Prescriber's Checklist:
Summary of Recommendations

GILENYA® (fingolimod)

Considerations in GILENYA® (fingolimod) Patient Selection

GILENYA is suitable for adult patients for the treatment of highly active 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

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 patients 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 (except cutaneous basal cell carcinoma), severe liver impairment, and hypersensitivity to the active substance or to any of the excipients.

The following patients should not be treated with GILENYA

- Those who are pregnant
- Those who are taking Class Ia or Class III antiarrhythmics

Not recommended

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

Consult cardiologist regarding appropriate first-dose monitoring

Bradyarrhythmia†, significant QT-interval prolongation^, severe untreated sleep apnoea, significant cardiovascular disease‡, uncontrolled hypertension, cerebrovascular disease, or recurrent syncope	**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.**

*RRMS=relapsing-remitting multiple sclerosis.

†Bradyarrhythmia includes the following: second-degree Mobitz type II or higher atrioventricular (AV) block, sick sinus syndrome, sinoatrial heart block, history of symptomatic bradycardia.

‡Significant cardiovascular disease includes the following: ischaemic heart disease (including angina pectoris), history of myocardial infarction, congestive heart failure, history of cardiac arrest.

§Includes verapamil, diltiazem, or ivabradine.

‖Includes digoxin, anticholinesteratic agents, or pilocarpine.

^QTc >470 msec (females) or >450 msec (males).

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 measurement
- ☐ Treatment with GILENYA is not recommended in the following patients, unless anticipated benefits outweigh the potential risks:
  - Those with bradyarrhythmia[¶], significant cardiovascular disease[#], significant QT-interval prolongation, uncontrolled hypertension, cerebrovascular disease, severe untreated sleep apnoea, or a history of recurrent syncope
    - ☐ 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 (eg, verapamil, diltiazem, ivabradine), or other substances which may decrease heart rate (eg, 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
- ☐ 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
- ☐ Obtain recent (within 6 months) transaminase, and bilirubin levels
- ☐ Obtain recent (within 6 months or after discontinuation of prior therapy) full blood count
- ☐ Confirm a negative pregnancy test result
- ☐ Counsel on the need for effective contraception in women of childbearing age due to teratogenic risk to foetus
- ☐ Delay initiation of treatment in patients with severe active infection until resolved
- ☐ 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
- ☐ Provide patients with a Patient Reminder Card

[¶]Bradyarrhythmia includes the following: second-degree Mobitz type II or higher AV block, sick sinus syndrome, sinoatrial heart block, history of symptomatic bradycardia.

[#]Significant cardiovascular disease includes the following: ischaemic heart disease (including angina pectoris), history of myocardial infarction, congestive heart failure, history of cardiac arrest.

Treatment initiation algorithm

All patients will need to be monitored for at least 6 hours during treatment initiation, as described in the algorithm below. 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
- ☐ ECG shows new-onset second-degree or higher AV block or QTc interval ≥500 ms

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.

The above first-dose monitoring procedure should also be followed at reinitiation of treatment if GILENYA therapy 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

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

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
  - Evaluate the fundus, including the macula, and discontinue treatment if macular oedema is confirmed
- ☐ Counsel patients to report signs and symptoms of infection
  - 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
  - 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
- ☐ Pregnancy tests should be repeated at suitable intervals. Discontinue treatment if a patient becomes pregnant
  - 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 21222872 or visiting https://psi.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 dialing 80062250

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 for up to 2 months after discontinuation
- ☐ Counsel patients that effective contraception is needed for 2 months after discontinuation

Summary of Prescribing Information

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 0.5 mg fingolimod (as hydrochloride).

INDICATIONS: Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups: Patients with high disease activity despite treatment with a beta-interferon. These patients may be defined as: those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year. 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. One 0.5 mg capsule to be taken orally once daily. Patients can switch directly from beta interferon or glatiramer acetate to Gilenya provided there are no signs of relevant treatment-related abnormalities, e.g. cytopenia. Use with caution in patients aged 65 years and over. Safety and efficacy of Gilenya in children up to 18 years has not been established. No dose adjustments required in patients with mild to severe renal impairment or mild to moderate hepatic impairment. Exercise caution in patients with mild to moderate hepatic impairment. Do not use in patients with severe hepatic impairment (Child-Pugh class C). Use with caution in patients with diabetes mellitus due to an increased risk of macular oedema. 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: 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, except for patients with cutaneous basal cell carcinoma, severe liver impairment (Child-Pugh class C), 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.. 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, 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).

The same precautions apply if Gilenya is discontinued for more than 2 weeks. Due to the risk of serious rhythm disturbances, Gilenya should not be used in patients with second degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope, or in patients with significant QT prolongation (QTc>470msec (female) or >450msec (male)). Since significant bradycardia may be poorly tolerated in patients with known ischaemic heart disease (including angina pectoris), cerebrovascular disease, history of myocardial infarction, congestive heart failure, 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. If treatment is considered, advice from a cardiologist should be 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. Experience with Gilenya is limited in patients receiving concurrent therapy with beta blockers, heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine). Since the initiation of Gilenya treatment is also associated with slowing of the heart rate, concomitant use of these substances during Gilenya initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment with Gilenya should not be initiated in patients who are concurrently treated with these substances. 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.*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. 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.*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*: Do not use Gilenya in patients with severe pre-existing hepatic injury (Child-Pugh class C). 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 (see section 4.8). 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.

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, hepatic enzyme increased (increased alanine transaminase (ALT), Gamma glutamyltransferase, Aspartate transaminase) transaminase elevation, back pain. *Common (≥1/100 to <1/10);* herpes viral infections, bronchitis,, , tinea versicolor, lymphopenia, leucopenia, depression, dizziness, , migraine, blurred vision, bradycardia, atrioventricular block, hypertension, dyspnoea, eczema, alopecia, pruritus, asthenia, increased gamma-glutamyl transferase (GGT), increased hepatic enzymes, abnormal liver function test, increased blood triglycerides, decreased weight. *Uncommon (≥1/1,000 to <1/100);* pneumonia, macular oedema, decreased neutrophil count. Rare: Posterior reversible encephalopathy syndrome (PRES) Very rare cases of haemophagocytic syndrome (HPS) with fatal outcome have been reported in patients treated with fingolimod in the context of an infection. Some cases of disseminated herpes infection, including fatal cases, have been reported even at the 0.5 mg dose. *Unknown*: Hypersensitivity, rash.

PREGNANCY AND LACTATION: There is potential for serious risk to the fetus with Gilenya. 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. 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.

OVERDOSE: Fingolimod can induce bradycardia upon treatment initiation. The decline in heart rate usually starts within one hour of the first dose, and is steepest within 6 hours. The negative chronotropic effect of Gilenya persists beyond 6 hours and progressively attenuates over subsequent days of treatment. There have been reports of slow atrioventricular conduction, with isolated reports of transient, spontaneously resolving complete AV block.If the overdose constitutes first exposure to Gilenya, it is important to monitor patients with a continuous (real time) ECG and hourly measurement of heart rate and blood pressure, at least during the first 6 hours. Additionally, if after 6 hours the heart rate is <45 bpm or if the ECG at 6 hours after the first dose shows second degree or higher AV block, or if it shows a QTc interval ≥500 msec, monitoring should be extended at least for overnight and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring including overnight monitoring.

LEGAL CATEGORY: POM.

PACK SIZES: Blister packs containing 28 hard capsules.

MARKETING AUTHORISATION HOLDER: Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom

MARKETING AUTHORISATION NUMBER: 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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Marketing Authorisation Holder: Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom
Local Representative: Novartis Pharma Services Inc. Representative Office Malta Tel. No. +356 21222872

NOVARTIS
PHARMACEUTICALS

GILENYA®
(fingolimod)

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