Fingolimod SUN Physician's checklist

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. You can report side effects to your doctor, or directly at www.tga.gov.au/reporting-problems.

- **Monitoring requirements at treatment initiation:**

Before first dose

- Perform baseline ECG prior to the first dose of FINGOLIMOD;
- Perform blood pressure measurement prior to the first dose of FINGOLIMOD;
- Perform a liver function test prior to (within 6 months) treatment initiation;
- Arrange ophthalmological assessment before starting FINGOLIMOD treatment in patients with diabetes mellitus or with a history of uveitis;
- A negative pregnancy test result must be confirmed prior to starting treatment

Until 6 hours after first dose

- Monitor the patient for 6 hours after the first dose of FINGOLIMOD has been administered for signs and symptoms of bradycardia, including hourly pulse and blood pressure checks. Continuous (real time)ECG monitoring is recommended;
- Perform an ECG at the end of the 6-hour monitoring period.

>6 to 8 hours after first dose

- If, at the 6-hour time point, the heart rate is at the lowest value following the first dose, extend heart rate monitoring for at least 2 more hours and until the heart rate increases again.

- **Recommendation for re-initiating FINGOLIMOD therapy after treatment interruption:**

The same first dose monitoring as for treatment initiation is recommended 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 at least 1 month of treatment.

- **Recommendation for overnight monitoring after the first dose (or if the first dose monitoring applies during treatment re-initiation):**

- Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients requiring pharmacological intervention during monitoring at treatment initiation/reinitiation. Repeat the first dose monitoring after the second dose of FINGOLIMOD;
- Extend heart rate monitoring for at least overnight in a medical facility and until resolution of findings in patients:
  - With third degree AV block occurring at any time;

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- Where at the 6-hour time point:
  a. Heart rate <45 bpm, <55 bpm in paediatric patients aged 12 years old and above, or <60 bpm in paediatric patients 10 to below 12 years of age;
  b. New onset second degree or higher AV block;
  c. QTc interval >500 msec.

- **FINGOLIMOD is contraindicated in patients with:**

  - 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);
  - In the previous 6 months, 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 antiarrhythmic drugs;
  - 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 not using effective Contraception
  - Hypersensitivity to the active substance or to any of the excipients.

- **FINGOLIMOD is not recommended in patients with:**

  - Sino-atrial heart block;
  - QTc prolongation >470 msec (adult females), QTc >460 msec (paediatric females) or >450 msec (adult and paediatric males);
  - History of cardiac arrest;
  - Severe sleep apnea;
  - History of symptomatic bradycardia;
  - History of recurrent syncope;
  - Uncontrolled hypertension;

If FINGOLIMOD treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to determine appropriate monitoring, at least overnight extended monitoring is recommended.

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- FINGOLIMOD is not recommended in patients concomitantly taking medicines known to decrease the heart rate. If FINGOLIMOD treatment is considered in these patients anticipated benefits must outweigh potential risks and a cardiologist must be consulted to switch to non-heart-rate-lowering therapy or, if not possible, to determine appropriate monitoring. At least overnight extended monitoring is recommended;
- FINGOLIMOD reduces peripheral blood lymphocyte counts. Peripheral lymphocyte count (CBC) should be checked in all patients prior to initiation (within 6 months or after discontinuation of prior therapy) and monitored during treatment with FINGOLIMOD. Treatment should be interrupted if lymphocyte count is confirmed as <0.2x109/L. The approved dosing of 0.5 mg once daily (or 0.25 mg once daily in paediatric patients 10 years of age and above with a body weight of ≤40 kg) when restarting Fingolimod should be administered. Other dosing regimens have not been approved.
- 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 fungoides) and other malignancies, particularly those of the skin. Surveillance should include vigilance for both skin malignancies and mycosis fungoides. 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.
    - Treatment initiation in patients with severe active infection should be delayed until the infection is resolved. Suspension of treatment during serious infections should be considered. Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered 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.
- Vigilance for basal cell carcinoma and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merckel cell carcinoma is recommended, with skin examination prior to treatment initiation and then every 6 to 12 months taking into consideration clinical judgement. Patients should be referred to a dermatologist if suspicious lesions are detected. Caution patients against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.
- Specific recommendations regarding vaccination for patients initiating or currently on FINGOLIMOD treatment.
    - 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.
- Patients should be instructed to report signs and symptoms of infections immediately to their prescriber during and for up to two months after treatment with FINGOLIMOD;
    - Prompt diagnostic evaluation should be performed in patient with symptoms and signs consistent with cryptococcal meningitis; appropriate treatment, if diagnosed, should be initiated.

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- 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.
- Cases of progressive multifocal leukoencephalopathy (PML) have occurred after approximately 2-3 years of monotherapy treatment although an exact relationship with the duration of treatment is unknown.
- Physicians should be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment with FINGOLIMOD should be suspended until PML has been excluded.
- Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported in the post-marketing setting. Cancer screening, including Pap test, and vaccination for HPV-related cancer is recommended for patients, as per standard of care.

- A full ophthalmological assessment should be considered:
  - 3-4 months after starting FINGOLIMOD therapy for the early detection of visual impairment due to drug induced macular edema;
  - During treatment with FINGOLIMOD in patients with diabetes mellitus or with a history of uveitis.

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 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, FINGOLIMOD must be discontinued. When stopping 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 FINGOLIMOD treatment and ultrasonography examinations should be performed.
- FINGOLIMOD must be stopped 2 months before planning a pregnancy.

- Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported. Therefore, liver function should be monitored carefully.
  - Before initiation of treatment, recent (i.e. within last 6 months) transaminase and bilirubin levels should be available;
  - 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;

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  - During treatment, 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.

- The approved dosing of 0.5 mg daily (or 0.25 mg once daily in paediatric patients 10 years of age and above with a body weight of ≤40 kg) should be administered. Other dosing regimens have not been approved.
- In the post-marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping fingolimod. The possibility of recurrence of exceptionally high disease activity should be considered.
- Cases of seizure, including status epilepticus, have been reported. Physicians should be vigilant for seizures and especially in those patients with underlying conditions or with a pre-existing history or family history of epilepsy.
- Physicians should reassess on an annual basis the benefit of FINGOLIMOD treatment versus risk in each patient, especially paediatric patients.
- Physicians should provide patients/parents/caregivers with the patients/parents/caregiver's guide and with the pregnancy-specific patient reminder card.

The safety profile in paediatric patients is similar to adults and therefore the warnings and precautions in adults also apply for paediatric patients.

Specifically with paediatric patients, physicians should also:

  - Assess Tanner staging and measure height and weight as per standard of care;
  - Perform cardiovascular monitoring;
  - Take precautions when the first dose is administered / patients are switched from 0.25 to 0.5 mg daily, due to the potential for bradyarrhythmia;
  - Monitor the patient for sign and symptoms of depression and anxiety;
  - Emphasize treatment compliance and misuse to patients, especially about treatment interruption and the importance of repeating cardiovascular monitoring;
  - Emphasize FINGOLIMOD immunosuppressive effects;
  - Consider a complete vaccination schedule before starting FINGOLIMOD;
  - Provide guidance on seizure monitoring.

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