Prescriber’s Checklist:
Summary of Recommendations
INDICATION

GILENYA® (Fingolimod) is indicated as monotherapy for the treatment of adult patients and paediatric patients of 10 years of age and above with the relapsing-remitting form of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the progression of physical disability.

Considerations in GILENYA® (Fingolimod)

Patient Selection

Fingolimod is suitable for adult and pediatric patients (10 years of age and above) for the treatment of 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 4 for more information. Caution regarding potential additive immune effects is required when switching patients from other disease modifying therapies to fingolimod.

Contraindications

• Known immunodeficiency syndrome
• Patients with increased risk for opportunistic infections (including immunocompromised patients)
• Severe active infections, active chronic infections
• Known active malignancies, except for patients with cutaneous basal cell carcinoma
• Severe liver impairment
• Patients who in the last 6 months had myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure, 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 wear a pacemaker)
• Patients with a baseline QTc interval of ≥500 msec
• Known hypersensitivity to the active substance or to any of the excipients.

The following patients should not be treated with fingolimod

• Those who are pregnant (all women of child bearing potential should be advised of the importance of contraception)
• Those who are breast-feeding

Not recommended

Consult cardiologist regarding appropriate first-dose monitoring

Consult cardiologist regarding possibility of switching to non-heart-rate–lowering drugs

Consult cardiologist regarding appropriate first-dose monitoring

Sino-atrial heart block, history of symptomatic bradycardia or recurrent syncope, significant QT-interval prolongation, history of cardiac arrest, uncontrolled hypertension or severe untreated sleep apnoea.

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†, or other substances that are known to lower the heart rate§

If change in medication is not possible, extend monitoring to at least overnight following the first dose.

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* RRMS=relapsing-remitting multiple sclerosis.
† QTc .470 msec (adult females), >460 msec (pediatric females), or >450 msec (adult and pediatric males)
‡ Includes verapamil or diltiazem.
§ Includes Class Ia and Class III antiarrhythmics, ivabradine, digoxin, anticholinesteratic agents, or pilocarpine.
Physician Checklist – 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.

<table>
<thead>
<tr>
<th>Prior to initiating treatment</th>
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<tbody>
<tr>
<td>□ Confirm that contraindications to the use of fingolimod are absent</td>
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<tr>
<td>□ Treatment with fingolimod is not recommended in the following patients, unless anticipated benefits outweigh the potential risks:</td>
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<td>□ For pediatric patients, assess Tanner staging, measure height and weight, and consider a complete vaccination schedule, as per standard of care</td>
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<tr>
<td>□ Ensure patients are not concomitantly taking Class Ia or Class III antiarrhythmic medicines</td>
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<tr>
<td>□ Conduct baseline electrocardiogram (ECG) and blood pressure (BP) measurement</td>
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<tr>
<td>□ Avoid co-administration of anti-neoplastic, immunomodulatory or immunosuppressive therapies due to the risk of additive immune system effects. For the same reason, corticosteroids should be co-administered with caution. Specific decisions as to the dosage and duration of treatment with corticosteroids should be based on clinical judgment. Caution should also be applied when switching patients from long-acting therapies with immune effects such as natalizumab or mitoxantrone</td>
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<tr>
<td>□ Obtain recent (within 6 months) transaminase, and bilirubin levels</td>
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<tr>
<td>□ Obtain recent (within 6 months or after discontinuation of prior therapy) full blood count</td>
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<tr>
<td>□ Confirm a negative pregnancy test result in women of child-bearing potential, including female adolescents</td>
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<tr>
<td>□ Inform women of child-bearing potential, including female adolescents, their parents and caregivers, about the serious risks of fingolimod to the foetus and the need for avoiding pregnancy and for effective contraception during treatment and for at least 2 months after treatment discontinuation</td>
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<tr>
<td>□ Delay initiation of treatment in patients with severe active infection until resolved</td>
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<td>□ 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</td>
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<tr>
<td>□ 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</td>
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<tr>
<td>□ Conduct an ophthalmologic evaluation in patients with history of uveitis or diabetes mellitus</td>
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<tr>
<td>□ 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</td>
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<tr>
<td>□ Exercise caution in using fingolimod in patients with a history of significant liver disease</td>
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<tr>
<td>□ Provide patients with the Patient Medication Guide and the Pregnancy-Specific Patient Reminder Card</td>
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</tbody>
</table>

*QTc >470 msec (adult females), >460 msec (pediatric females), or >450 msec (adult and pediatric males).
Treatment initiation algorithm

All patients, including pediatric 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 pediatric patients when the dosage is switched from 0.25 mg to 0.5 mg fingolimod once daily*

This procedure 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 for this group.

Monitor for a minimum of 6 hours

- Perform baseline ECG and BP measurement prior to dosing
- Monitor for a minimum of 6 hours for signs and symptoms of bradycardia, with hourly HR and BP checks. If patient is symptomatic, initiate appropriate clinical management and continue monitoring until resolution
  - Continuous (real-time) ECG is recommended throughout the 6-hour period
- Perform ECG and BP measurement at 6 hours after the first dose

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

YES

NO

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

YES

NO

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

- HR < 45 bpm in adults, HR < 55 bpm in paediatric patients, 12 years of age and above
- HR < 60 bpm in pediatric patients aged 10 to ≤12 years of age
- ECG shows new-onset second-degree or higher AV block or QTc interval ≥500 msec

NO

YES

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

YES

NO

First-dose monitoring is complete.

NO

YES

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

Monitor overnight in a medical facility. The first-dose monitoring should be repeated after the second dose of fingolimod.

Extend monitoring at least overnight, until the findings have resolved.

BP = blood pressure; ECG = electrocardiogram; HR = heart rate; QTc = heart-rate–corrected QT interval.

* For pediatric 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.
During treatment

- Conduct a full ophthalmologic evaluation at 3 to 4 months after starting treatment
  - Conduct periodic ophthalmologic evaluations in patients with history of uveitis or diabetes mellitus
  - Counsel patients to report any visual disturbance during treatment immediately
  - 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
  - Prompt antimicrobial treatment should be initiated if indicated
  - Perform prompt diagnostic evaluation in patients with symptoms and signs consistent with cryptococcal meningitis, and initiate appropriate treatment if diagnosed
  - 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
  - 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 <0.2x10⁹/L*

- Monitor blood pressure regularly during treatment

- Check liver transaminases at months 1, 3, 6, 9, and 12 and periodically thereafter, or at any time there are signs or symptoms of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine
  - Monitor more frequently, including serum bilirubin and alkaline phosphatase (ALP) measurement, if liver transaminases rise above 5 times the ULN, and interrupt treatment if liver transaminases remain elevated above this level until recovery*

- 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 with GILENYA® (Fingolimod), women should not become pregnant and effective contraception is recommended during treatment and for 2 months after stopping treatment. Pregnancy tests should be repeated at suitable intervals and medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment. Discontinue GILENYA® (Fingolimod) if a patient becomes pregnant. GILENYA® (Fingolimod) should be stopped 2 months before planning a pregnancy, and the possible return of disease activity after treatment discontinuation should be considered. Due to the potential for serious adverse reactions to GILENYA® (Fingolimod) in nursing infants, women receiving fingolimod should not breastfeed.
  - 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 Novartis by dialing +65 6722 6010 or visiting www.novartis.com, in order to allow monitoring of these patients through the Pregnancy Outcomes Intensive Monitoring Program (PRIM). Physicians may also enroll a pregnant MS patient under their care in the fingolimod pregnancy registry by visiting https://www.gilenyapregnancyregistry.com/

- 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

*Approved dose of 0.5 mg once daily (or 0.25 mg once daily in pediatric 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.
### During treatment

- Fingolimod has an immunosuppressive effect and can increase the risk of developing lymphomas (including mycosis fungoids), and other malignancies (particularly those of the skin), and serious opportunistic infections. Surveillance should include vigilance for both skin malignancies and mycosis fungoids. Closely monitor patients during treatment, especially those with concurrent conditions, or known factors, such as previous immunosuppressive therapy; and discontinue treatment if a risk is suspected.

- 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.

- Reassess on an annual basis the benefit of fingolimod treatment versus risk in each patient, especially pediatric patients.

### 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 one month of treatment

- Counsel patients to report signs and symptoms of infection immediately for up to 2 months after discontinuation.

- Inform women of child-bearing potential, including female adolescents, their parents, and caregivers, that effective contraception is needed for 2 months after discontinuation.

- In case of pregnancy (intended or unintended) during treatment, or in 2 months after stopping treatment with GILENYA® (Fingolimod), medical advice should be given regarding the risk of harmful effects to the foetus associated with fingolimod treatment and medical follow-up examination (e.g. ultrasonography examination) should be performed.

- Vigilance for the possibility of severe exacerbation of disease following discontinuation of treatment is recommended:
  - In cases of severe exacerbation appropriate treatment should be initiated as required.

### Summary guidance specifically for pediatric patients

- Consider a complete vaccination schedule before starting GILENYA® (Fingolimod).

- Counsel patients and their parents/caregivers on GILENYA®'s (Fingolimod) 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 pediatric patients when the dosage is switched from 0.25 mg to 0.5 mg GILENYA® (Fingolimod) once daily.

- Emphasize the importance of treatment compliance to patients, 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 female adolescent patients of child bearing potential and their parents/caregivers.

*For pediatric patients (≥10 years old), the approved dosing for GILENYA® (Fingolimod) is 0.25 mg once daily for patients weighing ≤40 kg, and 0.5 mg once daily for patients weighing >40 kg.