Fingolimod is a sphingosine 1-phosphate receptor (S1P) modulator indicated for the treatment of patients with the relapsing-remitting form of multiple sclerosis (MS). Fingolimod has been shown to reduce the frequency of clinical exacerbations and to delay the progression of physical disability due to MS.

Mylan is providing the following information concerning potential risks to consider when prescribing fingolimod.

Bradyarrhythmia (Including conduction defects and bradycardia complicated by hypotension) occurring post-first dose

Initiation of fingolimod treatment results in a reversible decrease in heart rate that may also be associated with AV conduction delays.

Symptoms of decreased heart rate usually happen within the first 6 hours of the first dose. The heart rate gradually recovers by 8 to 10 hours post-dose, although not to baseline levels. The heart rate returns to baseline progressively over approximately one month during chronic treatment. Bradycardia can be asymptomatic or some patients might experience mild to moderate symptoms, including hypotension, dizziness, fatigue, palpitations, dyspnea, arrhythmia, and/or chest pain or chest discomfort, which resolve within the first 24 hours of treatment.

Patients treated with fingolimod may also experience transient AV conduction delays. The conduction abnormalities are usually transient and asymptomatic and resolve within the first 24 hours of treatment. The patient may occasionally require treatment with atropine or isoproterenol to treat the resultant abnormalities.

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 initiate fingolimod treatment, 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.

If patient experiences symptoms of slow heart rate (such as dizziness, tiredness, feeling like heart is beating slowly or skipping beats, or chest pain), the health care professional monitoring the patient can help manage these symptoms.

<u>Recommendations for first dose monitoring:</u>

- For all patients, obtain an electrocardiogram (ECG) and measure blood pressure prior to and 6-hours after the first dose of fingolimod
- Monitor all patients for signs and symptoms of bradyarrhythmia, with hourly pulse and blood pressure measurements, for at least 6 hours after the first dose
- If symptoms of bradyarrhythmia or atrioventricular (AV) block occur, initiate appropriate management, with continued monitoring (e.g., continuous ECG monitoring) until the symptoms have resolved
- If the ECG at 6 hours after the first dose shows a QTc interval ≥500 msec, patients should be monitored overnight
- Should a patient require pharmacological intervention during the first dose observation period, continuous overnight monitoring (e.g., continuous ECG monitoring) in a medical facility should be instituted and the first dose monitoring strategy should be repeated when the second dose of fingolimod is administered

- First-dose monitoring is also recommended if fingolimod treatment is interrupted ≥1 day within first 2 weeks or >7 days during weeks 3 and 4, or >14 days after the first month of treatment because effects on heart rate and AV conduction may occur upon re-initiation
- Extended monitoring, until the finding has resolved, may be required:
    - if the heart rate at 6 hours post-dose is <45 bpm in adults, <55 bpm in pediatric patients aged 12 years and above, or <60 bpm in pediatric patients aged 10 to below 12 years, or is the lowest value post-dose,
    - if the ECG at 6 hours after the first dose shows new-onset second-degree or higher-grade AV block

Contraindications:

- Patients who in the last 6 months had myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure
- Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs
- Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not have a pacemaker
- Patients with a baseline QTc interval ≥500 msec

Liver transaminase elevation

Elevations of liver enzymes, mostly alanine aminotransaminase (ALT), may occur in patients receiving fingolimod. Recent (i.e., within last 6 months) transaminase and bilirubin levels should be referred before initiating the fingolimod therapy. Elevations 3- and 5-fold the upper limit of normal have occurred with fingolimod. The majority occurred within 6 to 9 months and returned to normal within 2 months after discontinuing fingolimod. Recurrence of liver transaminase elevations can occur with rechallenge. Patients with preexisting liver disease may be at increased risk of developing elevated liver enzymes when taking fingolimod.

Fingolimod exposure doubles in patients with severe hepatic impairment. Thus, the risk of adverse reactions is greater in them. Such patients should be closely monitored.

Recommendations for the treatment:

- Obtain transaminase and bilirubin levels prior to initiating treatment if no recent (i.e. within the last 6 months) result is available, every 3 months during the first year of treatment and periodically thereafter in the absence of symptoms or when symptoms suggestive of hepatic injury develop
- If liver transaminases rise above 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurement
- Monitor the levels of liver enzymes and bilirubin in patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine
- Fingolimod therapy should be discontinued if significant liver injury is confirmed

Contraindication:

Patients with severe hepatic impairment (Child-Pugh Class C)

Macular edema

Macular edema, a vision problem that can cause some of the same vision symptoms as an MS attack (optic neuritis), or no symptoms. Fingolimod increases the risk of macular edema. If it happens, macular edema usually starts in the first 3 to 4 months after starting fingolimod therapy. Some patients may present with blurred vision or decreased visual acuity, but in others it might be asymptomatic, and the condition gets diagnosed on routine ophthalmologic examination. Macular edema generally improves or resolved with or without treatment after drug discontinuation, but some patients might have residual visual acuity loss even after resolution of macular edema.

Recommendations for the treatment:

- An ophthalmic evaluation should be performed 3-4 months after treatment initiation in all patients, and at any time in any patient complaining of visual disturbances
- Patients with diabetes mellitus or a history of uveitis are at increased risk of macular edema and should undergo an ophthalmic evaluation prior to initiating fingolimod therapy and have regular ophthalmic evaluations while receiving fingolimod therapy
- Fingolimod be discontinued if a patient develops macular edema. A decision on whether or not fingolimod therapy should be re-initiated after resolution of macular edema needs to take into account the potential benefits and risks for the individual patient
- Encourage the patients who receive fingolimod to contact their healthcare provider if they experience blurriness, shadows, or a blind spot in the center of vision; sensitivity to light; or unusually colored vision.

Opportunistic infections including progressive multifocal leukoencephalopathy (PML), varicella zoster virus (VZV) infections, herpes viral infections other than VZV and fungal infections

Fingolimod causes a dose-dependent reduction of peripheral lymphocyte count to 20-30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues. Because elimination of fingolimod after discontinuation of the therapy may take up to 2 months, peripheral lymphocyte counts gradually recovers to baseline values. Fingolimod thus increases the risk of infections, including opportunistic infections during treatment and for up to 2 months after discontinuation of treatment. Continuous monitoring is recommended for infections during this period.

During fingolimod treatment, serious infections have been reported with opportunistic pathogens, including viruses (e.g., John Cunningham virus [JCV] causing PML, herpes simplex viruses 1 and 2, varicella zoster virus [VZV]), fungi (e.g., cryptococci), bacteria (e.g., atypical mycobacteria), and Kaposi's sarcoma). Suspension of fingolimod therapy should be considered if a patient develops a serious infection.

Healthcare providers should be vigilant for clinical symptoms or MRI findings suggestive of PML and suspend fingolimod until PML has been excluded. Cases of PML have been reported 2-3 years after fingolimod treatment.

Patients should contact their healthcare provider if they have fever, tiredness, body aches, chills, nausea, vomiting, or headache accompanied by fever, neck stiffness, sensitivity to light, nausea, and/or confusion. These may be symptoms of meningitis, an infection of the lining around the brain and the spine. Perform

prompt diagnostic evaluation in patients with symptoms and signs consistent with meningitis, and initiate appropriate treatment if diagnosed. Cryptococcal meningitis (sometimes fatal) has been reported 2-3 years after fingolimod treatment.

Recommendation before initiating fingolimod:

- Obtain a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) before initiating treatment. Treatment with fingolimod should not be initiated when lymphocyte counts are consistently below the normal range.
- Treatment should not be initiated when there are signs and symptoms of a severe active bacterial, fungal or viral infection. Instruct patients to promptly report symptoms or signs suggestive of any infection, during and for up to 2 months after discontinuation of treatment, to facilitate early diagnosis and initiation of appropriate treatments
- Patients without a history of chicken pox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with fingolimod, following which initiation of treatment with fingolimod should be postponed for one month to allow for full effect of vaccination to occur.
- The use of live attenuated vaccines during fingolimod treatment and for two months after discontinuing treatment is not recommended due to the risk of infection from the vaccine

Contraindications:

- Patients with increased risk for opportunistic infections, including those who are immunocompromised due to treatment (e.g. antineoplastic, immunosuppressive or immunomodulating therapies, total lymphoid irradiation or bone marrow transplantation) or disease (e.g. immunodeficiency syndrome).

- Patients with severe active infections including active chronic bacterial, fungal or viral infections (e.g., hepatitis, tuberculosis).

Reproductive toxicity

Fingolimod may cause fetal harm if taken during conception or pregnancy.

Recommendation for treatment:

Mylan-Fingolimod is contraindicated in patients with:

- Pregnant women and women of childbearing potential not using effective contraception;

Mylan-Fingolimod has an immunosuppressive effect that predisposes patients to a risk of infection. Mylan-Fingolimod is teratogenic. It is contraindicated in women of childbearing potential (including female adolescents) not using effective contraception and in pregnant women,

- A negative pregnancy test result must be confirmed prior to starting treatment, and it must be repeated at suitable intervals.
- Women of child-bearing potential, including adolescent females, their parents (or legal representatives), and caregivers, should be counselled before treatment initiation and regularly thereafter about the serious risks of Mylan-Fingolimod to the foetus, facilitated by the pregnancy-specific patient reminder card.

- Women of childbearing potential must use effective contraception during treatment and for two months following treatment discontinuation.
- While on treatment, women must not become pregnant. If a woman becomes pregnant while on treatment, Mylan-Fingolimod must be discontinued. When stopping Mylan-Fingolimod therapy due to pregnancy or for planning a pregnancy, the possible return of disease activity should be considered. Medical advice should be given regarding the risk of harmful effects to the foetus associated with Mylan-Fingolimod treatment and ultrasonography examinations should be performed.
- Mylan-Fingolimod must be stopped 2 months before planning a pregnancy.
- Physicians are encouraged to enrol pregnant patients, or pregnant women may register themselves in the Mylan-Fingolimod pregnancy registry.
- Physicians should provide patients/parents/caregivers with the patient/parents/caregiver's guide and with the pregnancy-specific patient reminder card. No data is available to suggest the association between fingolimod and male reproductive toxicity.

Skin Cancer

(Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma)

Vigilance for basal cell carcinoma and other cutaneous neoplasms is recommended with skin examination every 6 to 12 months and referral to a dermatologist if suspicious lesions are detected

- Caution patients against exposure to sunlight without protection
- Ensure patients are not receiving concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy

Fingolimod has an immunosuppressive effect and can increase the risk of developing lymphomas and other malignancies, particularly those of the skin and serious opportunistic infections. Closely monitor patients during treatment, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of fingolimod should be considered by the physician on a case-by-case basis.

Convulsions

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

Recommendation for treatment:

Caution should be exercised when administering MYLAN-FINGOLIMOD to patients with pre-existing seizure disorder. In the pivotal studies, cases of seizures were reported at a greater incidence for fingolimod-treated patients compared to their respective control arms. It is not known whether these events were related to the effects of MS alone, to fingolimod, or to a combination of both.

Pregnancy Registry

Since there are no adequate and well-controlled studies of fingolimod in pregnant women, Mylan established a pregnancy registry to collect information about the effects of fingolimod during pregnancy.

Physicians are encouraged to register patients who become pregnant while exposed to fingolimod or within 2 months after stopping therapy.

Innomar Strategies Inc. is managing The Mylan-Fingolimod Pregnancy Registry on behalf of Mylan. Healthcare providers with an eligible patient, can contact Innomar Strategies Inc. by calling 1-888-246-5830, sending a fax to 1-833-677-0484 or sending an e-mail to mylanfpr@innomar-strategies.com.

Use of fingolimod in lactating women

Fingolimod is excreted in the milk of animals treated during lactation. 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. 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.

Patient Counseling

Prescribers should inform patients about the benefits and risks of fingolimod before a decision is made to prescribe. Patients should be instructed to read the consumer information and should be handed over the patient educational material. Patients should be given an opportunity to discuss the contents of the consumer information with their physician or healthcare professional and to obtain answers to any questions they may have.

Reporting Adverse Events

Healthcare providers should report all suspected adverse events associated with the use of Mylan-Fingolimod. Please contact 1-844-596-9526.

Summary of Recommendations:

Timing	Check if done	Recommendation
Considerations prior to initiating treatment		Availability of suitable resources to manage symptomatic bradycardia before the first dose of fingolimod is administered
		Obtain an electrocardiogram (ECG) prior to the first dose of fingolimod and at the end of the observation period
		Obtain a recent (i.e. within 6 months) CBC
		Obtain a recent (i.e. within 6 months) liver transaminase and bilirubin levels
		Obtain results of baseline ophthalmologic examination
		Counsel women of childbearing age on potential for adverse fetal outcomes and need for contraception
		Consider serology for patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV). If patient is antibody negative, VZV vaccine should be considered.
		Do not begin fingolimod therapy on patients who get VZV vaccination within one month
		Vigilance for basal cell carcinoma and other cutaneous neoplasms is recommended with skin examination prior to treatment initiation and referral to a dermatologist if suspicious lesions are detected. Caution patients against exposure to sunlight without protection

		Fingolimod treatment is **contraindicated** in patients a. with recent (within last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure b. with a history or presence of Mobitz Type II 2nd or 3rd degree AV block or sick sinus syndrome, unless patient has a functioning pacemaker c. with a baseline QTc interval ≥500 msec d. receiving treatment with Class Ia or III anti-arrhythmic drugs
Treatment initiation (first dose)		Monitor blood pressure and pulse hourly
		Observe all patients for signs and symptoms of bradycardia for a period of at least 6 hours after the first dose of fingolimod
		Obtain an ECG prior to treatment initiation and 6 hours after the dose administration
		Continue observation beyond 6 hours (until resolution) if: • the lowest post-dose heart rate is observed at end of the observation period • heart rate is < 45 bpm • new onset of 2nd degree or higher AV block
		Overnight observation in a medical facility with continuous ECG monitoring should be initiated in: • Patients at a higher risk for symptomatic bradycardia or bradyarrhythmia due to coexisting medical conditions • Patients receiving concurrent therapies that slow heart rate or AV conduction should be evaluated with possibility of switching off these drugs prior to initiation of fingolimod. In patients who cannot switch, this observation is recommended. • Patients with prolonged QTc interval at baseline or during the observation period, or taking drugs with known risk of torsades de pointes or at additional risk for QT prolongation
During treatment		Monitor blood pressure regularly
		Encourage patients to report symptoms of infection (and HPS) as soon as possible
		Vigilance for basal cell carcinoma and other cutaneous neoplasms is recommended with skin examination every 6 to 12 months and referral to a dermatologist if suspicious lesions are detected ☐ Caution patients against exposure to sunlight without protection ☐ Ensure patients are not receiving concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy
		Fingolimod has an immunosuppressive effect and can increase the risk of developing lymphomas and other malignancies, particularly those of the skin and serious opportunistic infections. Closely monitor patients during treatment, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of fingolimod should be considered by the physician on a case-by-case basis.
		Advise patients to avoid live attenuated vaccines
		Perform ophthalmologic examination 3-4 months after starting fingolimod, and at any time if patient reports visual disturbances. Perform regular follow-up ophthalmologic evaluations in patients with diabetes mellitus or a history of uveitis.
		Counsel women of childbearing potential about the importance of contraception use
		A negative pregnancy test result must be confirmed prior to starting treatment, and it must be repeated at suitable intervals.
		Women of child-bearing potential, including adolescent females, their parents (or legal representatives), and caregivers, should be counselled before treatment initiation and regularly thereafter about the serious risks of Mylan-Fingolimod to the fetus, facilitated by the pregnancy-specific patient reminder card.

		While on treatment, women must not become pregnant. If a woman becomes pregnant while on treatment, Mylan-Fingolimod must be discontinued and the event must be reported. Medical advice should be given regarding the risk of harmful effects to the fetus associated with Mylan-Fingolimod treatment and ultrasonography examinations should be performed.
		Physicians should provide patients/parents/caregivers with the patient/parents/caregiver's guide and with the pregnancy-specific patient reminder card.
		When stopping Mylan-Fingolimod therapy due to pregnancy or for planning a pregnancy, the possible return of disease activity should be considered.
		Monitor liver enzymes, particularly in patients who develop symptoms suggestive of hepatic dysfunction every 3 months during the 1st year of treatment and periodically thereafter
		Monitor CBC count regularly
		Discontinue treatment if pregnancy occurred and report the event
		Cases of seizures, including status epilepticus, have been reported
		Monitor patients for any cardiac symptoms
		Encourage patients to report symptoms of infection (and HPS) for up to 2 months
After treatment discontinuation		If fingolimod therapy is discontinued for more than 14 days after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of fingolimod treatment and the same precautions (first dose monitoring) as for initial dosing should apply. Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of one day or more. During weeks 3 and 4 of treatment, first dose procedures are recommended after treatment interruption of more than 7 days.
		Counsel women of childbearing potential on the need for continuing contraception for 2 months