During treatment

- ❒ A full ophthalmologic assessment is recommended:
  - 3 to 4 months after starting treatment for the early detection of visual impairment due to drug–induced macular oedema
  - Periodically during treatment in patients with diabetes mellitus or history of uveitis
  - Counsel patients to immediately report any visual disturbances during treatment
  - Evaluate the fundus, including the macula. Discontinue treatment if macular oedema is confirmed
- ❒ Counsel patients to report signs and symptoms of infection immediately to their prescriber during treatment and for up to 2 months after discontinuation
- • Patients with symptoms and signs consistent with cryptococcal meningitis (e.g. headache accompanied by mental changes such as confusion, hallucinations, and/or personality changes) should undergo prompt diagnostic evaluation. If cryptococcal meningitis is diagnosed, fingolimod should be suspended and appropriate treatment should be initiated. A multidisciplinary consultation (i.e. infectious disease specialist) should be undertaken if re–initiation of fingolimod is warranted.
  –Reports of cryptococcal meningitis (sometimes fatal) have been received after approximately 2–3 years of treatment, although an exact relationship with the duration of treatment is unknown
- ❒ Perform prompt diagnostic evaluation in patients with symptoms and signs consistent with encephalitis, meningitis or meningoencephalitis. If diagnosed, discontinue fingolimod and initiate appropriate treatment.
- • Serious, life–threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex virus (HSV) and VZV were reported while on fingolimod treatment.
- • Be vigilant for clinical symptoms or MRI findings that may be suggestive of progressive multifocal leukoencephalopathy (PML). If PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with fingolimod should be suspended until PML has been excluded
  – Cases of PML have occurred after approximately 2–3 years of monotherapy treatment although an exact relationship with the duration of treatment is unknown
- • Suspend treatment during serious infections
- • Opportunistic infections:
  – Fingolimod has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal.
- ❒ Check full blood count periodically during treatment, at month 3 and at least yearly thereafter, and interrupt treatment if lymphocyte count is confirmed as <0.2x109/L
- ❒ Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported.

  During treatment, in the absence of clinical symptoms, liver transaminases and serum bilirubin should be monitored at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter until 2 months after fingolimod discontinuation.
  –If liver transaminases are greater than 3 but less than 5 times the upper limit of normal (ULN) without increase in serum bilirubin, more frequent monitoring including serum bilirubin and alkaline phosphatase (ALP) measurement should be instituted to determine if further increases occur and in order to discern if an alternative aetiology of hepatic dysfunction is present.
  –If liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin, fingolimod should be discontinued and hepatic monitoring continued.
  –If serum levels return to normal (including if an alternative cause of the hepatic dysfunction is discovered), fingolimod may be restarted based on a careful benefit–risk assessment of the patient
- ❒ During treatment and for up to 2 months after discontinuation
  –Vaccinations may be less effective
  –Live attenuated vaccines may carry a risk of infection and should be avoided
- ❒ Vigilance for basal cell carcinoma and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma 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 (including mycosis fungoides) and other malignancies, particularly those of the skin. Surveillance should include vigilance for both skin malignancies and mycosis fungoides. Closely monitor patients during treatment, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy.Treatment discontinuation should be considered in those with a suspected risk on an individual basis.
- ❒ Cases of seizure, including status epilepticus, have been reported. Vigilance for seizures, especially in those patients with underlying conditions or with a pre–existing history or family history of epilepsy is recommended
- ❒ Monitor paediatric patients for signs and symptoms of depression and anxiety
- ❒ Reassess on an annual basis the benefit of fingolimod treatment versus risk in each patient, especially paediatric patients

During treatment: Information for women and girls of childbearing potential

- ❒ **While on treatment, women must not become pregnant. Discontinue treatment if a woman becomes pregnant.** Fingolimod should be stopped 2 months before planning a pregnancy, and the possible return of disease activity after discontinuation should be considered In the event of a pregnancy during treatment, or in the 2 months following discontinuation, ultrasonography examinations should be performed and medical advice about the harmful effects of fingolimod to the foetus should be provided.
- ❒ Advise WOCBP (including adolescents and their parents/caregivers) that effective contraception must be used during treatment and for at least 2 months after treatment discontinuation. Pregnancy tests must be repeated at suitable intervals.
- ❒ **WOCBP** (including adolescents and their parents/legal representatives/caregivers) **must be informed regularly about the serious risks of fingolimod to the foetus**
- ❒ Ensure WOCBP (including adolescents), their parents (or legalrepresentatives), and caregivers receive regular counselling facilitated by the **Pregnancy Specific Patient Reminder Card**
- ❒ To help determine the effects of fingolimod exposure in pregnant women with MS, **physicians are encouraged to report pregnant patients who may have been exposed to fingolimod at any time during pregnancy** (from 8 weeks prior to last menstrual period onward) Pregnancy reports should be reported to the HPRA and relevant MAH at thecontact details provided on Page 6 of this checklist

After treatment discontinuation

- ❒ Repeat first–dose monitoring as for treatment initiation when treatment is interrupted for
  – One day or more during the first 2 weeks of treatment
  – More than 7 days during weeks 3 and 4 of treatment
  – More than 2 weeks after 1 month of treatment
- ❒ Counsel patients to report signs and symptoms of infection immediately to their prescriber for up to 2 months after discontinuation
  – Instruct patients to be vigilant for signs of encephalitis, meningitis or meningoencephalitis, infection and PML
- ❒ Inform WOCBP (including adolescents and their parents/caregivers) that effective contraception must be used for 2 months after discontinuation because of the serious risks of fingolimod to the foetus
- ❒ Advise women who stop treatment with fingolimod because they are planning a pregnancy that their disease activity may return
- ❒ In the post–marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping fingolimod (rebound). The possibility of recurrence of exceptionally high disease activity should be considered.

Summary guidance specifically for paediatric patients

- ❒ Perform first–dose monitoring on treatment initiation due to the risk of bradyarrhythmia
- ❒ Repeat first–dose monitoring in paediatric patients when the dosage is switched from 0.25 mg to 0.5 mg fingolimod once daily*
- ❒ Counsel patients and their parents/caregivers on fingolimod's immunosuppressive effects
- ❒ Perform cardiovascular monitoring
- ❒ Assess physical development (Tanner staging), and measure height and weight, as per standard of care
- ❒ Consider a complete vaccination schedule before starting fingolimod
- ❒ Emphasize the importance of treatment compliance topatients, their parents and other caregivers, especially with regard to treatment interruption and the need to repeat first–dose monitoring
- ❒ Provide guidance on seizure monitoring
- ❒ Provide pregnancy–specific guidance including the Pregnancy Specific Patient Reminder Card to adolescent patients of child–bearing potential and their parents/caregivers.
- ❒ Paediatric patients should be monitored for symptoms of anxiety and depression

* 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.

For further copies, for new or existing prescribers, please contact enquiry.ire@viatris.com

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. Healthcare professionals are asked to report any suspected adverse reactions to HPRA Pharmacovigilance:
Website: www.hpra.ie

Adverse reactions/events should also be reported to Mylan IRE Healthcare Limited at: pv.ireland@viatris.com

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Fingolimod Mylan 0.5 mg hard capsules Physician's Checklist

Important points to remember before, during and after treatment

This checklist contains important safety information about fingolimod and advice on risk minimisation.

This checklist should be used in conjunction with the full prescribing information. Please refer to Summary of Product Charecteristics (SMPC) for the product youintend to prescribe, which can be found at www.hpra.ie and www.medicines.ie.

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Considerations in fingolimod patient selection

Considerations for treatment initiation
Fingolimod causes transient heart rate reduction and may cause atrioventricular (AV) conduction delays following initiation of treatment. All patients should be monitored for a minimum of 6 hours on treatment initiation. Below is a brief overview of monitoring requirements. Refer to page 4 for information on first–dose monitoring.

Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 in the SmPC.
- Immunodeficiency syndrome.
- Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies).
- Severe active infections
- Active chronic infections (hepatitis, tuberculosis).
- Active malignancies.
- Severe liver impairment (Child–Pugh class C).
- Patients who in the previous 6 months had myocardia infarction (MI), unstable angina pectoris, stroke/transient is chaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure.
- Patients with severe cardiac arrhythmias requiring anti–arrhythmic treatment with class Ia or class III anti–arrhythmic medicinal products (see section 4.4 in the SmPC).
- Patients with second–degree Mobitz type II atrioventricular (AV) block or third–degree AV block, or sick–sinus syndrome, if they do not wear a pacemaker.
- Patients with a baseline QTc interval ≥ 500 msec.
- During pregnancy and in women of childbearing potential not using effective contraception

Fingolimod should not be used in the following patients:
- Women who are breast–feeding
- Fingolimod has not been studied in patients with arrhythmias requiring treatment with class 1a or class III antiarrhythmicmedicinal products. Fingolimod should not be used concomitantly with these patients

Not recommended **Consider only after performing risk/benefit analysis and consulting a cardiologist**	
Sino–atrial heart block, history of symptomatic bradycardia or recurrent syncope, significant QT–interval prolongation*, history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea.	• At least overnight extended monitoring is recommended • Consult cardiologist regarding appropriate first–dose monitoring
Taking beta–blockers, heart–rate–lowering calcium channel blockers**, or other substances that are known to lower the heart rate***.	• Consult cardiologist regarding possibility of switching to non–heartrate–lowering drugs • If change in medication is not possible,extend monitoring to at least overnight and consult cardiologist regarding first dose monitoring

* QTc >470 msec (adult females), >460 msec (paediatric females), or >450 msec (adult and paediatric males).
** Includes verapamil or diltiazem, for example.
*** Includes ivabradine, digoxin, anticholinesterases, or pilocarpine, for example.

Recommended steps to managing patients on fingolimod

The checklist and schematic that follow are intended to assist in the management of patients on fingolimod.
Key steps and considerations while starting,continuing, or discontinuing treatment are provided.
Patient's name:
Date of birth:
Consultant:
Hospital number:

Prior to initiating treatment

- ❒ Ensure patients are not concomitantly taking Class Ia or Class III antiarrhythmic medicines
- ❒ Treatment with fingolimod is not recommended in the following patients, unless anticipated benefits outweigh the potential risks:

  – Those with sino-atrial heart block, history of symptomatic bradycardia or recurrent syncope, significant QT–interval prolongation*, history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea
- ❒ Seek advice from a cardiologist in order to determine the most appropriate monitoring at treatment initiation; at least overnight extended monitoring is recommended
  – Those receiving concurrent therapy with betablockers, heart–rate–lowering calcium channel blockers (eg, verapamil, diltiazem), or other substances which may decrease heart rate (eg, ivabradine, digoxin, anticholinesteratic agents, pilocarpine)
- ❒ Seek advice from a cardiologist regarding a switch to non–heart–rate–lowering medicinal products prior to initiation of treatment
- ❒ If heart–rate–lowering medication cannot be stopped, seek advice from a cardiologist in order to determine the most appropriate monitoring at treatment initiation; at least overnight extended monitoring is recommended
- ❒ For paediatric patients, assess Tanner staging, measure height and weight, and consider a complete vaccination schedule, as per standard of care
- ❒ Conduct baseline electrocardiogram (ECG) and blood pressure measurement
- ❒ A baseline MRI should be available (usually within 3 months) as a reference
- ❒ Avoid co–administration of anti–neoplastic, immunomodulatory or immunosuppressive therapies due to the risk of additive immune system effects. For the same reason, a decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration
- ❒ Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported, obtain recent (within 6 months) transaminase, and bilirubin levels
- A core pharmacodynamic effect of fingolimod is a dose–dependent reduction of the peripheral lymphocyte count to 20–30% of baseline values
- ❒ Obtain recent (within 6 months or after discontinuation of prior therapy) full blood count including absolute lymphocyte levels
- Inform WOCBP (women of childbearing potential) (including adolescents and their parents/caregivers) that fingolimod is contraindicated in pregnant women and WOCBP not using effective contraception
- ❒ Fingolimod is teratogenic. Confirm a negative pregnancy test result in WOCBP (including adolescents) prior to starting treatment and repeat at suitable intervals during treatment
- ❒ Inform WOCBP (including adolescents and their parents/caregivers) about the serious risks of fingolimod to the foetus
- ❒ Provide all patients, parents (or legal representatives) and caregivers with the Pregnancy–Specific Patient Reminder Card
- ❒ Counsel WOCBP (including adolescents and their parents/caregivers) that they must avoid pregnancy and use effective contraception both during treatment and for 2 months after treatment discontinuation. Counselling should be facilitated by the Pregnancy–Specific Patient Reminder Card
- ❒ Delay initiation of treatment in patients with severe active infection until resolved
- ❒ Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV related cancer, has been reported in the post–marketing setting. Cancer screening (including a Pap test), and vaccination for HPV–related cancer is recommended for patients as per standard of care
- ❒ Check varicella zoster virus (VZV) antibody status in patients without a healthcare–professional–confirmed history of chickenpox or documentation of a full course of varicella vaccination. If negative, a full course of vaccination with varicella vaccine is recommended and treatment initiation should be delayed for 1 month to allow full effect of vaccination to occur
- ❒ Conduct an ophthalmologic evaluation in patients with history of uveitis or diabetes mellitus
- ❒ Conduct a dermatologic examination at initiation. The patient should be referred to a dermatologist if suspicious lesions, potentially indicative of basal cell carcinoma or other cutaneous neoplasms (including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma), are detected
- ❒ Provide patients, parents and caregivers with the Patient/Parent/Caregiver's guide

* QTc >470 msec (adult females), >460 msec (paediatric females), or >450 msec (adult and paediatric males).

Treatment initiation algorithm

All patients, including paediatric patients, need to be monitored for at least 6 hours during treatment initiation, as described in the algorithm below.
This procedure should also be followed in paediatric patients when the dosage is switched from 0.25 mg to 0.5 mg fingolimod once daily.*
It should also be followed at re-initiation of treatment if fingolimod is discontinued for:
- One day or longer within the first 2 weeks of treatment
- More than 7 days during weeks 3 and 4
- More than 2 weeks after the first month of treatment

In addition, for patients in whom fingolimod is not recommended (see page 2), advice should be sought from a cardiologist regarding appropriate monitoring; at least overnight monitoring is recommended in this group

Monitor for a minimum of 6 hours
- ❒ Perform ECG and BP measurement
- ❒ Monitor for a minimum of 6 hours for signs and symptoms of bradycardia, with hourly pulse and BP checks. If patient is symptomatic, continue monitoring until resolution.
  – Continuous (real-time) ECG is recommended throughout the 6-hour period
- ❒ Perform ECG at 6 hours

Did the patient require pharmacologic intervention at any time during the monitoring period?

NO

YES

Monitor overnight in a medical facility (for example as an inpatient on a hospital ward).The first dose monitoring should be repeated after the 2nd dose of fingolimod

Did third-degree AV block occur at any time during the monitoring period?

NO

YES

Extend monitoring at least overnight, until the findings have resolved

At the end of the monitoring period, have any of the following criteria been met?
- HR<45bpm in adults, <55bpm in paediatric patients aged ≥12 years of age, or <60bpm in paediatric patients aged 10 to <12 years of age
- ECG shows new-onset second degree or higher AV block or QTc interval ≥500msec

NO

YES

Extend monitoring at least overnight, until the findings have resolved

At the end of the monitoring period, is the HR the lowest since the first dose was administered?

NO

YES

Extend monitoring by at least 2 hours and until heart rate increases

First dose monitoring is complete

BP=blood pressure
ECG=electrocardiogram
HR=Heart rate
QTc=heart rate corrected QT interval
* For paediatric patients (≥10 years old), the approved dosing for Fingolimod is 0.25 mg once daily for patients weighing ≤40 kg, and 0.5 mg once daily for patients weighing > 40 kg.