NOVARTIS

Updated Direct Healthcare Professional Communication on cardiovascular monitoring during treatment initiation with Gilenya (fingolimod) ▼ - PLEASE CASCADE AS APPROPRIATE

Dear Healthcare Professional

In January 2012 Novartis informed you about interim measures regarding the first dose monitoring during treatment initiation with Gilenya in patients with Relapsing Remitting Multiple Sclerosis. Following a comprehensive risk/benefit assessment of Gilenya (fingolimod) by the European Medicines Agency's scientific committee, CHMP, the following updated recommendations are effective immediately for patients treated with Gilenya.

These recommendations follow case reports of cardiovascular events including a patient who died of unknown cause after the first dose of Gilenya.

Gilenya is not recommended in patients
a) with the following medical conditions:

- 2nd degree Mobitz Type II or higher degree AV block, Sick-sinus syndrome, or Sino-atrial heart block
- Significant QT prolongation (QTc>470 msec (female) or >450 msec (males))
- History of symptomatic bradycardia or recurrent syncope, known ischaemic heart disease, cerebrovascular disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, uncontrolled hypertension, or severe sleep apnoea.

b) receiving the following antiarrhythmic or heart-rate-lowering drugs:

- Class Ia (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol) antiarrhythmics.
- Beta blockers
- Heart rate lowering calcium channel blockers (e.g. verapamil, diltiazem or ivabradine)
- other substances which may decrease heart rate (e.g. digoxin, anticholinesteratic agents or pilocarpine).

In such patients, treatment with Gilenya should be considered only if the anticipated benefits outweigh the potential risks and advice from a cardiologist should be sought prior to initiation of treatment including, if appropriate, the possibility to switch to non heart rate lowering drugs. If treatment with Gilenya is considered for these patients, monitoring at least overnight should be initiated.

For all patients, monitoring should include:

- A 12-lead ECG and blood pressure measurement before starting the first dose and after 6 hours
- blood pressure and heart rate measurement every hour after the first dose for 6 hours

During the first 6 hours of treatment continuous real time ECG monitoring is recommended

If the patient's heart rate at the end of the 6-hour period is the lowest following first dose administration, the monitoring should be extended by at least 2 hours and until the heart rate increases.

Criteria for extended monitoring:
In those patients with evidence of clinically important cardiac effects during the first 6 hours, monitoring should be extended, including at least overnight monitoring, until resolution. Recommended criteria for extending monitoring include:

- The occurrence at **anytime** during the monitoring period after first dose of:
  - New onset 3rd degree atrioventricular block
- The presence **at the end** of the monitoring period after first dose of:
  - Heart rate less than 45 beats per minute
  - QTc interval ≥500 msec.
  - Persistent new-onset 2nd degree atrioventricular block, Mobitz Type I (Wenckebach) or higher degree atrioventricular block

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:

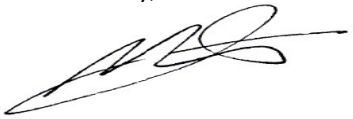
- **upon request by mail: "FREEPOST YELLOW CARD"**
- **at the back of the British National Formulary (BNF)**
- **by telephoning the Commission of Human Medicines (CHM) free phone line: 0800-731-6789**
- **or by electronic download through the MHRA website (http://yellowcard.mhra.gov.uk/downloads)**

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 Mark Bechter
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23rd April 2012