild hepatic impairment, but is prolonged by about 50% in patients with moderate or severe hepatic impairment.

Patients with severe hepatic impairment (Child-Pugh class C) should be closely monitored, as the risk of adverse reactions is greater (see WARNINGS AND PRECAUTIONS).

No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh class A and B).

Drug Interactions

Ketoconazole

The coadministration of ketoconazole (a potent inhibitor of CYP3A and CYP4F) 200 mg twice daily at steady-state and a single dose of fingolimod 5 mg led to a 70% increase in AUC of fingolimod and fingolimod-phosphate. Patients who use Fingolimod and systemic ketoconazole concomitantly should be closely monitored, as the risk of adverse reactions is greater (see DRUG INTERACTIONS).

Carbamazepine

The coadministration of carbamazepine (a potent CYP450 enzyme inducer) 600 mg twice daily at steady-state and a single dose of fingolimod 2 mg decreased blood concentrations (AUC) of fingolimod and fingolimod-phosphate by approximately 40%. The clinical impact of this decrease is unknown.

Other strong CYP450 enzyme inducers, e.g., rifampicin, phenytoin, phenobarbital, and St. John's wort, may also reduce AUC of fingolimod and fingolimod-phosphate. The clinical impact of this potential decrease is unknown.

Potential of Fingolimod and Fingolimod-phosphate to Inhibit the Metabolism of Comedications

In vitro inhibition studies using pooled human liver microsomes and specific metabolic probe substrates demonstrate that fingolimod has little or no capacity to inhibit the activity of the following CYP enzymes: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11 (fingolimod only), and similarly fingolimod-phosphate has little or no capacity to inhibit the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 at concentrations up to 3 orders of magnitude of therapeutic concentrations. Therefore, fingolimod and fingolimod-phosphate are unlikely to reduce the clearance of drugs that are mainly cleared through metabolism by the major CYP isoenzymes described above.

Potential of Fingolimod and Fingolimod-phosphate to Induce its Own and/or the Metabolism of Comedications

Fingolimod was examined for its potential to induce human CYP3A4, CYP1A2, CYP4F2, and MDR1 (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 MDR1 with respect to the vehicle control; therefore, no clinically relevant induction of the tested CYP enzymes or MDR1 by fingolimod are expected at therapeutic concentrations. Fingolimod-phosphate was also examined for its potential to induce mRNA and/or activity of human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A, CYP4F2, CYP4F3B, and CYP4F12. Fingolimod-phosphate is not expected to have clinically significant induction effects on these enzymes at therapeutic doses of fingolimod. In vitro experiments did not provide an indication of CYP induction by fingolimod-phosphate.

Transporters

Based on in vitro data, fingolimod as well as fingolimod-phosphate are not expected to inhibit the uptake of comedications and/or biologics transported by the organic anion transporting polypeptides OATP1B1, OATP1B3, or the sodium taurocholate co-transporting polypeptide (NTCP). Similarly, they are not expected to inhibit the efflux of comedications 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-glycoprotein (P-gp) at therapeutic concentrations.

Oral Contraceptives

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

Cyclosporine

The pharmacokinetics of single-dose fingolimod was not altered during coadministration with cyclosporine at steady-state, nor was cyclosporine steady-state pharmacokinetics altered by fingolimod. These data indicate that Fingolimod is unlikely to reduce or increase the clearance of drugs cleared mainly by CYP3A4. Potent inhibition of transporters MDR1 (P-gp), MRP2, and OATP-1B1 does not influence fingolimod disposition.

Isoproterenol, Atropine, Atenolol, and Diltiazem

Single-dose fingolimod and fingolimod-phosphate exposure was not altered by coadministered 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 coadministration of the latter 2 drugs individually with fingolimod.

Population Pharmacokinetics Analysis

A population pharmacokinetics evaluation performed in MS patients did not provide evidence for a significant effect of fluoxetine and paroxetine (strong CYP2D6 inhibitors) on fingolimod or fingolimod-phosphate predose concentrations. In addition, the following commonly coprescribed substances had no clinically relevant effect (<20%) on fingolimod or fingolimod-phosphate

predose concentrations: baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin, and corticosteroids.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill
Pregelatinised starch
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide
Yellow iron oxide

Printing ink
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide
Yellow iron oxide
Potassium hydroxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.
Fingolimod must be kept out of the reach and sight of children.

6.5 Nature and contents of container

Available in PVC/PVDC-Alu blister packs of 2x14 hard capsules.

6.6 Special precautions for disposal

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

7. PRODUCT REGISTRATION HOLDER

Accord Healthcare Sdn Bhd (1035160 D)
Suite 12A-15, Level 12A, Wisma Zelan
No 1 Jalan Tasik Permaisuri 2
Bandar Tun Razak
56000 Kuala Lumpur

8. MANUFACTURER

Intas Pharmaceuticals Limited
Plot No 457-458 Matoda Plot No
191/218P Chacharwadi, Sarkhej
Bavla Highway, Sanand
Ahmedabad, 382 210, INDIA

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

July 2026