

Direct Healthcare Professional Communication on strengthening the cardiovascular monitoring during treatment initiation with Gilenya (fingolimod) ▼ in patients with Relapsing Remitting Multiple Sclerosis

PLEASE CASCADE AS APPROPRIATE

Dear Healthcare Professional

Novartis would like to inform you about important additional recommendations to strengthen the monitoring of cardiovascular status for 6 hours after initiating treatment with Gilenya and to extend it, when necessary.

Gilenya is known to cause a transient bradycardia and might be associated with atrioventricular block, after the first dose as reflected in the current product information. The additional recommendations follow case reports of cardiovascular events including a patient who died of unknown cause after the first dose of Gilenya (fingolimod).

In agreement with the European Medicines Agency, the following recommendations are effective immediately for patients treated with Gilenya:

For all patients starting treatment, monitoring during the first 6 hours after dosing should include:

- A 12-lead ECG at baseline and 6 hours after the first dose
- Continuous 6-hour ECG monitoring
- Blood pressure and heart rate measurement every hour

In those patients with evidence of clinically important cardiac effects, monitoring should be extended until resolution. The following criteria for extended monitoring are recommended:

- The presence at the 6-hour time point after first dose of:
 - Heart rate less than 40 beats per minute
 - Decrease in heart rate of more than 20 beats per minute compared with baseline
 - Persistent new-onset 2nd degree atrioventricular block, Mobitz Type I (Wenckebach)
- The occurrence at anytime during the 6-hour monitoring of:
 - Symptomatic bradycardia
 - New onset 2nd degree atrioventricular block, Mobitz Type II
 - New onset 3rd degree atrioventricular block

Further information on the safety concern

Novartis has received case reports of cardiovascular events including a spontaneous report of a 59 year-old female patient with multiple sclerosis who died within 24 hours of

taking the first dose of Gilenya. The patient was being treated with metoprolol and amlodipine for hypertension. The exact cause of death in this patient remains unknown at present. The updated recommendations aim to minimise the cardiovascular risk with Gilenya.

At the request of the European Medicines Agency, Novartis is conducting a complete review of cardiovascular events including data from clinical trials and post-marketing experience.

The content of this letter has been agreed with the MHRA.

Call for Reporting

Healthcare professionals should report any suspected adverse reactions associated with use of Gilenya.

Suspected adverse drug reactions should be reported to the MHRA via the [Yellow Card Scheme](#). Reporting forms and information can be found at www.yellowcard.gov.uk.

Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail: "FREEPOST YELLOW CARD"
- at the back of the British National Formulary (BNF)
- by telephoning the Commission of Human Medicines (CHM) free phone line: 0800-731-6789
- or by electronic download through the MHRA website (<http://yellowcard.mhra.gov.uk/downloads>)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Adverse reactions should also be reported to Novartis Pharmaceuticals UK Ltd; please call 01276 698370 or e-mail: adecseuk.phgbfr@Novartis.com

For additional questions regarding this issue, please call the Medical Information Department at Novartis Pharmaceuticals UK Ltd on 01276 698370.

Yours faithfully,



Dr Tim Cave
Medical Director – Chief Scientific Officer UK.

23rd January 2012

See overleaf for Prescribing Information

Abbreviated Prescribing Information:**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. One 0.5 mg capsule 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 infections, active chronic infections (hepatitis, tuberculosis), known active malignancies, except for patients with cutaneous basal cell carcinoma, severe liver impairment (Child-Pugh class C), hypersensitivity to the active substance or to any of the excipients.

Warnings/Precautions: Bradycardia: Initiation of treatment results in a transient decrease in heart rate which may be associated with atrioventricular conduction delays. Observe all patients for 6 hours for bradycardia. In the event of bradycardia-related symptoms, initiate appropriate clinical management and observe until symptoms resolve. The same precautions apply if Gilenya is discontinued for more than 2 weeks. Gilenya has not been studied in patients with sitting heart rate <55 beats per minute, second degree or higher AV block, sick-sinus syndrome, ischaemic cardiac disease, congestive heart failure, significant cardiovascular disease, a history of syncope or those taking beta blockers. Seek advice from a cardiologist before initiation of treatment in these patients. Gilenya should not be co-administered with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Exercise caution at treatment initiation 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. Avoid medicinal 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 $<0.2 \times 10^9/L$ is confirmed. Consider VZV vaccination of patients without a history of chickenpox or VZV antibody negative patients prior to commencing 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 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) 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. Resume 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 values for forced expiratory volume (FEV₁) and diffusion capacity for carbon monoxide (DLCO). **Prior immunosuppressant treatment:** No washout is necessary when switching patients from interferon or glatiramer acetate to Gilenya assuming any immune effects (e.g. neutropenia) have resolved. Exercise caution when switching patients from natalizumab to Gilenya owing to the long half life of natalizumab and concomitant immune effects. **Stopping therapy:** Gilenya is cleared from the circulation in 6 weeks. Caution is indicated with the use of immunosuppressants soon after the discontinuation of Gilenya due to possible additive effects on the immune system.

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. Due to additive effects on heart rate, exercise caution when initiating Gilenya in patients receiving beta blockers, or class Ia and III antiarrhythmics, calcium channel blockers like 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 contraceptives 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* ($\geq 1/10$): Influenza viral infections, headache, cough, diarrhoea, increased alanine transaminase (ALT), back pain. *Common* ($\geq 1/100$ 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* ($\geq 1/1,000$ to $<1/100$): pneumonia, macular oedema, decreased neutrophil count.

Packs and price: Perforated unit dose blister packs containing 7 x 0.5 mg hard capsules: £367.50. Blister packs containing 28 x 0.5 mg hard capsules: £1470. **Legal classification:** POM

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

Marketing Authorisation Numbers: 7 x 0.5 mg hard capsules: EU/1/11/677/001, 28 x 0.5 mg hard capsules: EU/1/11/677/005

Date of last revision of prescribing information: January 2012

Full Prescribing Information available from: Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Surrey, GU16 7SR. Tel: (01276) 692255 Fax: (01276) 692508.

**Adverse events should be reported. Reporting forms and information can be found at <http://yellowcard.mhra.gov.uk>
Adverse events should also be reported to Novartis (01276) 698370**

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