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Direct Healthcare Professional Communication, refined guidance on when first dose monitoring procedures should be repeated for Gilenya (fingolimod) ▼ - PLEASE CASCADE AS APPROPRIATE

Dear Healthcare Professional

Summary
In April 2012, Novartis informed you about enhanced first dose monitoring procedures in relation to the transient decrease in heart rate and atrioventricular conduction delay upon treatment initiation with Gilenya. These recommendations were included in the Summary of Product Characteristics.

The purpose of the present communication is to provide guidance on repeat "first dose cardiovascular monitoring" in case of treatment interruption and for patients requiring pharmacological intervention to treat bradyarrhythmia-related symptoms after first dose.

New advice:
Treatment interruption
The same first dose monitoring as for treatment initiation should be repeated if treatment is interrupted for:

- 1 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.

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

Patients requiring pharmacological intervention to treat bradyarrhythmia-related symptoms after first dose
As per the current SmPC, patients requiring pharmacological intervention during the first dose monitoring should be monitored overnight in a medical facility.

In these patients, it is recommended to repeat the first dose monitoring after the second dose of Gilenya.

These recommendations are reflected in a new version of the Summary of Product Characteristics and the Patient Leaflet and are effective immediately for patients treated with Gilenya.

Further information on the safety concern
It is known that the effects of GILENYA on heart rate and atrioventricular conduction may recur on reintroduction of GILENYA treatment following interruption. Further analyses of clinical pharmacology and dose titration data indicate that the risk of occurrence of these effects depends upon the duration of the interruption and time since initiation of GILENYA treatment.

The updated guidance from the Summary of Product Characteristics on the management of the transient decrease in heart rate and atrioventricular conduction delay upon treatment initiation with Gilenya can be found in the Annex.

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

Annex
Extract from the revised Product Information (with changes made visible)

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

Yours faithfully,

Dr Monica Shaw
Chief Scientific Officer UK
04 January 2013

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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. 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: *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 observed for 6 hours with hourly HR and BP. Continuous ECG monitoring is recommended for 6 hours. In the event of bradyarrhythmia-related symptoms, initiate appropriate clinical management and monitor overnight. Also monitor overnight if at 6 hrs:HR <45 bpm, 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 hrs monitor for >2 hrs until HR increases. The same precautions apply if Gilenya is discontinued for more than 2 weeks. Do not use Gilenya in patients with Mobitz type II or higher AV block, sick-sinus syndrome, sino-atrial block, symptomatic bradycardia, recurrent syncope, QTc >450 msec significant cardiovascular disease, 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 (eg digoxin, diltiazem, ivabradine) unless in consultation with a cardiologist. *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 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 (FEV_1) 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, Gilenya should not be given to patients receiving beta blockers, or class Ia and III antiarrhythmics, calcium channel blockers, digoxin, anticholinesteratic agents, pilocarpine or other HR lowering substances. 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 (≥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, parasthesia, 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, macular oedema, decreased neutrophil count. Rarely, reports of lymphoma, posterior reversible encephalopathy syndrome, peripheral arterial occlusive disease.

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: December 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://mhra.gov.uk/yellowcard Adverse events should also be reported to Novartis (01276) 698370 medinfo.uk@novartis.com

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Annex

Updated sections in the revised Summary of Product Characteristics and Package Leaflet

(Updated text in relation to the revised recommendations is indicated in **bold underlined**)

Summary of Product Characteristics

4.2 Posology and method of administration

The treatment should be initiated and supervised by a physician experienced in multiple sclerosis.

Posology

The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:

- **1 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.**

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned (see section 4.4).

4.4 Special warnings and precautions for use:

Bradyarrhythmia

Initiation of Gilenya treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete AV block (see sections 4.8 and 5.1).

After the first dose, the decline in heart rate starts within one hour and is steepest within 6 hours. The negative chronotropic effect of Gilenya persists beyond 6 hours and progressively attenuates over subsequent days of treatment. With continued administration, heart rate returns to baseline within one month. Conduction abnormalities were typically transient and asymptomatic. They usually did not require treatment and resolved within the first 24 hours on treatment. If necessary, the decrease in heart rate induced by fingolimod can be reversed by parenteral doses of 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. All patients should be monitored for a period of 6 hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurement. Continuous (real time) ECG monitoring during this 6 hour period is recommended.

Should post-dose bradyarrhythmia-related symptoms occur, appropriate clinical management should be initiated and monitoring should be continued until the symptoms have resolved. Should a patient require pharmacological intervention during the first-dose monitoring, overnight monitoring in a medical facility should be instituted **and the first-dose monitoring should be repeated after the second dose of Gilenya**.

If the heart rate at 6 hours is the lowest since the first dose was administered (suggesting that the maximum pharmacodynamic effect on the heart may not yet be manifest), 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, extended monitoring (at least overnight monitoring), should be performed, and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring (at least overnight monitoring).

Due to the risk of serious rhythm disturbances, Gilenya should not be used in patients with second degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block, a history of symptomatic bradycardia or recurrent syncope, or in patients with significant QT prolongation (QTc>470msec (female) or >450msec (male)). Since significant bradycardia may be poorly tolerated in patients with known ischaemic heart disease (including angina pectoris), cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension or severe sleep apnoea, Gilenya should not be used in these patients. In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring, at least overnight extended monitoring is recommended for treatment initiation (see also section 4.5).

Gilenya has not been studied in patients with arrhythmias requiring treatment with class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Class Ia and class III antiarrhythmic medicinal products have been associated with cases of torsades de pointes in patients with bradycardia. Since initiation of Gilenya treatment results in decreased heart rate, Gilenya should not be used concomitantly with these medicinal products.

Experience with Gilenya is limited in patients receiving concurrent therapy with beta blockers, heart-rate-lowering calcium channel blockers (such as verapamil, diltiazem or ivabradine), or other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine). Since the initiation of Gilenya treatment is also associated

with slowing of the heart rate (see also section 4.8, Bradyarrhythmia), concomitant use of these substances during Gilenya initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment with Gilenya should not be initiated in patients who are concurrently treated with these substances (see also section 4.5). In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks. If treatment with Gilenya is considered, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products prior to initiation of treatment. If the heart-rate-lowering medication cannot be stopped, cardiologist's advice should be sought to determine appropriate first dose monitoring, at least overnight extended monitoring is recommended (see also section 4.5).

The effects on heart rate and atrioventricular conduction may recur on re-introduction of Gilenya treatment depending on duration of the interruption and time since start of GILENYA treatment. The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:

- **1 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.**

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

Package Leaflet

2. What you need to know before you take Gilenya

Warnings and precautions

Slow heart rate (bradycardia) and irregular heartbeat: At the beginning of treatment, Gilenya causes the heart rate to slow down. As a result, you may feel dizzy or tired, or be consciously aware of your heartbeat, or your blood pressure may drop. If these effects are pronounced, tell your doctor, because you may need treatment right away. Gilenya can also cause an irregular heartbeat, especially after the first dose. Irregular heartbeat usually returns to normal in less than one day. Slow heart rate usually returns to normal within one month.Your doctor will ask you to stay at the surgery or clinic for at least 6 hours, with hourly pulse and blood pressure measurements, after taking the first dose of Gilenya so that appropriate measures can be taken in the event of side effects that occur at the start of treatment. You should have an electrocardiogram performed prior to the first dose of Gilenya and after the 6-hour monitoring period. Your doctor may monitor your electrocardiogram continuously during that time. If after the 6-hour period you have a very slow or decreasing heart rate, or if your electrocardiogram shows abnormalities, you may need to be monitored for a longer period (at least 2 more hours and possibly overnight) until these have resolved. **The same may apply if you are resuming Gilenya after a break in treatment, depending on both how long the break was and how long you had been taking Gilenya before the break**.

If you have, or if you are at risk for, an irregular or abnormal heartbeat, if your electrocardiogram is abnormal, or if you have heart disease or heart failure, Gilenya may not be appropriate for you.

If you have a history of sudden loss of consciousness or decreased heart rate, Gilenya may not be appropriate for you. You will be evaluated by a cardiologist (heart specialist) to advise how you should start treatment with Gilenya, including overnight monitoring.

If you are taking medicines that can cause your heart rate to decrease, Gilenya may not be appropriate for you. You will need to be evaluated by a cardiologist, who will check whether you can be switched to alternative medication that does not decrease your heart rate in order to allow treatment with Gilenya. If such a switch is impossible, the cardiologist will advise how you should start treatment with Gilenya, including overnight monitoring.

3. How to take Gilenya

If you forgot to take Gilenya

If you have been taking Gilenya for less than 1 month and you forget to take 1 dose for a whole day, call your doctor before you take the next dose. Your doctor may decide to keep you under observation at the time you take the next dose.

If you have been taking Gilenya for at least 1 month and have forgotten to take your treatment for more than 2 weeks, call your doctor before you take the next dose. Your doctor may decide to keep you under observation at the time you take the next dose. However, if you have forgotten to take your treatment for up to 2 weeks, you can take the next dose as planned.

Never take a double dose to make up for a forgotten dose.

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