Physician's checklist:

Summary of recommendations

Gilenya®
0.25 mg and 0.5 mg hard capsules (fingolimod)

NOVARTIS

Considerations for Gilenya® (fingolimod) patient selection

Gilenya® is indicated as monotherapy for the treatment of adult patients and pediatric 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 for treatment initiation

Gilenya® is contraindicated in patients with cardiac conditions. Do not initiate Gilenya® in patients with cardiac conditions or who are taking medicinal products for which Gilenya® is contraindicated. Refer to the subsection on contraindications for more details.

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.

- ☐ 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 Ia or Class III anti-arrhythmic medicinal products. Fingolimod should not be used concomitantly in these patients

Contraindications

- ☐ Known immunodeficiency syndrome
- ☐ Patients with increased risk for opportunistic infections (including immunocompromised patients)
- ☐ 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)
- ☐ 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 who have concomitant 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

Monitoring requirements

Consider treatment with Gilenya® only after performing risk/benefit analysis and consulting a cardiologist

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

Monitor for a minimum of 6 hours

After first dose and when re-initiating following discontinuation or increase in daily dose

- ☐ 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

* 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.

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

Treatment with Gilenya® is not recommended in the following patients, unless anticipated benefits outweigh the potential risks:

Sino-atrial heart block, history of symptomatic bradycardia or recurrent syncope, significant QTc 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 ☐ Ensure patients are not concomitantly taking Class Ia or Class III antiarrhythmic medicines

Treatment initiation algorithm

☐ 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®
☐ 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
At the end of the monitoring period, did any of the following occur? ☐ HR <45 bpm in adults, <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
☐ 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

First-dose monitoring is complete

† 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.

Recommendations for managing patients on Gilenya®

Key safety assessments and considerations before, during and after discontinuing treatment.

Prior to initiating treatment

- ☐ Confirm that contraindications to the use of Gilenya® are absent (Refer to Page 2 “Contraindications”). Do not initiate Gilenya® in patients with any of these conditions
- ☐ Conduct baseline ECG and BP measurement
- ☐ Obtain recent (within 6 months) transaminase, and bilirubin levels
- ☐ Exercise caution in using Gilenya® in patients with a history of significant liver disease
- ☐ Obtain recent (within 6 months or after discontinuation of prior therapy) full blood count
- ☐ Gilenya® is teratogenic. Confirm a negative pregnancy test result in women of child bearing potential (WOCBP) (including female adolescents) prior to starting treatment and verify the patient’s pregnancy status at suitable intervals during treatment
- ☐ Inform WOCBP (including female adolescents and their parents/caregivers) that Gilenya® should not be used in pregnant women and WOCBP not using effective contraception, and 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
- ☐ 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
- ☐ 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
- ☐ Do not treat with Gilenya® in patients with suspected or confirmed progressive multifocal leukoencephalopathy (PML)
- ☐ Ensure patients have a baseline MRI usually within 3 months before initiating Gilenya®
- ☐ 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 Patient, Parent and Caregiver Medication Guide

During treatment

- [ ] Obtain an ophthalmologic assessment in all patients:
  - 3–4 months after starting treatment for the early detection of visual impairment due to drug-induced macular edema
  - During treatment periodically in patients with diabetes mellitus or with a history of uveitis
  - Counsel patients to report any visual disturbance during treatment immediately. If reported, an evaluation of the fundus, including the macula, should be carried out
  - Discontinue Gilenya® in patients who develop macular edema. Restart only after careful benefit-risk consideration
- [ ] Counsel patients to report signs and symptoms of infection immediately to their prescriber during, and for up to 2 months after treatment with Gilenya® has been discontinued
  - Symptoms such as fever, flu-like symptoms, headache accompanied by stiff neck, sensitivity to light, nausea, shingles and/or confusion, or seizures may be symptoms of meningitis and/or encephalitis
  - Perform prompt diagnostic evaluation in patients with symptoms and signs consistent with encephalitis or meningitis and initiate appropriate treatment if diagnosed
    - Serious, life-threatening, and sometimes fatal cases of encephalitis or meningitis caused by herpes simplex virus (HSV) and VZV were reported while on Gilenya® treatment.
    - Reports of cryptococcal meningitis (sometimes fatal) have been received after approximately 2–3 years of treatment, although an exact relationship with the duration of treatment is unknown
  - Gilenya® should be discontinued in patients with CNS herpes and infections. Gilenya® should be suspended in patients with cryptococcal meningitis with careful consideration with a specialist before reinitiating
  - Inform patients that during Gilenya® treatment and for up to 2 months after discontinuation, they should not receive live attenuated vaccines and that other vaccines may be less effective
  - PML has been predominantly observed after 2 or more years of fingolimod treatment
  - Annual MRIs, or MRI in accordance with national and local recommendations, may be considered especially in patients with multiple risk factors generally associated with PML
  - If PML is suspected, perform a diagnostic MRI immediately and suspend Gilenya® until PML has been excluded. Permanently discontinue Gilenya® if PML is confirmed
  - For potentially serious infections, evaluate the patient promptly and consider an infectious disease referral. Consider suspending Gilenya® and the benefit-risk of any subsequent reinitiation
- [ ] Monitor peripheral blood lymphocyte counts prior to and during treatment with Gilenya®. Interrupt treatment for lymphocyte count $<0.2x10^9$/L until recovery
- [ ] Monitor blood pressure regularly during treatment
- [ ] 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 at months 1, 3, 6, 9, and 12 on therapy and periodically thereafter until 2 months after Gilenya® discontinuation
    - 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
- [ ] For patients with clinical symptoms of liver dysfunction, evaluate promptly and discontinue Gilenya® if significant liver injury is confirmed, i.e. ALT is greater than 3 times the reference range and serum total bilirubin is greater than 2 times the reference range. If serum levels return to normal (including if an alternative cause of the liver dysfunction is discovered), Gilenya® may be restarted if the benefit-risk assessment is favorable for the patient

- [ ] While on treatment with Gilenya®, women should not become pregnant and effective contraception is recommended during treatment and for 2 months after stopping treatment.
    - The patient's pregnancy status should be verified at suitable intervals and medical advice should be given regarding the risk of harmful effects to the fetus associated with treatment. Discontinue Gilenya® if a patient becomes pregnant and perform medical follow up examination (e.g. ultrasonography examination).
    - Gilenya® should be stopped 2 months before attempting to become pregnant, and the possible return of disease activity after treatment discontinuation should be considered.
    - Ensure WOCBP (including female adolescents), their parents (or legal representatives), and caregivers receive regular counseling facilitated by the Pregnancy-Specific Patient Reminder Card
    - Due to the potential for serious adverse reactions to Gilenya® in nursing infants, women receiving fingolimod should not breastfeed.
    - Novartis has put in place a PRegnancy outcomes Intensive Monitoring (PRIM) programme, which is a registry based on enhanced follow-up mechanisms to collect information about pregnancy in patients exposed to fingolimod immediately before or during pregnancy and on infant outcomes 12 months post delivery
    - To help determine the effects of Gilenya® exposure in pregnant women with MS, physicians are encouraged to report cases of pregnancy in patients who may have been exposed to Gilenya® at any time during pregnancy (from 8 weeks prior to last menstrual period onward), regardless of it being associated with an adverse outcome, to Novartis by calling (65) 6019 6483, emailing patientsafety.sg@novartis.com or visiting https://www.novartis.com/report
- [ ] 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
    - Instruct patients to avoid 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
- [ ] Reassess on an annual basis the benefit of Gilenya® treatment versus risk in each patient

After treatment discontinuation

- [ ] 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 or 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
    - In case of pregnancy (intended or unintended) during treatment, or in 2 months after stopping treatment with Gilenya®, medical advice should be given regarding the risk of harmful effects to the fetus 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

All warnings, precautions and monitoring in adults also apply to pediatric patients. In addition:

Prior to initiating treatment

- ☐ Ensure that vaccination status is up to date before starting Gilenya®
- ☐ Assess physical development (Tanner staging), and measure height and weight, as per standard of care

During treatment

- ☐ 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

* 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

Summary of Prescribing Information

Please scan the QR code or visit https://www.novartis.com.sg/product-list/gilenya to access the full prescribing information for Gilenya®.

Gilenya® is a registered trademark of Novartis Pharma AG

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