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Fingolimod capsule 0.5 mg

FIGO-MS

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To be sold by retail only on the prescription of Neurologists/Internal medicine Specialists only.

WARNINGS

- **The patient should be monitored for Bradyarrhythmia and Atrioventricular blocks during Fingolimod treatment initiation.**
- **Patients with symptoms and signs consistent with Herpes Viral Infection should undergo prompt diagnostic evaluation and appropriate treatment.**

PRESCRIBING INFORMATION

1. GENERIC NAME

Fingolimod capsule 0.5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fingolimod capsule 0.5 mg

Each hard gelatin capsules contains

Fingolimod hydrochloride IP

Equivalent to Fingolimod…..0.5 mg

3. DOSAGE FORM AND STRENGTH

Fingolimod is provided as 0.5 mg hard gelatin capsules for oral use.

4. CLINICAL PARTICULARS

4.1. Indications

Fingolimod is indicated for the treatment of patients 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 Fingolimod

Cardiac Evaluation

Obtain a cardiac evaluation in patients with certain pre-existing 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 Fingolimod (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 Fingolimod.

Vaccinations

Test patients for antibodies to varicella zoster virus (VZV) before initiating Fingolimod; VZV vaccination of antibody negative patients is recommended prior to commencing treatment with Fingolimod.

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

Important Administration Instructions

Patients who initiate Fingolimod 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.

Fingolimod can be taken with or without food.

Recommended Dosage

In adults and pediatric patients 10 years of age and older weighing more than 40 kg, the recommended dosage of Fingolimod is 0.5 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 Fingolimod 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 Fingolimod 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 are present (even in the absence of symptoms) after 6 hours:

- The heart rate 6 hours post dose 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 post dose is at the lowest value post dose suggesting that the maximum pharmacodynamic effect on the heart may not have occurred.
- The ECG 6 hours post dose shows new onset second degree or higher atrioventricular (AV) block.

If post dose 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 done in:

- 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 Fingolimod
- 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 atrioventricular conduction.

Monitoring After Reinitiation of Therapy Following Discontinuation

When restarting Fingolimod 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 Fingolimod 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.

4.3. Contraindications

Fingolimod is contraindicated in patients who have:

- in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (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 atrioventricular (AV) block or sick sinus syndrome, unless patient has a functioning pacemaker.
- a baseline QTc interval ≥500 msec
- concomitant treatment with Class Ia or Class III anti-arrhythmic drugs
- had a hypersensitivity reaction to Fingolimod or any of the excipients in Fingolimod. Observed reactions include rash, urticaria and angioedema upon treatment initiation.
- 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).
- During pregnancy and in women of childbearing potential not using effective contraception.

4.4. Special Warnings and Precautions for Use

Bradyarrhythmia and Atrioventricular Blocks

Because of a risk for bradyarrhythmia and atrioventricular (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 post dose. 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 were rarely observed. 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 valuation 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. 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.

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.

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

Serious, life-threatening events of disseminated varicella zoster and herpes simplex infections, including cases of encephalitis and multiorgan failure, have occurred with Fingolimod. Include disseminated herpetic infections in the differential diagnosis of patients who are receiving Fingolimod and present with an atypical MS relapse or multiorgan failure. Patients with symptoms and signs consistent with Herpes Viral Infection should undergo prompt diagnostic evaluation and appropriate treatment.

Cases of Kaposi's sarcoma have been reported with Fingolimod. Kaposi's sarcoma is an antiproliferative 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. 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

Concomitant use of Fingolimod with any of these therapies, and also with corticosteroids, would be expected to increase the risk of immunosuppression.

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 varicella zoster virus (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.

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. 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. 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 3–4 months after starting treatment, and again at any time after a patient reports visual disturbances while on Fingolimod therapy.

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 addition to the examination of the fundus including the macula prior to treatment and at 3–4 months after starting treatment, MS patients with diabetes mellitus or a history of uveitis should have regular follow-up examinations.

Posterior Reversible Encephalopathy Syndrome

There have been rare cases of posterior reversible encephalopathy syndrome (PRES) reported in 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 haemorrhage. 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. 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.

Liver Injury

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.

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.

Fetal Risk

Based on findings from animal studies, Fingolimod may cause fetal harm when administered to a pregnant woman. In animal reproduction studies conducted in rats and rabbits, developmental toxicity was observed with administration of Fingolimod at doses less than the recommended human dose. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Because it takes approximately 2 months to eliminate Fingolimod from the body, women of childbearing potential should use effective contraception to avoid pregnancy during and for 2 months after stopping Fingolimod treatment.

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. 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. 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

Hypertension was reported as an adverse reaction in patients on Fingolimod. 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. Melanoma, Squamous cell carcinoma and Merkel cell carcinoma has been reported with Fingolimod. 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.

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).

Hypersensitivity Reactions

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

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.

4.5. Drug Interactions

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, and 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 atrioventricular 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 prescribing physician 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. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk Summary

Based on findings from animal studies, Fingolimod may cause fetal harm when administered to a pregnant woman. Data from prospective reports to the Fingolimod Pregnancy Registry (GPR) are currently not sufficient to allow for an adequate assessment of the drug-associated risk for birth defects and miscarriage in humans. In oral studies conducted in rats and rabbits, Fingolimod demonstrated developmental toxicity, including an increase in malformations (rats) and embryolethality, when given to pregnant animals. In rats, the highest no-effect dose was less than the recommended human dose of 0.5 mg/day on a body surface area (mg/m^2) basis. The most common fetal visceral malformations in rats were persistent truncus arteriosus and ventricular septal defect. The receptor affected by fingolimod (sphingosine 1-phosphate receptor) is known to be involved in vascular formation during embryogenesis. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

In females planning to become pregnant, Fingolimod should be stopped 2 months before planned conception. The possibility of severe increase in disability should be considered in women who discontinue or are considering discontinuation of Fingolimod because of pregnancy or planned pregnancy. In many of the cases in which increase in disability was reported after stopping Fingolimod, patients had stopped Fingolimod because of pregnancy or planned pregnancy.

Lactation

Risk Summary

There are no data on the presence of fingolimod in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Fingolimod is excreted in the milk of treated rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fingolimod and any potential adverse effects on the breastfed infant from Fingolimod or from the underlying maternal condition.

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Before initiation of Fingolimod treatment, women of childbearing potential should be counselled on the potential for a serious risk to the fetus and the need for effective contraception during treatment with Fingolimod. Since it takes approximately 2 months to eliminate the compound from the body after stopping treatment, the potential risk to the fetus may persist and women should use effective contraception during this period.

Pediatric Use

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

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

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

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

Geriatric use

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.

4.7. 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 treatment. On initiation of Fingolimod it is recommended that patients be observed for a period of 6 hours.

4.8. Undesirable Effects

Adverse reactions are listed by System Organ Class (SOC) and within each frequency grouping [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)] the adverse reactions are presented in order of decreasing seriousness.

System organ class	ADRs with frequency
Infections and infestations	Very common: Influenza, Sinusitis
	Common: Herpes viral infections, Bronchitis, Tinea versicolor
	Uncommon: Pneumonia
	Not known: Progressive multifocal leukoencephalopathy (PML), Cryptococcal infections
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common: Basal cell carcinoma
	Uncommon: Malignant melanoma
	Rare: Lymphoma, Squamous cell carcinoma
	Very rare: Kaposi's sarcoma
	Not known: Merkel cell carcinoma
Blood and lymphatic system disorders	Common: Lymphopenia, Leucopenia
	Uncommon: Thrombocytopenia
	Not known: Autoimmune haemolytic anaemia, Peripheral oedema
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 oedema
Cardiac disorders	Common: Bradycardia, Atrioventricular block
	Very rare: T-wave inversion
Vascular disorders	Common: Hypertension
Respiratory, thoracic and mediastinal disorders	Very common: Cough
	Common: Dyspnoea
Gastrointestinal disorders	Very common: Diarrhoea
	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, Gamma glutamyltransferase, Aspartate transaminase)
	Common: Weight decreased, Blood triglycerides increased
	Uncommon: Neutrophil count decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

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

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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

5.2 Pharmacodynamic Properties

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.

Immune System

Effects on Immune Cell Numbers in the Blood

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.

Pulmonary Function

Single Fingolimod doses ≥ 5 mg (10-fold the recommended dose) are associated with a dose-dependent increase in airway resistance.

5.3 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 exposure (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 stereo selective 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 nonpolar ceramide analogues 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 ($t_{1/2}$) 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 faeces 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 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 0.25 mg dose is appropriate for use in 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 AUC0-96 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. No dose adjustment is needed in patients with mild or moderate hepatic impairment.

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.

Carbamazepine

The coadministration of carbamazepine (a potent CYP450 enzyme inducer) 600 mg twice-daily at steady-state and a single dose of Fingolimod 2mg 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 co-medications

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 inductions 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 dose 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 co-medications and/or biologics transported by the breast cancer resistance protein (BCRP), the bile salt export pump (BSEP), the multidrug resistance-associated protein 2 (MRP2), or P-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 co-administered isoproterenol or atropine. Likewise, the single-dose pharmacokinetics of Fingolimod and Fingolimod-phosphate and the steady-state pharmacokinetics of both atenolol and diltiazem were unchanged during the 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 co-prescribed substances had no clinically relevant effect (<20%) on Fingolimod or Fingolimod-phosphate predose concentrations: baclofen, gabapentin, oxybutynin, amantadine, modafinil, amitriptyline, pregabalin, and corticosteroids.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral carcinogenicity studies of Fingolimod were conducted in mice and rats. In mice, Fingolimod was administered at oral doses of 0, 0.025, 0.25, and 2.5 mg/kg/day for up to 2 years. The incidence of malignant lymphoma was increased in males and females at the mid and high dose. The lowest dose tested (0.025 mg/kg/day) is less than the RHD of 0.5 mg/day on a body surface area (mg/m^2) basis. In rats, Fingolimod was administered at oral doses of 0, 0.05, 0.15, 0.5, and 2.5 mg/kg/day. No increase in tumors was observed. The highest dose tested (2.5 mg/kg/day) is approximately 50 times the RHD on a mg/m^2 basis.

Fingolimod was negative in a battery of ***in vitro*** (Ames, mouse lymphoma thymidine kinase, chromosomal aberration in mammalian cells) and ***in vivo*** (micronucleus in mouse and rat) assays.

When Fingolimod was administered orally (0, 1, 3, and 10 mg/kg/day) to male and female rats prior to and during mating, and continuing to Day 7 of gestation in females, no effect on fertility was observed up to the highest dose tested (10 mg/kg), which is approximately 200 times the RHD on a mg/m^2 basis.

6.2 Animal Toxicology or Pharmacology

Lung toxicity was observed in 2 different strains of rats and in dogs and monkeys. The primary findings included increase in lung weight, associated with smooth muscle hypertrophy, hyperdistention of the alveoli, and/or increased collagen. Insufficient or lack of pulmonary collapse at necropsy, generally correlated with microscopic changes, was observed in all species. In rats and monkeys, lung toxicity was observed at all oral doses tested in chronic studies. The lowest doses tested in rats (0.05 mg/kg/day in the 2-year carcinogenicity study) and monkeys (0.5 mg/kg/day in the 39-week toxicity study) are similar to and approximately 20 times the RHD on a mg/m^2 basis, respectively.

In the 52-week oral study in monkeys, respiratory distress associated with ketamine administration was observed at doses of 3 and 10 mg/kg/day; the most affected animal became hypoxic and required oxygenation. As ketamine is not generally associated with respiratory depression, this effect was attributed to Fingolimod. In a subsequent study in rats, ketamine was shown to potentiate the bronchoconstrictive effects of Fingolimod. The relevance of these findings to humans is unknown ***[Reference GILENYA USFDA Label, dated December-2019].***

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities

Not applicable.

7.2 Shelf life

Please see Mfg. Date/ Expiry Date printed on pack.

Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

7.3 Packing Information

10's Blister pack

7.4 Storage and Handling Instructions

Do not store above 30°C

Keep out of reach of children

8. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,
Formulation Division, Unit-II, Sy.no. 1277, 1319 to 1324,
Nandigama (Village & Mandal), Rangareddy (District),
Telangana - 509 228, India.

9. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

5/MN/TS/2014/F/G

10. DATE OF REVISION

April-2021.

D03527-01