Fingolimod prescriber's checklist

Important points to remember before, during and after treatment

Healthcare professionals are asked to report any suspected adverse reactions.

Suspected Adverse Drug Reactions should be reported either to the Medicines Authority or to Tillomed.

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to; P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 E: postlicensing.medicinesauthority@gov.mt

When reporting, please provide as much information as possible. By reporting side effects, you can help provide more information on the safety of this medicine.

Adverse events should also be reported to Tillomed at +44 (0)1480 402 400 or email id PVUK@tillomed.com

If you have a question about the product, please contact Tillomed Medical information department at +44 (0)1480 402 400 or by email medical.information@tillomed.com.

Checks required before starting fingolimod

Key safety assessments and considerations before treatment.

☐ Do not initiate fingolimod in patients with severe liver impairment (Child-Pugh class C).

☐ Obtain recent (within 6 months) transaminase, and bilirubin levels

☐ Obtain recent (within 6 months or after discontinuation of prior therapy) full blood count

☐ Inform women of childbearing potential (including female adolescents and their parents/caregivers) that fingolimod is contraindicated in pregnant women and those of childbearing potential not using effective contraception, and about the serious risks of fingolimod to a foetus

☐ Fingolimod is teratogenic. Confirm a negative pregnancy test result in women of childbearing potential (including female adolescents) prior to starting treatment and repeat at suitable intervals during treatment

☐ Provide women of childbearing (WOCB) potential, parents (or legal representatives) and caregivers with the Pregnancy-Specific Patient Reminder Card

☐ Counsel women of childbearing potential (including adolescents and their parents/caregivers) to 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

☐ Fingolimod is contraindicated in patients with immunodeficiency syndrome, increased risk for opportunistic infections including immunocompromised patients or severe active or active chronic infections (i.e. hepatitis or tuberculosis). Do not initiate fingolimod in patients with any of these conditions

☐ Delay initiation of treatment in patients with severe active infection until resolved

☐ 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

☐ Cancer screening (including a Pap test) and vaccination for HPV-related cancer is recommended for patients as per standard of care

☐ Do not treat with fingolimod in patients with suspected or confirmed progressive multifocal leukoencephalopathy (PML)

☐ Ensure patients have a baseline MRI usually within 3 months before initiating fingolimod

☐ 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. The patient should be referred to a dermatologist in case 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 and Caregiver Guide

Cardiac contraindications and warnings

Fingolimod is contraindicated in patients with certain cardiac disorders and it should not be started in those taking medicines that may cause bradycardia. Please read the guidance provided in the summary of product characteristics on the management of patients with cardiac disorders when considering fingolimod treatment and seek cardiology advice when necessary.

Fingolimod is contraindicated in patients:

- who in the previous 6 months had myocardial infarction, unstable angina, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure.
- with severe cardiac arrhythmias requiring treatment with class Ia or class III anti-arrhythmic medicinal products.
- 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.
- with a baseline QTc interval ≥ 500 msec.

Consider patients with the following conditions 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 apnea.

In these patients, overnight extended monitoring is recommended and it is important to consult a cardiologist regarding appropriate first-dose monitoring.

If taking beta-blockers, heart-rate–lowering calcium channel blockers‡, or other substances that are known to lower the heart rate§, consult a cardiologist regarding possibility of switching to non-heart-rate-lowering drugs. If change in medication is not possible, extend monitoring to at least overnight. Ensure patients are not concomitantly taking Class Ia or Class III antiarrhythmic medicines.

QTc=heart-rate–corrected QT interval. †QTc >470 msec (adult females), >460 msec (paediatric females), or >450 msec (adult and paediatric males). ‡Includes verapamil or diltiazem. §Includes Class Ia and Class III antiarrhythmics, ivabradine, digoxin, anticholinesteratic agents, or pilocarpine.

Treatment initiation algorithm

☐ Did the patient require pharmacologic intervention at any time during the monitoring period?	No Si → Monitor overnight in a medical facility. The first-dose monitoring should be repeated after the second dose of fingolimod
☐ Did third-degree AV block occur at any time during the monitoring period?	No Si → Extend monitoring at least overnight, until resolved
At the end of the monitoring period, did any of the following occur? ☐ HR <45 bpm in adults, <55 bpm in paediatric patients aged ≥12 years old, or <60 bpm 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 Si → 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 Si → Extend monitoring by at least 2 hours and until the heart rate increases

First-dose monitoring is complete

BP=blood pressure; ECG=electrocardiogram; HR=heart rate; QTc=heart-rate–corrected QT interval. †QTc >470 msec (adult females), >460 msec (paediatric females), or >450 msec (adult and paediatric males). ‡Includes verapamil or diltiazem. §Includes Class Ia and Class III antiarrhythmics, ivabradine, digoxin, anticholinesteratic agents, or pilocarpine. ¶ 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.

Management of patients during treatment

- ☐ Obtain an ophthalmologic assessment in all patients:

  - 3–4 months after starting treatment for the early detection of visual impairment due to drug-induced macular oedema
  - Discontinue fingolimod in patients who develop macular oedema. Restart only after careful benefit-risk consideration

- ☐ Counsel patients to report signs and symptoms of infection immediately to their prescriber during and for up to 2 months after treatment with fingolimod has been discontinued
  • Perform prompt diagnostic evaluation in patients with symptoms and signs consistent with opportunistic infections of the CNS and initiate appropriate treatment if diagnosed

  • 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

  • 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

  • Fingolimod should be discontinued in patients with CNS herpes infections. Fingolimod should be suspended in patients with cryptococcal meningitis with careful consideration with a specialist before reinitiating

  • Inform patients that during fingolimod treatment, they should not receive live attenuated vaccines and that other vaccines may be less effective

  • Progressive Multifocal Leukoencephalopathy (PML) has been predominantly observed after 2 or more years of fingolimod treatment

  • Annual MRIs may be considered especially in patients with multiple risk factors generally associated with PML

• If PML is suspected, perform a diagnostic MRI immediately and suspend fingolimod until PML has been excluded. Permanently discontinue fingolimod if PML is confirmed

• Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated with S1P receptors modulators, including fingolimod, who developed PML and subsequently discontinued treatment. The time to onset of IRIS in patients with PML was usually from weeks to months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

• For potentially serious infection, evaluate the patient promptly and consider an infectious disease referral. Consider suspending fingolimod and the benefit-risk of any subsequent reinitiation.

☐ Monitor peripheral blood lymphocyte counts prior to and during treatment with fingolimod. Interrupt treatment for lymphocyte count <0.2x109/L until recovery.

☐ 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

• 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) measurements should be carried out to determine if further increases occur, and in order to discern if an alternative aetiology of liver dysfunction is present

• Discontinue fingolimod if liver transaminases are at least 5 times the ULN or at least 3 times the ULN associated with any increase in serum bilirubin. Hepatic monitoring should be continued. Restart fingolimod only after careful benefit-risk consideration

☐ For patients with clinical symptoms of liver dysfunction, evaluate promptly and discontinue fingolimod if significant liver injury is confirmed. If serum levels return to normal (including if an alternative cause of the liver dysfunction is discovered), Fingolimod may be restarted if the benefit-risk assessment is favorable for the patient

☐ Discontinue treatment if a woman becomes pregnant.

- ☐ Fingolimod should be stopped 2 months before attempting to become pregnant, and the possible return of disease activity should be considered. An ultrasonography examination should be performed and medical advice about the harmful effects of fingolimod to a foetus should be provided

- ☐ Women of childbearing potential (including adolescents and their parents/legal representatives/caregivers) must be informed regularly about the serious risks of fingolimod to a foetus. Pregnancy tests must be repeated at suitable intervals

- ☐ To help determine the effects of fingolimod exposure in pregnant patients with Multiple Sclerosis (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.
- ☐ Perform skin examination every 6 to 12 months and consider a referral to a dermatologist if suspicious lesions are detected

  • Caution patients against exposure to sunlight without protection

  • Instruct patients to avoid concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy

- ☐ Consider suspending fingolimod and re-evaluate the benefit-risk to the patient of any subsequent re-initiation.

Additional Guidance for paediatric patients aged at least 10 years

All warnings, precautions and monitoring in adults also apply to paediatric patients. In addition:

Prior to initiating treatment

- ☐ Ensure that vaccination status is up to date before starting fingolimod
- ☐ Assess physical development (Tanner staging), and measure height and weight, as per standard of care

During treatment

- ☐ 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*
- ☐ Monitor the patient for signs and symptoms of depression and anxiety

*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.