Gilenya®

0.25 mg and 0.5 mg hard capsules (fingolimod)

Physician's checklist:

Summary of recommendations

NOVARTIS

Considerations in Gilenya® (fingolimod) patient selection

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

- 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. fingolimod should not be used concomitantly with 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
- 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

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**

†QTc >470 msec (adult females), >460 msec (pediatric females), or >450 msec (adult and pediatric males).
‡Includes verapamil or diltiazem.
§Includes ivabradine, digoxin, anticholinesteratic agents, or pilocarpine.

Recommended steps to managing patients on Gilenya®

The checklists 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

- ☐ Confirm that contraindications to the use of Gilenya® are absent
- ☐ 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, 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
- ☐ Obtain recent (within 6 months) transaminase, and bilirubin levels
- ☐ 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 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 women of child bearing potential (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
- ☐ Exercise caution in using Gilenya in patients with a history of significant liver disease

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

☐ 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, Parents and Caregiver Guide and the Pregnancy-Specific Patient Reminder Card

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®

☐ 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, have any of the following criteria been met?

☐ 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

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

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 periodically in patients with diabetes mellitus or with a history of uveitis

– Counsel patients to report any visual disturbance during treatment immediately

– Evaluate the fundus, including the macula, and discontinue treatment if macular oedema is confirmed

☐ Counsel patients to report signs and symptoms of infection immediately to their prescriber during, and for up to 2 months after, treatment

- 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

- Be vigilant for clinical symptoms or MRI findings suggestive of progressive multifocal leukoencephalopathy (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 $<0.2x10^9/L$*

☐ 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

☐ 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*

☐ While on treatment with Gilenya®, women should not become pregnant and effective contraception is recommended during treatment and for 2 months after stopping treatment.

– Pregnancy tests should be repeated at suitable intervals and medical advice should be given regarding the risk of harmful effects to the fetus associated with treatment. Discontinue Gilenya® if a patient becomes pregnant.

– GILENYA® (Fingolimod) should be stopped 2 months before planning a pregnancy, and the possible return of disease activity after treatment discontinuation should be considered.

– 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® (Fingolimod) in nursing infants, women receiving fingolimod should not breastfeed.

– Should a pregnancy occur during treatment with Gilenya® or 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, please report it to Novartis by calling (65) 6722 6409, emailing at patientsafety.sg@novartis.com or visiting https://psi.novartis.com

– 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

*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.

- ☐ 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
- ☐ 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 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 foetus associated with fingolimod treatment and medical follow-up examination (e.g. ultrasonography examination) should be performed
- ☐ Vigilance for the possibility of severe exacerbation of disease following discontinuation of treatment is recommended. In cases of severe exacerbation appropriate treatment should be initiated as required

Summary guidance specifically for pediatric patients

- ☐ Consider a complete vaccination schedule before starting Gilenya®
- ☐ 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 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 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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