Fingolimod Tillomed Prescriber's Checklist

Summary of Recommendations

For full prescribing information, please also refer to the Summary of Product Characteristics (SmPC) for Fingolimod Tillomed available via www.hpra.ie

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 via HPRA Pharmacovigilance: Website: www.hpra.ie.

Side effects should also be reported to Tillomed Pharmacovigilance department: Tel +44 (0)800 9706115 or email medical.information@tillomed.com

Considerations in fingolimod patient selection

Fingolimod is suitable for adult and paediatric patients (≥10 years old) for the treatment of highly active relapsing remitting multiple sclerosis (RRMS)*.

While many patients may be suitable for treatment, the following section highlights patients in whom fingolimod is contraindicated or not recommended.

Considerations for treatment initiation

Fingolimod causes transient heart rate reduction and may cause 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 5 for more information.

Appropriate

Eligible adult and paediatric patients (≥10 years old) with highly active RRMS who have not responded to a full and adequate course of at least one disease modifying therapy or those with rapidly evolving, severe RRMS*.

*Fingolimod is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older: patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy, or patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Contraindications

- Known 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);
- Known active malignancies;
- Severe liver impairment (Child-Pugh class C);
- Patients who in the previous 6 months had myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure;
- Severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia or class III anti-arrhythmic medicinal products;
- 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;
- Pregnant women and women of childbearing potential (including adolescents) not using effective contraception
- Hypersensitivity to the active substance or to any of the excipients

The following patients should not be treated with fingolimod

- Women who are breast feeding
- Fingolimod has not been studied in patients with arrhythmias requiring treatment with class 1a or Class III anti-arrhythmic medicinal products. Fingolimod should not be used concomitantly with these patients

Not recommended		
Consider only after performing benefit/risk analysis and consulting a cardiologist		
Consult cardiologist regarding appropriate first-dose monitoring		
Due to the risk of serious rhythm disturbances, fingolimod should not be used in patients with Sino-atrial heart block, a history of symptomatic bradycardia, or recurrent syncope, or in patients with significant QT-interval prolongation (QTc > 470 msec (adult females) , QTc>460msec (paediatric females) or >450 msec (adult and paediatric males)). Since significant bradycardia may be poorly tolerated in patients with a history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea fingolimod should not be used in these patients. In such patients treatment with fingolimod should be considered only if the anticipated benefits outweigh the potential risks	→	At least overnight extended monitoring is recommended
Consult cardiologist regarding possibility of switching to non-heart-rate–lowering drugs		
Taking beta-blockers, heart-rate–lowering calcium channel blockers (including verapamil, or diltiazem), or other substances that are known to lower the heart rate (including ivabradine, digoxin, anticholinesterase agents, or pilocarpine for example).	→	If change in medication is not possible, extend monitoring to at least overnight

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.

Prior to initiating treatment

☐	For paediatric patients, assess Tanner staging, measure height and weight, and consider a complete vaccination schedule as per standard of care
☐	Ensure patients are not concomitantly taking Class Ia or Class III antiarrhythmic medicines
☐	Conduct baseline electrocardiogram (ECG) and blood pressure measurement
☐	Before initiating treatment with fingolimod, a baseline MRI should be available (usually within 3 months) as a reference
☐	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 (QTc >470 msec [adult females], >460 msec [paediatric females], or >450 msec [adult and paediatric males]), 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 beta-blockers, 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.

☐	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.
☐	Obtain recent (within 6 months or after discontinuation of prior therapy) full blood count including absolute lymphocyte levels before initiating treatment.
☐	A core pharmacodynamic effect of fingolimod is a dose-dependent reduction of the peripheral lymphocyte count to 20-30% of baseline values
☐	Inform Women of childbearing potential (including female adolescents and their parents/caregivers) that fingolimod is contraindicated in pregnant women and Women of childbearing potential not using effective contraception
☐	Fingolimod is teratogenic. A negative pregnancy test must be confirmed in Women of child-bearing potential (including female adolescents) prior to starting treatment.
☐	Inform Women of child-bearing potential (including female adolescents and their parents/caregivers) about the serious risks of fingolimod to the foetus
☐	Counsel Women of child-bearing potential (including female 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
☐	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
☐	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 is recommended for patients as per standard of care
☐	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 Guide
☐	Provide Women of child-bearing potential, including adolescent females, their parents (or legal representatives), or caregivers with a pregnancy-specific patient reminder card

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 3), advice should be sought from a cardiologist regarding appropriate monitoring; at least overnight monitoring is recommended for this group.

Monitor for a minimum of six 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

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

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

YES → Monitor overnight. First dose monitoring should be repeated after the second dose of fingolimod

NO

☐ Did third degree AV block occur at any time during the monitoring

YES → Extend monitoring at least overnight, until the findings have resolved

NO

At the end of the monitoring period, have any of the following criteria been met?

☐ HR <45 bpm in adults, <55 bpm in paediatric patients aged 12 years or older, or <60 bpm in paediatric patients aged 10 to <12 years

☐ ECG shows new-onset second-degree or higher AV block or QTc interval ≥500 msec

YES → Extend monitoring at least overnight, until the findings have resolved

NO

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

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

NO

First dose monitoring is complete

During treatment

☐	Conduct a full ophthalmologic evaluation at 3 to 4 months after starting treatment for the early detection of drug-induced macular oedema • Conduct periodic ophthalmologic evaluations during treatment in patients with history of uveitis or diabetes mellitus • Counsel patients to immediately report any visual disturbance during treatment • Evaluate the fundus, including the macula, and discontinue treatment if macular oedema is confirmed
☐	Counsel patients to report signs and symptoms of infection immediately to their prescriber while on treatment and for two months following treatment discontinuation • Cases of cryptococcal meningitis (a fungal infection), sometimes fatal, have been reported in the postmarketing setting 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 signs and symptoms (e.g. headache accompanied by mental changes such as confusion, hallucinations, and/or personality changes). 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 • Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex and varicella zoster viruses have occurred with fingolimod at any time during treatment. If herpes encephalitis, meningitis or meningoencephalitis occur, fingolimod should be discontinued and appropriate treatment for the respective infection should be administered • Progressive multifocal leukoencephalopathy (PML) has been reported under fingolimod treatment since marketing authorisation. Be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. MRI imaging may be considered as part of increased vigilance in patients considered at increased risk of 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 • Suspend treatment during serious infections
☐	Check full blood count periodically during treatment, at month 3 and at least yearly thereafter, and interrupt treatment if lymphocyte count is confirmed as $<0.2x10^9/L$*
☐	Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported. In the absence of clinical symptoms: • Check liver transaminases and serum bilirubin at months 1, 3, 6, 9 and 12 on therapy and periodically thereafter until 2 months after fingolimod discontinuation • In the absence of clinical symptoms, 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. Hepatic monitoring should be 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
☐	While on treatment, women must not become pregnant. Discontinue treatment if a woman becomes pregnant. Fingolimod must be stopped 2 months before planning a pregnancy, and the possible return of disease activity after treatment discontinuation should be considered. • Advise women of child bearing potential (including female adolescents and their parents/caregivers) that effective contraception must be used during treatment and for 2 months after treatment discontinuation • Pregnancy tests must be repeated at suitable intervals

	• Ensure women of child bearing potential (including female adolescents and their parents/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) to Tillomed by calling on number +44 (0)800 9706115 or email at medical.information@tillomed.co.uk, in order to allow monitoring of these patients.
☐	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 that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas (including mycosis fungoids), and other malignancies (particularly those of the skin). Physicians should carefully monitor patients during treatment, especially those with concurrent conditions or known factors such as previous immunosuppressive therapy. Surveillance should include vigilance for both skin malignancies and mycosis fungoides. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case 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

*Approved dose of 0.5 mg once daily (or 0.25 mg once daily in paediatric patients (≥10 years old) with a body weight of ≤ 40 kg) to be used when restarting treatment as other dosing regimens have not been approved.

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 and PML
☐	Inform Women of child-bearing potential (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 due to pregnancy or because they are planning a pregnancy that their disease activity may return
☐	In case of pregnancy (intended or unintended) during treatment, or in the 2 months after stopping treatment with fingolimod, medical advice should be given regarding the risk of harmful effects to the foetus associated with fingolimod treatment and ultrasonography examinations should be performed.
☐	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. Patients should be monitored for relevant signs and symptoms and appropriate treatment initiated as required

Summary guidance specifically for paediatric patients

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	
☐	Consider a complete vaccination schedule before starting fingolimod.
☐	Counsel patients and their parents/caregivers on fingolimod's immunosuppressive effects
☐	Assess physical development (Tanner staging), and measure height and weight, as per standard of care
☐	Perform cardiovascular monitoring
☐	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
☐	Emphasize the importance of treatment compliance to patients, their parents and other caregivers, especially with regard to treatment interruption and the need to repeat first-dose monitoring
☐	Paediatric patients should be monitored for symptoms of anxiety and depression
☐	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