Prescribing Information:
GILENYA® ▼ (fingolimod)

Important note: Before prescribing consult Summary of Product Characteristics (SmPC).

Presentation: Hard capsule containing 0.5 mg fingolimod (as hydrochloride) and hard capsule containing 0.25 mg fingolimod (as hydrochloride).

Indications: Gilenya is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:

– Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy.

– Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Dosage and administration: Treatment should be initiated and supervised by a physician experienced in multiple sclerosis. In adults one 0.5 mg capsule to be taken orally once daily. In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight. Paediatric patients with body weight ≤40 kg: one 0.25 mg capsule taken orally once daily. Paediatric patients with body weight >40 kg: one 0.5 mg capsule to be taken orally once daily. Paediatric patients who start on 0.25 mg capsules and subsequently reach a stable body weight above 40 kg should be switched to 0.5 mg capsules. When switching from a 0.25 mg to a 0.5 mg daily dose, it is recommended to repeat the same first dose monitoring as for treatment initiation.The capsules should always be swallowed intact, without opening them. Use with caution in patients aged 65 years and over. 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).

Contraindications: Immunodeficiency syndrome, patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies), severe active infections, active chronic infections (hepatitis, tuberculosis), active malignancies, severe liver impairment (Child-Pugh class C). Patients who in the previous 6 months had myocardial infarction (MI), unstable angina pectoris, stroke/ transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure in the previous 6 months. Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia or class III anti-arrhythmic medicinal products. 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 ≥500 msec. During pregnancy and in women of childbearing potential not using effective contraception. Hypersensitivity to the active substance or to any of the excipients.

Warnings/Precautions: *Bradyarrhythmia:* Initiation of treatment results in a transient decrease in heart rate (HR), which may be associated with atrioventricular block. Patients should have an ECG pre-dose, 6 hours post-dose and be observed for 6 hours with hourly HR and BP. Continuous ECG monitoring is recommended for 6 hours. The same precautions as for the first dose are recommended when patients are switched from the 0.25 mg to the 0.5 mg daily dose. In the event of bradyarrhythmia-related symptoms, initiate appropriate clinical management and monitor overnight. Also monitor overnight if at 6 hours: HR <45 bpm in adults, <55 bpm in paediatric patients aged 12 years and above, or <60 bpm in paediatric patients aged 10 to below 12 years, new onset 2nd degree heart block or higher, QTc >500 msec, or 3rd degree heart block at any time. If HR is lowest at 6 hours, monitor for >2 hours until HR increases. The same precautions apply if treatment is interrupted for 1 day or more during the first 2 weeks of treatment, if treatment is interrupted for more than 7 days during weeks 3 and 4 of treatment, or if Gilenya is discontinued for more than 2 weeks. Do not use Gilenya in patients with sino-atrial heart block, symptomatic bradycardia, recurrent syncope, history of cardiac arrest, QTc >470 msec (adult female), QTc >460 msec (paediatric female) or QTc >450 msec (adult and paediatric male), significant cardiovascular disease, uncontrolled hypertension or severe sleep apnoea unless in consultation with a cardiologist and monitored overnight. Gilenya should not be given to patients taking beta blockers, HR lowering calcium channel blockers or other HR lowering substances (e.g. digoxin, diltiazem, ivabradine) unless in consultation with a cardiologist. Very rare cases of T-wave inversion have been reported in adult patients treated with Gilenya. In case of T-wave inversion, ensure no associated myocardial ischaemia signs or symptoms. If myocardial ischaemia is suspected, seek advice from a cardiologist. *Immunosuppressive effects:* Gilenya has an immunosuppressive effect that predisposes patients to an infection risk, and increases the risk of developing lymphomas and other malignancies, particularly those of the skin. *Infections:* Gilenya may increase the risk of infection, including opportunistic infections which may be fatal. Reduction of the lymphocyte count to 20–30% of baseline values occurs with Gilenya. Before initiating treatment, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are recommended periodically during treatment, at 3 months and at least yearly thereafter, and in case of signs of infection. Absolute lymphocyte count <0.2 x 10^9/l, if confirmed, should lead to treatment interruption until recovery. Patients need to be assessed for their immunity to varicella (chickenpox) prior to treatment. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment. If a patient develops a serious infection, suspension of Gilenya and referral to a physician experienced in treating infections should be considered. Cryptococcal meningitis (CM) have been reported in the post-marketing setting. If CM is diagnosed, Gilenya should be suspended and appropriate treatment initiated. A multidisciplinary consultation (i.e. infectious disease specialist) should be undertaken if re-initiation of Gilenya is warranted. Employ effective diagnostic and therapeutic strategies in patients with symptoms of infection while on Gilenya and for 2 months after discontinuation. Progressive multifocal leukoencephalopathy (PML) has been reported. PML is an opportunistic infection caused by John Cunningham virus (JCV) and may be fatal or cause severe disability. Before initiating Gilenya, baseline MRI should be available (within 3 months). MRI is considered as part of vigilance in patients at risk of PML as MRI findings may be apparent before clinical signs or symptoms. If PML is suspected, perform diagnostic MRI immediately and suspend Gilenya treatment until PML is excluded. Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported with Gilenya in the post-marketing setting. Vaccination against HPV should be considered prior to treatment initiation taking into account vaccination recommendations. Cancer screening, including Pap test, is recommended as per standard of care. *Macular oedema:* Macular oedema with or without visual symptoms has been reported. 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). Increased hepatic enzymes, in particular alanine aminotransaminase (ALT) but also gamma glutamyltransferase (GGT) and aspartate transaminase (AST), have been reported in adult multiple sclerosis patients treated with Gilenya. Delay Gilenya initiation in patients with active viral hepatitis until resolution. Recent transaminase and bilirubin levels should be available before treatment initiation. 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) measurements. 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 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 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). *Posterior reversible encephalopathy syndrome:* Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported. If PRES is suspected, Gilenya should be discontinued. *Prior immunosuppressant or immunomodulatory treatment:* There have been no studies performed to evaluate the efficacy and safety of Gilenya when switching patients from teriflunomide, dimethyl fumarate (DMF) or alemtuzumab treatment to Gilenya. When switching patients from another disease modifying therapy to Gilenya, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time minimising the risk of disease reactivation. A CBC is recommended prior to initiating Gilenya to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved. No washout is necessary when switching patients from interferon or glatiramer acetate to Gilenya. For DMF, the washout period should be sufficient for the CBC to recover before treatment with Gilenya is started. Due to the long half-life of natalizumab, elimination usually takes up to 2–3 months following discontinuation. Teriflunomide is also eliminated slowly from the plasma; clearance from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide SmPC is recommended or alternatively the washout period should not be shorter than 3.5 months. Caution regarding potential concomitant immune effects is required when switching patients from natalizumab or teriflunomide to Gilenya. Alemtuzumab has profound and prolonged immunosuppressive effects. As the actual duration of these effects is unknown, initiating treatment with Gilenya after alemtuzumab is not recommended unless the benefits of such treatment clearly outweigh the risks for the patient. *Malignancies:* Basal cell carcinoma and other cutaneous neoplasms including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma have been reported. Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, and then every 6 to 12 months. Refer to dermatologist if suspicious lesions occur. Patients should be cautioned against unprotected sunlight exposure and should not receive concomitant phototherapy. Heterogeneous cases of lymphoma have been reported in clinical studies and the post-marketing setting. If lymphoma is suspected, Gilenya should be discontinued. *Women of childbearing potential:* Due to risk to the foetus, Gilenya is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. *Tumefactive lesions:* Rare cases of tumefactive lesions associated with MS relapse have been reported. In cases of severe relapses, MRI should be performed to exclude tumefactive lesions. Discontinuation of Gilenya should be considered. *Return of disease activity (rebound) after Gilenya discontinuation:* Severe exacerbation of disease has been observed rarely in some patients stopping Gilenya. If discontinuation is deemed necessary, the possibility of recurrence of exceptionally high disease activity should be considered and patients should be monitored for relevant signs and symptoms and appropriate treatment initiated as required. *Stopping therapy:* Gilenya is cleared from the circulation in 6 weeks. Caution is indicated with the use of immunosuppressants soon after the discontinuation due to possible additive immune system effects. *Paediatric population:* The safety profile in paediatric patients is similar to that in adults and the warnings and precautions for adults also apply to paediatric patients. In the controlled paediatric trial, cases of seizures, anxiety, depressed mood and depression have been reported with a higher incidence in patients treated with Gilenya compared to patients treated with interferon beta-1a. Caution is required in this subgroup population. It is recommended that paediatric patients complete all immunisations in accordance with current immunisation guidelines before starting therapy.

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 additive effects on heart rate, Gilenya should not be given to patients receiving beta blockers, or class Ia or III antiarrhythmics, calcium channel blockers, digoxin, anticholinesteratic agents, pilocarpine or other HR lowering substances. Caution is indicated with substances that may inhibit or cause strong induction of CYP3A4 or CYP4F2, as this could potentially impair the efficacy of Gilenya. Concomitant administration with St John's wort is not recommended. No interaction has been observed with oral contraceptives when co-administered with Gilenya.

Fertility, pregnancy and lactation: Gilenya is contraindicated in women of childbearing potential not using effective contraception. Post-marketing data suggest that use of Gilenya is associated with a 2-fold increased risk of major congenital malformations when administered during pregnancy compared with the rate observed in the general population. Before initiation of treatment, a negative pregnancy test result must be available and counselling should be provided regarding the serious risk to the foetus. Female patients must use effective contraception during treatment with Gilenya and for 2 months after discontinuation. Gilenya should be stopped 2 months before planning a pregnancy. When stopping therapy for planning a pregnancy the possible return of disease activity should be considered. If a patient becomes pregnant during treatment, Gilenya must be discontinued. Gilenya is excreted into breast milk. Women receiving Gilenya should not breastfeed. Gilenya is not associated with a risk of reduced fertility. Specific measures are included in the Physician Information Pack, which must be implemented before Gilenya is prescribed to female patients and during treatment.

Undesirable effects: Very common (≥1/10): influenza, headache, cough, diarrhoea, sinusitis, increased hepatic enzymes (ALT, AST, GGT), back pain. Common (≥1/100 to <1/10): basal cell carcinoma, herpes viral infections, bronchitis, tinea versicolor, lymphopenia, leucopenia, depression, dizziness, migraine, blurred vision, bradycardia, atrioventricular block, hypertension, dyspnoea, eczema, alopecia, pruritus, myalgia, arthralgia, asthenia, weight decreased, increased blood triglycerides. Cases of posterior reversible encephalopathy syndrome (PRES) have been reported rarely (≥1/10,000 to <1/1,000) at the 0.5 mg dose. Very rare cases (<1/10,000) of haemophagocytic syndrome (HPS) with fatal outcome have been reported in patients treated with Gilenya in the context of an infection. In the post-marketing setting, cases of opportunistic infections (some fatal) have been reported, e.g viral (e.g. varicella zoster virus [VZV], JCV causing PML, herpes simplex virus [HSV]), Cryptococcal meningitis or bacterial (e.g. atypical mycobacterium). In the controlled paediatric trial the safety profile was similar to in adults however more neurological and psychiatric disorders were observed. Caution is needed in this population due to very limited knowledge available from the clinical study. *Other Adverse Effects:* Please consult the Summary of Product Characteristics for a detailed listing of all adverse events before prescribing.

Legal classification: POM. **Marketing authorisation (MA) numbers, quantities and price:** EU/1/11/677/001 Perforated unit dose blister packs containing 7 x 0.5 mg hard capsules: £367.50; EU/1/11/677/005 Blister packs containing 28 x 0.5 mg hard capsules: £1470. EU/1/11/677/008 Blister packs containing 28 x 0.25 mg hard capsules: £1470. **Date of last revision of prescribing information:** December 2019. **Full Prescribing Information available from:** Novartis Pharmaceuticals UK Ltd, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Tel: (01276) 692255, Fax: (01276) 692508.

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Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.UK/yellowcard.
Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the patient safety information (PSI) tool at https://psi.novartis.com
If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com