GILENYA® (fingolimod)

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

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: Adults: Treatment should be initiated and supervised by a physician experienced in multiple sclerosis.

Important note: Do not use Gilenya if the patient is pregnant. Gilenya is contraindicated in pregnant women. Female patients must use effective contraception. Gilenya is also contraindicated in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease.

- Initial dose: 0.5 mg capsule daily for 1 week, then increased to 1 mg daily for 1 week prior to initiation of Gilenya. The 1 mg dose is recommended 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. neutropenia. 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.

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 lesions involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the total blood volume. Laboratory tests to determine peripheral blood lymphocyte counts require larger blood volumes due to reduction in the total blood volume. Do not use Gilenya in patients with severe hepatic impairment (Child-Pugh class C).

Warnings/Precautions: Bradycardia: Initiation of treatment results in a transient decrease in heart rate which may be associated with arrhythmia, such as first degree atrioventricular (AV) block, sinus bradycardia, or AV block. Conduction delays, including third degree or complete AV block, spontaneously resolving complete AV block. After the first dose, the decline in heart rate starts within one hour and is steepest within 6 hours. The effect on heart rate progressively attenuates over subsequent days of treatment and returns to baseline within one month. Conduction abnormalities were typically transient, asymptomatic and usually did not require treatment. If necessary, the decrease in heart rate can be reversed by IV 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. Monitor all patients for 6 hours for 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 bradycardia-related symptoms, initiate appropriate clinical management and observe until symptoms resolve. If pharmacological intervention is required, overnight monitoring should be instituted. If the heart rate at 6 hours is the lowest since the first dose was administered, 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, or occurrence at any time of third degree AV block extended monitoring (at least overnight), should be performed. The same precautions apply if Gilenya is discontinued for more than 2 weeks. Gilenya should not be used in patients with second degree or higher AV block, sick-sinus syndrome, sino-atrial heart block, significant QT prolongation, ischaemic cardiac disease, cerebrovascular disease, congestive heart failure, uncontrolled hypertension, or severe sleep apnoea, a history of symptomatic bradycardia, recurrent syncope, MI or cardiac arrest. ... Seek advice from a cardiologist before initiation of treatment in these patients to determine appropriate monitoring (at least overnight). Gilenya should not be co-administered with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmics. Gilenya should not be used in patients receiving beta blockers, or other substances which may decrease heart rate (e.g. verapamil, digoxin, anticholinesteratic agents or pilocarpine) due to possible additive effects. Seek advice from a cardiologist before initiation of treatment in these patients to switch to non-heart-rate lowering agents or, if not possible, to determine appropriate monitoring. At least overnight monitoring should be avoided for 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 considered. Consider VZV vaccination before initiating Gilenya and in VZV negative patients prior to commencement of Gilenya. Gilenya may increase the risk of infections. 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. Monitor liver transaminases at 3, 6, 9 and 12 months. Typically 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. Resumption of 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 forced expiratory volume (FEV1) and diffusion capacity for carbon monoxide (DLCO). Pneumocystis jirovecii or Mycobacterium avium complex (MAC). Delay Gilenya initiation in patients with a history of significant respiratory disease (e.g. chronic obstructive pulmonary disease, bronchiectasis). In patients with a history of significant respiratory disease (e.g. chronic obstructive pulmonary disease, bronchiectasis) perform chest radiography and haemoglobin levels before initiation of Gilenya. A negative chest radiograph and haemoglobin levels are not a substitute for adequate diagnostic and therapeutic strategies in patients with severe respiratory disease. Patients requiring treatment with Gilenya. Laboratory tests to determine peripheral blood lymphocyte counts require larger blood volumes due to reduction in the total blood volume.

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 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. Gilenya should not be initiated in patients receiving beta blockers, or class Ia and III antiarrhythmics, heart rate lowering calcium channel blockers (e.g. verapamil or diltiazem), digoxin, anticholinesteratic agents or pilocarpine. 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 anticoagulants when co-administered with fingolimod.

Fertility, 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.

**Undesirable effects:** Very common (≥1/10); Influenza viral infections, headache, cough, diarrhoea, increased alanine transaminase (ALT), back pain. Common (≥1/100 to <1/10); herpes viral infections, bronchitis, sinusitis, gastroenteritis, tinea infections, lymphopenia, leucopenia, depression, dizziness, paraesthesia, migraine, blurred vision, eye pain, 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, depressed mood, macular oedema, decreased neutrophil count.

**Marketing Authorisation Holder:** Novartis Europharm Ltd, Wimblehurst Rd, Horsham, W Sussex, RH12 5AB, UK.

**Marketing Authorisation Numbers:** EU/1/11/677/001-005.

**Date of last revision of prescribing information:** June 2012.