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 post-marketing 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, fingolomod should be suspended and appropriate treatment should be initiated. A multidisciplinary consultation (i.e. infectious disease specialist) should be undertaken if re-initiation of Gilenya 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 Gilenya at any time during treatment. If herpes encephalitis, meningitis or meningoencephalitis occur, Gilenya should be discontinued and appropriate treatment for the respective infection should be administered
  - Progressive multifocal leukoencephalopathy (PML) has been reported under Gilenya 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 Gilenya 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 $<0.2 \times 10^9$/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 Gilenya 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, Gilenya 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), Gilenya 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. Treatment must be discontinued if a women becomes pregnant. Gilenya 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 (WOCBP) (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
  - WOCBP (including female adolescents and their parents/caregivers) must be informed about the serious risks of Gilenya to the foetus
  - Ensure WOCBP (including female adolescents and their parents/caregivers) receive regular counselling facilitated by the Pregnacy-Specific Patient Reminder Card
  - To help determine the effects of Gilenya exposure in pregnant women with MS, physicians are encouraged to report pregnant patients who may have been exposed to Gilenya at any time during pregnancy (from 8 weeks prior to last menstrual period onwards) to Novartis by dialing **1800 554 631** or emailing **gpr@outcome.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 Gilenya pregnancy registry by dialing **1800 554 631** or emailing **gpr@outcome.com**
- ☐ Vigilance for basal cell carcinoma and other cancerous neoplasms, including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma, is recommended with skin examinations 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
- ☐ Gilenya 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 Gilenya 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 one 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.
- ☐ Inform women of child-bearing potential (including female adolescents and their parents/caregivers) that effective contraceptive must be used for 2 months after discontinuation of treatment.
- ☐ In case of pregnancy (intended or unintended) during treatment, or in the 2 months after stopping treatment with GILENYA®, medical advice should be given regarding the risk of harmful effects to the foetus associated with Gilenya treatment and ultrasonography examinations should be preformed
- ☐ Advise women who stop treatment with Gilenya because they are planning a pregnancy that their disease activity may return
- ☐ 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 paediatric patients

- ☐ Consider a complete vaccination schedule before starting Gilenya
- ☐ Counsel patients and their parents/caregivers on Gilenya's immunosuppressive effects
- ☐ Assess physical development (Tanner staging), and measure height and weight, as per standard of care
- ☐ Perform cardiovascular monitoring
- ☐ Perform first-dose cardiovascular monitoring on treatment initiation due to the risk of bradyarrhythmia
- ☐ Repeat first-dose cardiovascular monitoring in paediatric patients when the dosage is switched from 0.25 mg to 0.5 mg Gilenya once daily*
- ☐ Emphasize the importance of treatment compliance to patients, especially with regard to treatment interruption and the need to repeat first dose cardiovascular monitoring
- ☐ Monitor the patient for signs and symptoms of depression and anxiety
- ☐ 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/caregiver

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

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GILENYA® (fingolimod)

Prescriber's Checklist:
Summary of Recommendations

Reporting suspected adverse reactions of the medicinal products allows continual monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions should be reported via HPRA Pharmacovigilance, website: www.hpra.ie. Adverse events could also be reported to Novartis preferably via www.report.novartis.com or by email: drugsafety.dublin@novartis.com or by calling 01 2080 612.

Date approved by the HPRA: 21st October 2022

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Considerations in GILENYA® (fingolimod) Patient Selection

Gilenya 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 Gilenya is contraindicated or not recommended.

Considerations for treatment initiation

Gilenya 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.

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*.

Contraindications

- Known immunodeficiency syndrome
- Patients with increased risk for opportunistic infections (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, unstable angina pectoris, stroke/transient ischaemic attack, decompensated heart failure (requiring inpatient treatment) or New York Heart Association class III/IV heart failure in the previous six months
- 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) 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
- Pregnant women or women of child-bearing potential (including female adolescents) not using effective contraception
- Hypersensitivity to the active substance or to any of the excipients.

The following patients should not be treated with Gilenya

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

Not recommended

Consider only after performing risk/benefit analysis and consulting a cardiologist

Consult cardiologist regarding appropriate first-dose monitoring

Due to the risk of serious rhythm disturbances, Gilenya 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[I] (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 Gilenya should not be used in these patients. In such patients treatment with Gilenya 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, diltiazem), or other substances that are known to lower the heart rate (ivabradine, digoxin, anticholinesteratic agents, or pilocarpine for example).

→ **If change in medication is not possible, extend monitoring to at least overnight**

*GILENYA® 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 multipls 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 compated to a previous recent MRI.
See below for further guidance for women of child-bearing potential.

Physician Checklist–Recommended Steps to Managing Patients on Gilenya

The checklist and schematic that follow are intended to assist in the management of patients on Gilenya. Key steps and considerations while starting, continuing, or discontinuing treatment are provided.

Prior to initiating treatment

- ☐ Ensure patients are not concomitantly taking Class Ia or Class III antiarrhythmic medicines
- ☐ Conduct baseline electrocardiogram (ECG) and blood pressure (BP) measurement
- ☐ Before initiating treatment with Gilenya, a baseline MRI should be available (usually within 3 months) as a reference
- ☐ Treatment with Gilenya is not recommended in the following patients, unless anticipated benefits outweigh the potential risks:
  - Those with sino-atrial heart block, history of symptomatic bradyarrhythmia or recurrent syncope, significant QT-interval prolongation[II], history of cardiac arrest, uncontrolled hypertension, or severe sleep apnoea
    - ☐ *Seek advice from a cardiologist prior to initiation of treatment 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 regarding 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
- ☐ 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 pharmacodynamics effect of Gilenya is a dose dependent reduction of the peripheral lymphocyte count to 20-30% baseline values
- ☐ Gilenya is teratogenic. A negative pregnancy test must be confirmed in women of child-bearing potential, WOCBP, (including female adolescents) prior to starting treatment and repeat at suitable intervals during treatment
- ☐ Inform (including female adolescents and WOCBP their parents/caregivers) about the serious risks of Gilenya to the foetus
- ☐ Provide all patients, parents (or legal representatives) and caregivers with the Pregnancy-Specific Patient Reminder Card
- ☐ Counsel WOCBP (including female adolescents) that they must avoid pregnancy and that they must use effective contraception during treatment and for 2 months after treatment discontinuation. Counseling 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. 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 the Patient/Parent/Caregiver guide

[II] 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 Gilenya once daily*

It should also be followed at re-initiation of treatment if Gilenya 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 Gilenya 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
- ☐ 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?

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

NO ↓

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

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, <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 ≥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 the heart rate increases

NO ↓

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 Gilenya is 0.25 mg once daily for patients weighing ≤40 Kg, and 0.5 mg once daily for patients weighing >40 kg.