Gilenya® (Fingolimod 0.5 mg)
Summary of Recommendations
Important Safety Information

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA.

Considerations in (fingolimod) Patient Selection

Fingolimod 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 Fingolimod is contraindicated or not recommended.

Considerations for treatment initiation

Fingolimod 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) not using effective contraception, and patients with 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**

*Fingolimod 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 Fingolimod

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

Prior to initiating treatment

- ☐ Ensure patients are not concomitantly taking Class Ia or Class III antiarrhythmic medicines.
- ☐ Conduct baseline electrocardiogram (ECG) and blood pressure (BP) measurement.
- ☐ Treatment with Fingolimod 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.
- ☐ 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.
- ☐ Inform WOCBP that fingolimod is contraidicated in pregnant women and WOCBP not using effective contraception.
- ☐ Fingolimod is teratogenic. Confirm a negative pregnancy test result in WOCBP prior to starting treatment and repeat at suitable intervals during treatment.
- ☐ Inform WOCBP about the serious risks of fingolimod to the fetus
- ☐ Provide all patients, parents (or legal representatives) and caregivers with the Pregnancy-Specific Patient Reminder Card.
- ☐ Counsel WOCBP 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.

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?**

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

NO

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

YES → Extend monitoring at least overnight, until the findings have resolved

NO

At the end of the monitoring period, have any of the following criteria been met?
- ☐ HR <45 bpm, <55 bpm in 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

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 fingolimod 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.
*For pediatric patients (≥10 years old), the approved dosing for Fingolimod 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 during, and for up to 2 months after, treatment
  - Perform prompt diagnostic evaluation in patients with symptoms and signs consistent with encephalitis, meningitis or meningoencephalitis and initiate appropriate treatment if diagnosed
    - Serious, life-threatening, and sometimes fatal cases of encephalitis, meningitis or meningoencephalitis caused by herpes simplex virus (HSV) and VZV were reported while on Fingolimod 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 PML. If PML is suspected, treatment with Fingolimod 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 and serum bilirubin before starting treatment and at months 1, 3, 6, 9, and 12 on therapy and periodically thereafter until 2 months after Gilenya discontinuation or at any time there are signs or symptoms of hepatic dysfunction.
  - Some cases of acute liver failure requiring liver transplant and clinically significant liver injury have been reported.
  - In case of absence of clinical symptoms, if liver transaminases are:
    - Greater than 3 times the upper limit of normal (ULN) but less than 5 times ULN without increase in serum bilirubin, more frequent monitoring including serum bilirubin and alkaline phosphatase (ALP) should be instituted.
    - At least 5 times ULN or at least 3 times ULN associated with any increase in serum bilirubin, fingolimod should be discontinued. If serum levels return to normal, fingolimod may be restarted based on a careful benefit- risk assessment of the patient.
  - In case of presence of clinical symptoms suggestive of hepatic dysfunction, the Liver enzymes and bilirubin should be checked immediately and fingolimod should be discontinued if significant liver injury is confirmed.
- ☐ While on treatment, women should not become pregnant. Discontinue treatment if a woman becomes pregnant. Gilenya should be stopped 2 months before planning a pregnancy, and the possible return of disease activity 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 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 must be informed regularly about the serious risks of Fingolimod to the fetus.
- ☐ Ensure WOCBP, 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 (8001240078) or visiting (https://www.report.novartis.com/ https:// psi.novartis .com) in order to allow monitoring of these patients through the pregnancy outcomes intensive monitoring program (PRIM). Physicians may also enrol a pregnant MS patient under their care in the gilenya pregnancy register by dialling (8001240078) or visiting (https://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.
- ☐ Fingolimod 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 encephalitis, meningitis or meningoencephalitis infection and PML.
- ☐ Inform WOCBP that effective contraception is needed for 2 months after discontinuation because of the serious risks of Fingolimod to the fetus.
- ☐ Advise women who stop treatment with Fingolimod 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 Figolimod.
- ☐ Counsel patients and their parents/caregivers on Figolimod 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 Figolimod once daily*.
- ☐ Emphasize the importance of treatment compliance to patients, especially with regard to treatment interruption and the need to repeat first-dose monitoring.
- ☐ Monitor the patient for signs and symptoms of depression and anxiety.
- ☐ Provide guidance on seizure monitoring.
- ☐ Provide pregnancy specific guidance including the Pregnancy specific patient reminder card to female adolescent patients of child bearing potential and their parents/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

Gilenya® Important note: Before prescribing, consult full prescribing information. **Presentation:** 0.5 mg hard capsules. **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 (for exceptions and information about washout periods see sections 4.4 and 5.1). 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: Adults:** One 0.5 mg capsule taken orally once daily. **Children and adolescents:** Children and adolescents with a body weight ≤ 40 kg: one 0.25 mg capsule per day; with a body weight > 40 kg: one 0.5 mg capsule per day. Not studied in pediatric patients below 10 years of age. "The strength 0.25mg supporting the age group between 10 and 18 years old with body weight of 40kg or under is not registered"**Special populations:** No dosage adjustment needed for renal impairment, mild to moderate hepatic impairment or elderly patients (caution as experience is limited). Caution in patients with severe hepatic impairment. **Contraindications:** Patients who in the last 6 months had myocardial infarction, unstable angina pectoris, stroke/transient ischemic attack, decompensated heart failure (requiring inpatient treatment), or New York Heart Association Class III/IV heart failure. •Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs. •Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not have a pacemaker. •Patients with a baseline QTc interval ≥500 msec. •Known hypersensitivity to fingolimod, or to any of the excipients. •During pregnancy and in women of childbearing potential not using effective contraception •Hypersensitivity to the active substance or to any of the excipients. **Warnings and precautions:** ECG to be performed in all patients prior to the first dose and at the end of the 6-hour first-dose observation period. Heart rate and blood pressure to be monitored hourly during the 6-hour observation period. Same recommendation applies after an interruption of one day or more during the first 2 weeks of treatment, or for more than 7 days during week 3 and 4 of treatment; or after an interruption for more than 2 weeks after the first month of treatment. If post-dose bradyarrhythmia-related symptoms occur, or new onset of second-degree or higher AV block, or the heart rate at 6 hours post-dose is the lowest value post-dose or is <45 bpm in adults, <55 bpm in pediatric patients aged 12 years and above, or <60 bpm in pediatric patients 10 to below 12 years, the patient should be observed until the symptoms or findings have resolved, and appropriate management should be initiated as necessary. Patients should be monitored overnight if ECG at 6 hours shows QTc ≥500 msec. If a patient requires pharmacological intervention during the first dose observation period, overnight monitoring should be instituted and the first dose monitoring strategy should be repeated for the second dose of Gilenya. •When switching pediatric patients from a 0.25 mg to a 0.5 mg daily dose, it is recommended to repeat the first-dose observation period. • Due to the risk of serious cardiac rhythm disturbances, Gilenya should not be used in patients with sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope or in patients with significant QT prolongation (QTc >470 msec (adult females), QTc >460 msec (pediatric females) or >450 msec (adult and pediatric males)). Gilenya is best avoided in patients with relevant risk factors for QT prolongation, for example, hypokalemia, hypomagnesemia or congenital QT prolongation. Gilenya should also not be used in patients with history of cardiac arrest, uncontrolled hypertension or severe untreated sleep apnea, since significant bradycardia may not be well tolerated in these patients. If treatment is being considered in patients with the aforementioned risk factors, pre-treatment consultation with a cardiologist is required to determine the most appropriate monitoring (should last overnight) for treatment initiation. •Gilenya should generally not be initiated in patients on concurrent therapy with beta-blockers, heart rate lowering calcium channel blockers or other substances that may decrease heart rate (limited experience is available and this may be associated with severe bradycardia and heart block). If treatment with Gilenya is being considered, advice should be sought from a cardiologist regarding switching to a non-heart rate lowering drug or appropriate monitoring (should last overnight) for treatment initiation. •After the first dose, the heart rate decrease starts within an hour and the Day 1 decline is maximal within 6 hours. Heart rate returns to baseline within 1 month of chronic dosing. •Caution is required in concomitant use with anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids). Specific decisions as to the dosage and duration of treatment with corticosteroids should be based on clinical judgment. Short courses of corticosteroids can be used in combination with Gilenya. •Patients without a healthcare professional confirmed history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV prior to treatment initiation. VZV vaccination is recommended in antibody-negative patients and initiation of treatment should be postponed for 1 month to allow the vaccination to take full effect. •In pediatric patients, a complete vaccination schedule is recommended before starting Gilenya. •Infection: Lymphocyte count is decreased during Gilenya therapy and up to 2 months after stopping Gilenya therapy. Before initiating treatment with Gilenya, a recent complete blood count (i.e. within 6 months or after discontinuation of prior therapy) should be available. Initiation of treatment with Gilenya should be delayed in patients with severe active infection until resolution. Effective diagnostic and therapeutic strategies should be used in patients with symptoms of infection while on therapy and up to two months after discontinuation. Consider discontinuing therapy if a serious infection develops, and re-evaluate benefit-risk before restarting therapy. Cases of progressive multifocal leukoencephalopathy (PML) have been reported in the post-marketing setting. PML cases without previous treatment with natalizumab have been reported after approximately 2-3 years of treatment although an exact relationship with the duration of treatment is unknown. The incidence rate for PML appears to be higher for patients in Japan; the reasons are currently unknown. Vigilance for clinical symptoms or MRI findings suggestive of PML is warranted. If PML is suspected, Gilenya treatment should be suspended until PML has been excluded. Cases of cryptococcal meningitis (CM) have been reported in the post-marketing setting after approximately 2 3 years of treatment. Although the estimated risk appears to increase with cumulative exposure over time, an exact relationship with the duration of treatment is unknown. CM may be fatal. For this reason patients with symptoms and signs consistent with CM should undergo prompt diagnostic evaluation. If diagnosed, appropriate treatment should be initiated. •Macular edema: Patients with history of uveitis and patients with diabetes mellitus are particularly at risk of developing macular edema. An ophthalmic examination is recommended 3 to 4 months after Gilenya therapy initiation and also before and regularly during Gilenya therapy in patients at risk. Discontinuing therapy should be considered if macular edema develops. •Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with Gilenya. A liver function test is recommended in patients who develop symptoms of hepatic dysfunction during treatment. Therapy should be discontinued if significant liver injury is confirmed. •Posterior reversible encephalopathy syndrome (PRES): Discontinue Gilenya treatment, if PRES is suspected. •Caution is required when switching patients from natalizumab or teriflunomide to Gilenya due to the long half-life of natalizumab or teriflunomide. Initiating treatment with Gilenya after alemtuzumab is not recommended unless the benefits clearly outweigh the risks. •Basal cell carcinoma (BCC) and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma have been reported in patients receiving Gilenya. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. Since there is a potential risk of malignant skin growths, patients treated with Gilenya should be cautioned against exposure to sunlight without protectionVigilance for BCC and other cutaneous neoplasms is warranted. • Cases of lymphoma, heterogeneous in nature, mainly Non-Hodgkin's Lymphoma, including B-cell and T-cell lymphomas as well as T cell lymphoma (mycosis fungoides) have been reported in clinical studies and/or the post-marketing setting. •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 into account individual benefits and risks. •Cases of severe exacerbation of the disease have been reported after discontinuation of Gilenya. These cases were generally observed within 12 weeks after stopping Gilenya, but in some cases up to and beyond 24 weeks after Gilenya discontinuation. Caution is indicated when stopping Gilenya therapy: patients should be monitored for relevant signs and symptoms and appropriate treatment should be initiated as required. During routine MRI (in accordance with national and local recommendations), vigilance for BCC and other cutaneous neoplasms is warranted. As with other MS medications, detection of JCV DNA in the cerebrospinal fluid and MRI findings may be apparent before clinical signs or symptoms. •The combination of fingolimod with potent CYP450 inducers should be used with caution. Concomitant administration with St John's wort is not recommended. •Gilenya should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease. Human papilloma virus (HPV) infection and HPV-related cancer have been reported under treatment with Gilenya in the post-marketing setting. Vaccination against HPV should be considered prior to treatment initiation with Gilenya taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care. **Pregnancy, lactation, females and males of reproductive potential Pregnancy:** While on treatment, females should not become pregnant and effective contraception is recommended. If a female becomes pregnant while taking Gilenya, discontinuation of Gilenya should be considered, taking into account the individual benefit risk assessment for both the mother and the fetus. **Lactation:** Not recommended. **Females and males of reproductive potential:** The pregnancy status of females of reproductive potential should be verified prior to starting treatment and Adequate effective contraceptive measures are recommended in women of childbearing potential during treatment with Gilenya and for 2 months after stopping treatment. **Adverse reactions:** Frequencies were defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). **Very common (≥10%):** Influenza, sinusitis, headache, cough, diarrhoea, back pain, hepatic enzymes increased. **Common (≥1 to <10%):** Herpes viral infections, Bronchitistinea versicolor, basal cell carcinoma, lymphopenia, leucopenia, Depression, dizziness, migraine,vision blurred, bradycardia, Atrioventricular block, hypertension, dyspnea, ,eczema, Alopecia, pruritus, Myalgia, Arthralgia, asthenia, Weight decreased, blood triglycerides increased. **Uncommon (≥0.1 to <1%):** Pneumonia, Malignant melanoma, Thrombocytopenia, Depressed mood, macular edema, Nausea, Neutrophil count decreased, seizures, including status epilepticus (in the pediatric study, cases of seizures were reported in 5.6% of fingolimod-treated patients and 0.9% of interferon beta-1a treated patients). **Rare (≥0.01 to <0.1%):** Lymphoma, Posterior reversible encephalopathy syndrome (PRES). **Very rare (<0.01%):** Kaposi's sarcoma, T-wave inversion. **Not known:** Progressive multifocal leukoencephalopathy (PML), Cryptococcal infections (including cryptococcal meningitis), Merkel cell carcinoma, Autoimmune haemolytic anaemia, Peripheral oedema, Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation, Severe exacerbation of disease after Gilenya discontinuation. Cases of infections with opportunistic pathogens, such as viral (e.g. VZV, JCV causing PML, HSV), fungal (e.g. cryptococci including cryptococcal meningitis) or bacterial (e.g. atypical mycobacterium), have been reported in the post-marketing setting. Isolated cases of transient spontaneously resolving complete AV block have been observed during the six hour observation period. **Interactions:** •Concomitant use is not recommended with Class Ia (e.g. quinidine, procainamide) and Class III (e.g. amiodarone, sotalol) anti-arrhythmic drugs •At treatment initiation concomitant use with beta-blockers, heart rate lowering calcium channel blockers (e.g. verapamil or diltiazem) or other drugs that may lower heart rate (e.g. ivabradine or digoxin) is not recommended. •Caution is required in concomitant use with anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids) during, and for up to 2 months after stopping Gilenya treatment. •Caution is required when switching therapy from drugs with a long-acting immune effect such as natalizumab, teriflunomide or mitoxantrone. •Concomitant use is not recommended with live attenuated vaccines; other vaccines may have reduced efficiency during and for up to 2 months after stopping Gilenya therapy. • caution should be done with substance that inhibit CYP3A4.

Packs and prices: Country specific.

Legal classification: Country specific.

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You can report any problem or adverse events or request additional copies of the materials through:

Patient Safety Department Novartis Pharma AG - Saudi Arabia:

Toll Free Number: 8001240078
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Email: adverse.events@novartis.com
Or by online: https://report.novartis.com/

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