Physician's checklist:

Summary of recommendations

NOVARTIS

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Considerations in Gilenya® (fingolimod) patient selection

Gilenya is suitable for adult and pediatric patients (≥10 years old) for the treatment of highly active relapsing remitting MS (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 atrioventricular (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 pediatric 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 immunocompromised patients), severe active infections, active chronic infections, known active malignancies, severe liver impairment, severe cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs, patients with second-degree Mobitz type II 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, patients who in the previous 6 months had myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure, or New York Heart Association class III/IV heart failure, pregnant women, women of child-bearing potential (WOCBP; including female adolescents) not using effective contraception, and patients with hypersensitivity to the active substance or to any of the excipients.

The following patients should not be treated with Gilenya

- Women who are breast-feeding

Not recommended

Consider 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.	**At least overnight extended monitoring is recommended** **Consult cardiologist regarding appropriate first-dose monitoring**
Taking beta-blockers, heart-rate–lowering calcium channel blockers‡, or other substances that are known to lower the heart rate§.	**Consult cardiologist regarding possibility of switching to non-heart-rate-lowering drugs** **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 pediatric 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.
†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.

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

- ☐ 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 bradycardia or recurrent syncope, significant QT-interval prolongation*, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnea
    - ☐ Seek advice from a cardiologist regarding 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 (e.g. verapamil or diltiazem), or other substances which may decrease heart rate (e.g. ivabradine, digoxin, anticholinesteratic agents, or 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 pediatric 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 (BP) measurement
- ☐ 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
- ☐ Perform a liver function test prior to (within 6 months) treatment initiation.
- ☐ Obtain recent (within 6 months or after discontinuation of prior therapy) full blood count
- ☐ Inform WOCBP (including female adolescents and their parents/caregivers) that Gilenya is contraindicated in pregnant women and WOCBP not using effective contraception
- ☐ Gilenya is teratogenic. Confirm a negative pregnancy test result in WOCBP (including female adolescents) prior to starting treatment and repeat at suitable intervals during treatment
- ☐ Inform WOCBP (including female adolescents and their parents/caregivers) about the serious risks of Gilenya to the fetus
- ☐ Provide all patients, parents (or legal representatives) and caregivers with the Pregnancy-Specific Patient Reminder Card
- ☐ Counsel WOCBP (including female adolescents and their parents/caregivers) to avoid pregnancy and use effective contraception both 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 patients, parents and caregivers with the Patients, Parent's and Caregiver's Guide

*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 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?

▼ NO

▶ YES

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

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

▼ NO

▶ YES

Extend monitoring at least overnight, until the findings have resolved

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

☐ HR <45 bpm, <55 bpm in pediatric patients aged ≥12 years old, or <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

Extend monitoring at least overnight, until the findings have resolved

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

▼ NO

▶ YES

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

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First-dose monitoring is complete

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

During treatment

- ☐ A full ophthalmologic assessment should be considered:
  - 3–4 months after starting treatment for the early detection of visual impairment due to drug-induced macular edema
  - During treatment in patients with diabetes mellitus or with a history of uveitis
- ☐ 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
    - 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
  - Be vigilant for clinical symptoms or MRI findings suggestive of PML. If PML is suspected, treatment with Gilenya should be suspended until PML has been excluded
    - Cases of PML have occurred after approximately 2–3 years of monotherapy treatment although an exact relationship with the duration of treatment is unknown
  - 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 $<0.2x10^9/L$*
- ☐ 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
  - Monitor more frequently 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, women should not become pregnant. Discontinue treatment if a woman becomes pregnant. Medical advice should be given regarding the risk of harmful effects to the foetus associated with treatment and ultrasonography examinations should be performed. Gilenya should be stopped 2 months before planning a pregnancy, and the possible return of disease activity after treatment discontinuation should be considered. An ultrasonography examination should be performed and medical advice about the harmful effects of Gilenya to the fetus should be provided.
- ☐ Advise WOCBP (including female adolescents and their parents/caregivers) that effective contraception must be used during treatment and for at least 2 months after treatment discontinuation. Pregnancy tests must be repeated at suitable intervals
- ☐ WOCBP (including female adolescents and their parents/legal representatives/caregivers) must be informed regularly about the serious risks of Gilenya to the fetus
- ☐ Ensure WOCBP (including female adolescents), their parents (or legal representatives), and caregivers receive regular counseling facilitated by the Pregnancy-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 onward) to Novartis by dialing +356 21222872 or visiting *www.report.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 Gilenya Pregnancy Register by visiting *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
- ☐ Gilenya 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 fungoides. 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
- ☐ Monitor pediatric 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 pediatric patients

*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.

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 meningitis infection and PML
- ☐ Inform WOCBP (including female adolescents and their parents/caregivers) that effective contraception is needed for 2 months after discontinuation because of the serious risks of Gilenya to the fetus
- ☐ 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 pediatric 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
- ☐ Perfom 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 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 Gilanya is 0.25 mg once daily for patients weighing ≤40 kg, and 0.5 mg once daily for patients weighing >40 kg.

Basic Succinct Statement

GILENYA® (fingolimod)

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.

PRESENTATION:
Hard capsule containing 0.25mg fingolimod (as hydrochloride),
Hard capsule containing 0.5 mg fingolimod (as hydrochloride).

INDICATIONS: 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 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.

DOSAGE AND ADMINISTRATION: Treatment should be initiated and supervised by a physician experienced in multiple sclerosis. In adults, the recommended dose is one 0.5 mg capsule to be taken orally once daily. In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight. Paediatric patients with body weight ≤40kg: one 0.25mg capsule taken orally once daily. Paediatric patients with body weight more than 40kg: one 0.5mg capsule taken orally once daily. Paediatric patients who start on 0.25mg capsules and subsequently reach a stable body weight above 40kg should be switched to 0.5mg capsules. When switching from a 0.25mg to a 0.5mg daily dose, it is recommended to repeat the same first dose monitoring as for treatment initiation. Gilenya can be taken with or without food. The capsules should always be swallowed intact without opening them. Use with caution in patients aged 65 years and over. Safety and efficacy of Gilenya in children below 10 years has not been established. The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for: 1 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. If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

CONTRAINDICATIONS: 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), active malignancies, severe liver impairment (Child-Pugh class C), patients who in the previous 6 months had myocardial infection, unstable angina pectoris, stroke, transient ischaemic attack, decompensated heart failure, New York Heart Association class III/IV heart failure, patients with severe cardiac arrhythmias requiring anti-arrythmic treatment with class 1a or class III anti-arrhythmic medicinal products, patients with second-degree Mobitz type II atrioventricular block or third-degree AV block, or sick-sinus syndrome, if they do not wear a pacemaker, patients with a baseline QTc interval ≥500msec, during pregnancy and in women of childbearing potential not using effective contraception, hypersensitivity to the active substance or to any of the excipients.

WARNINGS/PRECAUTIONS: ♦Bradyarrhythmia: Initiation of treatment results in a transient decrease in heart rate which may be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete AV block. After the first dose, the decline in heart rate starts within one hour and is maximal within 6 hours. This post-dose effect persists over the following days, although usually to a milder extent, and usually abates over the next weeks. With continued administration, the average heart rate returns towards baseline within one month. However individual patients may not return to baseline heart rate by the end of the first month. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. If necessary, the decrease in heart rate induced by fingolimod can be reversed by parenteral doses of atropine or isoprenaline. All patients should have an ECG and blood pressure measurement performed prior to and 6 hours after the first dose of Gilenya. All patients should be monitored for a period of 6 hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurement. Continuous (real time) ECG monitoring during this 6 hour period is recommended. The same precautions as for the first dose are recommended when patients are switched from the 0.25mg to the 0.5mg daily dose. In the event of bradyarrhythmia-related symptoms, initiate appropriate clinical management and monitoring until symptoms resolve. Should a patient require pharmacological intervention during the first-dose monitoring, overnight monitoring in a medical facility should be instituted and the first-dose monitoring should be repeated after the second dose of Gilenya. If the heart rate at 6 hours is the lowest since the first dose was administered (suggesting that the maximum pharmacodynamic effect on the heart may not yet be manifest), monitoring should be extended by at least 2 hours and until heart rate increases again. Additionally, if after 6 hours, the heart rate is <45 bpm in adults, <55 bpm in paediatric patients aged 12 years and above, or <60 bpm in paediatric patients aged 10 to below 12 years, or the ECG shows new onset second degree or higher grade AV block or a QTc interval ≥500 msec, extended monitoring (at least overnight monitoring), should be performed, and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring (at least overnight monitoring). Very rare cases of T-wave inversion have been reported in adults. In case of T-wave inversion, the prescriber should ensure that there are no associated myocardial ischaemia signs or symptoms. If myocardial ischaemia is suspected, it is recommended to seek advice from cardiologist.The same precautions apply if Gilenya is discontinued for more than 2 weeks. Due to the risk of serious rhythm disturbances or significant bradycardia, Gilenya should not be used in patients with sino-atrial heart block, a history of symptomatic bradycardia, recurrent syncope or cardiac arrest or in patients with significant QT prolongation (QTc>470msec (adult female), QTc>460 msec [paediatric female] or >450msec [adult and paediatric male]) uncontrolled hypertension or severe sleep apnoea. In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks and advice from a cardiologist sought prior to initiation of treatment in order to determine the most appropriate monitoring, at least overnight extended monitoring is recommended for treatment initiation. Gilenya

should not be used concomitantly with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Since the initiation of Gilenya treatment is also associated with slowing of the heart rate, concomitant use of heart-rate lowering substances during Gilenya initiation may be associated with severe bradycardia and heart block. In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment with Gilenya is considered, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products prior to initiation of treatment. If the heart-rate-lowering medication cannot be stopped, cardiologist's advice should be sought to determine appropriate first dose monitoring, at least overnight extended monitoring is recommended.♦Avoid medicinal products that may prolong QTc interval. ♦ Immunosuppressive effects: 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 and other malignancies, particularly those of the skin. 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 (refer to SmPC).♦*Infections*: Reduction of the lymphocyte count to 20-30% of baseline values occurs with Gilenya. Perform a complete blood count (CBC) at baseline and periodically during treatment, and in case of signs of infection, stop Gilenya until recovery if absolute lymphocyte count $<0.2x10^9$/L is confirmed. Consider VZV vaccination of patients without a history of chickenpox or VZV antibody negative patients prior to commencing Gilenya. Gilenya may increase the risk of infections, including opportunistic infections. Cases of cryptococcal meningitis, sometimes fatal have been reported after 2-3 years of treatment. Patients with symptoms and signs consistent with cryptococcal meningitis should undergo prompt diagnostic evaluation. Employ effective diagnostic and therapeutic strategies in patients with symptoms of infection while on Gilenya and for 2 months after discontinuation. Progressive multifocal leukoencephalopathy (PML) has been reported under fingolimod treatment. Before initiating treatment with fingolimod, a baseline MRI should be available (usually within 3 months) as a reference. During routine MRI (in accordance with national and local recommendations), physicians should pay attention to PML suggestive lesions. Human Papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with fingolimod in post-marketing setting. Vaccination should be considered prior to treatment initiation with fingolimod due to its immunosuppressive properties taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care. ♦*Macular oedema*: Macular oedema with or without visual symptoms has been reported in patients taking Gilenya. Perform an ophthalmological evaluation 3-4 months after Gilenya initiation. Evaluate the fundus, including the macula in patients reporting visual disturbances. Perform ophthalmological evaluation prior to initiating therapy and periodically thereafter in patients with diabetes mellitus or a history of uveitis. Discontinue Gilenya if a patient develops macular oedema. ♦*Liver function*: Delay Gilenya initiation in patients with active viral hepatitis until resolution. Recent transaminase and bilirubin levels should be available before initiation of Gilenya. Increased hepatic enzymes, in particular alanine aminotransaminase (ALT) but also gamma glutamyltransferase (GGT) and aspartate transaminase (AST) have been reported in multiple sclerosis patients treated with Gilenya. Transaminase elevations, monitor liver transaminases at months 1, 3, 6, 9 and 12 and periodically thereafter. Institute more frequent monitoring if transaminases rise above 5 times the ULN, including serum bilirubin and alkaline phosphatase (ALP) measurement. Stop Gilenya treatment with repeated confirmation of liver transaminases above 5 times the ULN and only re-commence once liver transaminase values have normalised. Patients with symptoms of hepatic dysfunction should have liver enzymes checked and discontinue Gilenya if significant liver injury is confirmed. Resume Gilenya only if another cause of liver injury is determined and if the benefits of therapy outweigh the risks. Exercise caution with Gilenya use in patients with a history of significant liver disease. ♦*Serological testing*: Peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with Gilenya. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes. ♦*Blood pressure effects*: Gilenya can cause a mild increase in blood pressure. Monitor blood pressure regularly during Gilenya treatment. ♦*Respiratory effects*: Use Gilenya with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease due to minor reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (DLCO). ♦*Prior immunosuppressant treatment*: No washout is necessary when switching patients from interferon or glatiramer acetate to Gilenya assuming any immune effects (e.g. neutropenia) have resolved. Exercise caution when switching patients from natalizumab to Gilenya owing to the long half life of natalizumab and concomitant immune effects. ♦*Stopping therapy*: Gilenya is cleared from the circulation in 6 weeks. Caution is indicated with the use of immunosuppressants soon after the discontinuation of Gilenya due to possible additive effects on the immune system. The combination of fingolimod with potent CYP450 inducers should be used with caution. Concomitant administration with St John's wort is not recommended. Patients need to be assessed for their immunity to varicella (chickenpox) prior to Gilenya treatment. It is recommended that patients without a health care professional confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo antibody testing to varicella zoster virus (VZV) before initiating Gilenya therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with Gilenya. Initiation of treatment with Gilenya should be postponed for 1 month to allow full effect of vaccination to occur. Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported at the 0.5 mg dose in clinical trials and in the post-marketing setting. Symptoms reported included sudden onset of severe headache, nausea, vomiting, altered mental status, visual disturbances and seizure. ♦Symptoms of PRES are usually reversible but may evolve into ischaemic stroke or cerebral haemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, Gilenya should be discontinued.♦ *Cutaneous Neoplasms*: Basal cell carcinoma and other cutaneous neoplasms have been reported in patients receiving Gilenya. Vigilance for skin lesions is warranted together with a medical evaluation of the skin at initiation, and then every 6 to 12 months since there is a potential risk of malignant skin growths, patients treated with fingolimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy. 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. If discontinuation of Gilenya is deemed necessary, patients should be monitored during this time for relevant signs of a possible rebound. ♦ Women of childbearing potential: due to risk to the foetus, fingolimod is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for 2 months after treatment discontinuation. ♦Tumefactive lesions: rare cases of tumefactive lesions associated with MS relapse were reported in the post-marketing setting. In case of severe relapses, MRI should be performed to exclude tumefactive lesions. Discontinuation of Gilenya should be considered by the physician on a case-by-case basis taking account individual benefits and risks. ♦Return of disease activity after fingolimod discontinuation: caution indicated upon stopping fingolimod therapy. ♦Paediatric population: the safety profile in paediatric patients is similar to that in adults and the warnings and precautions for adults therefore apply to paediatric patients. Refer to SmPC for all details.

INTERACTIONS: Anti-neoplastic, immunosuppressive or immune-modulating therapies should not be co-administered due to the risk of additive immune system effects. Exercise caution when switching patients from long-acting therapies with immune effects, e.g. natalizumab, teriflunomide or mitoxantrone. No increased rate of infection was seen with concomitant treatment of relapses with a short course of corticosteroids. Vaccination may be less effective during and for up to 2 months after Gilenya treatment. Avoid use of live attenuated vaccines due to infection risk. Due to potential additive effects on heart rate, treatment should not be initiated in patients receiving beta blockers, or class Ia and III antiarrhythmics, calcium channel blockers like ivabradine, verapamil or diltiazem, digoxin, anticholinesteratic agents or pilocarpine. If treatment with Gilenya is considered in such patients, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products or appropriate monitoring for treatment initiation, at least overnight monitoring is recommended, if the heart-rate-lowering medication cannot be stopped.Caution is indicated with substances that may inhibit CYP3A4. Co-administration of fingolimod with ketoconazole increases fingolimod exposure. No interaction has been observed with oral contraceptives when co-administered with fingolimod.

ADVERSE REACTIONS: *Very common (≥1/10);* sinusitis, Influenza, headache, cough, diarrhoea, back pain hepatic enzyme increased*. Common (≥1/100 to <1/10);* herpes viral infections, bronchitis, tinea versicolor, Basal cell carcinoma, lymphopenia, leucopenia, depression, dizziness, migraine, blurred vision, bradycardia, atrioventricular block, hypertension, dyspnoea, eczema, alopecia, pruritus, asthenia, increased blood triglycerides, myalgia, arthralgia. For a full list of adverse reactions please refer to the SmPC.

PREGNANCY AND LACTATION: Fingolimod is contraindicated in women of childbearing potential not using effective contraception. A negative pregnancy test is required before initiation of Gilenya. Female patients must use effective contraception during treatment with Gilenya and for 2 months after discontinuation. Fingolimod should be stopped 2 months before planning a pregnancy. Discontinue Gilenya if a patient becomes pregnant. Fingolimod is excreted into breast milk. Women receiving Gilenya should not breast feed. Fingolimod is not associated with a risk of reduced fertility.

LEGAL CATEGORY: POM.

PACK SIZES: Blister packs containing 28 hard capsules.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

MARKETING AUTHORISATION NUMBERS:
Gilenya 0.25mg: EU/1/11/677/007-008
Gilenya 0.5mg: EU/1/11/677/005.

Please refer to Summary of Product Characteristics (SmPC) before prescribing. Full prescribing information is available on request from Novartis Pharma Services Inc., Representative Office Malta, P.O. Box 4, Marsa, MRS 1000, Malta. Tel: +356 21222872

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Any suspected adverse reactions and medication errors can be reported via the national Adverse Drug Reactions (ADRs) reporting system. Report forms can be downloaded from http://www.medicinesauthority.gov.mt/adrportal and posted to:

Medicines Authority Post-licensing Directorate,
Sir Temi Zammit Buildings,
Malta Life Sciences Park,
San Gwann. SGN 3000.

Or sent by e-mail to postlicensing.medicinesauthority@gov.mt.

Healthcare Professionals may also report any adverse events suspected to be associated with the use of Gilenya to Novartis Pharma Services Inc., Representative Office, Malta, by phone on +356 21222872, by fax on +356 22487219 or e-mail at drug_safety.malta@novartis.com.

Marketing Authorization Holder: Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland.

Local Representative: Novartis Pharma Services Inc., Representative Office Malta.
Tel No.: +356 21222872

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