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25 April 2012

Updated Direct Healthcare Professional Communication on cardiovascular monitoring during treatment initiation with Gilenya (fingolimod)

Dear .....

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 apnea.

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

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appropriate, the possibility to switch to non heart rate lowering durgs. 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 Irish Medicines Board.

Call for Reporting

Healthcare professionals should report any suspected adverse reactions associated with use of Gilenya to Novartis at 01-2601255 or to the Irish Medicines Board online at www.imb.ie or using the Yellow card system.
Should you have any queries or require additional information please contact the Novartis Medical Director, Dr. Greg Hays at (01) 2601255.

Yours sincerely,

Dr Greg Hays

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Medical Director