24th April 2012

Circular No. P10/2012

Dear Healthcare Professionals and Patients,

Re: European Medicines Agency gives new advice to better manage risk of adverse effects on the heart with Gilenya.

Gilenya has been authorised in the EU since March 2011 and marketed in member states including Malta for the treatment of relapsing-remitting MS in patients who have not responded to treatment with beta-interferon or whose disease is severe and getting worse rapidly. It contains the active substance fingolimod and is the first disease-modifying MS treatment available as an oral formulation.

It has been known since the initial authorisation that Gilenya may cause transient bradycardia – a short-lived decrease in heart rate – and may also be associated with heart rhythm disorders related to AV block. The product information contains warnings about these risks. In January 2012 the European Medicines Agency's (EMA) Committee for Human Medicinal Products (CHMP) started a review of the cardiovascular safety of Gilenya following receipt of information related to an unexplained sudden death in a patient within 24 hours of taking Gilenya for the first time (see Medicines Authority Circular **P02/2012** for more information). In this review the CHMP analysed other adverse event cases with heart related adverse effects to Gilenya and it was observed that these effects occurred mostly in patients with pre-existing heart disease and that these effects occurred at their maximum within six hours after the first dose. The CHMP also noted that this decrease in heart rate was reversible using appropriate treatment.

On the basis evidence from this review on Gilenya the Agency's Committee for Medicinal Products for Human Use (CHMP) gave the following recommendations to healthcare professionals and patients:

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(1) Doctors should not prescribe Gilenya to patients with a history of cardiovascular and cerebrovascular disease or who take heart-rate lowering medication. When treatment with Gilenya is considered necessary in these patients, their heart activity should be monitored at least overnight following the first dose of Gilenya and doctors should seek advice from a cardiologist on appropriate monitoring.

(2) All patients starting treatment with Gilenya should have their heart activity monitored before receiving the first dose of the medicine and continuously for at least six hours after. Monitoring should be extended for at least two hours in patients whose heart rate is lowest six hours after receiving the first dose of Gilenya.

(3) In patients who develop clinically significant heart problems monitoring should continue at least overnight and until the problems have resolved.

The CHMP is of the opinion that the possible risk of heart problems in patients taking Gilenya could be minimised by further strengthening the existing warnings on the cardiovascular effects of the medicine and ensuring close monitoring of all patients. The marketing authorisation holder, Novartis has committed to changing the products' information and the Medicines Authority is currently reviewing a 'Dear Doctor Letter/Direct Healthcare Professional Communication' to be sent to healthcare professionals by Novartis so that they are informed about these warnings and recommendations for safe use. With these risk-minimisation measures in place, the EMA concludes that the benefits of Gilenya continue to outweigh the risks.

The Medicines Authority is in agreement with the **press release** and **question-and-answer document** issued by the EMA. Healthcare professionals are encouraged to maintain vigilance on Gilenya. Suspected Adverse Drug Reactions may be reported using the Medicines Authority yellow card scheme or online at **http://www.medicinesauthority.gov.mt/pub/adr.doc** or to the marketing authorisation holder or their local representatives.

Healthcare professionals are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

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