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Questions and answers on the review of Gilenya

Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004

On 19 April 2012, the European Medicines Agency completed a review of Gilenya, following cases of death and serious cardiovascular events (problems related to the heart and blood vessels) in patients who had recently started treatment with the medicine. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of Gilenya continue to outweigh its risks but recommended changes to the product information to strengthen the warnings and ensure close monitoring of all patients following the first dose.

What is Gilenya?

Gilenya is a medicine used to treat adults with highly active multiple sclerosis (MS). MS is a disease of the nerves, in which inflammation destroys the protective sheath surrounding the nerve cells. Gilenya is used in the type of MS known as 'relapsing-remitting', when the patient has attacks (relapses) in between periods with decreased symptoms (remissions). It is used when the disease has failed to respond to beta-interferon (another type of medicine used in MS), or is severe and getting worse rapidly. Gilenya is available as capsules. It is the only disease-modifying MS treatment available to be taken by mouth.

The active substance in Gilenya, fingolimod, blocks the action of a receptor called 'the sphingosine-1-phosphate receptor' on T cells (a type of immune cell involved in inflammation). This stops the movement of T cells from the lymph nodes to the brain and spinal cord, thus limiting the damage to nerve cells.

Gilenya has been authorised in the European Union (EU) since March 2011 and has been marketed in 16 EU Member States[1] as well as Norway. In total, more than 30,000 patients have received Gilenya worldwide.

The current European public assessment report for Gilenya can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

[1] Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Italy, Poland, Portugal, Slovakia, Spain, Sweden, the Netherlands and United Kingdom.

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Why was Gilenya reviewed?

On 12 December 2011, the company that markets Gilenya, Novartis Europharm Ltd., informed the Agency of the unexplained sudden death of a patient in the United States of America within 24 hours of taking Gilenya for the first time.

While no cases of sudden or unexplained death had been reported in clinical studies at the time of its authorisation, it was known that Gilenya causes a transient bradycardia (a short-lived decrease in heart rate) and might be associated with atrioventricular block (a type of heart rhythm disorder). Warnings on these important cardiovascular effects had been included in the medicine's product information and doctors had been recommended to observe patients for signs and symptoms of bradycardia for at least six hours after the first dose (or when the last dose had been administered more than two weeks earlier).

On 18 January 2012, the CHMP started a review of Gilenya following the reported death, to assess the need for further measures to ensure the safe use of the medicine. While the review was ongoing, the CHMP issued temporary recommendations to doctors, including the recommendation to monitor patients continuously with ECG (a test that measures the electrical activity of the heart) for six hours after taking the first dose. Doctors were also advised to consider extending the monitoring of patients who developed any clinically relevant heart problem (such as bradycardia or atrioventricular block).[2]

Which data has the CHMP reviewed?

The CHMP reviewed the available safety data from clinical studies and post-marketing surveillance, including data on cardiovascular problems following the first dose of Gilenya. The Committee also looked at the circumstances surrounding the reported cases of death. In total, 15 cases of sudden or unexplained death in patients treated with Gilenya were assessed by the Committee. Most of the deaths and cardiovascular problems had occurred in patients with a history of cardiovascular problems and/or taking other medicines. However, the data reviewed were not conclusive as to whether Gilenya was the cause of the deaths.

What are the conclusions of the CHMP?

The CHMP considered that there is clear evidence of the benefit of Gilenya in relapsing-remitting multiple sclerosis. However, considering that certain patients have an increased risk of cardiovascular problems, particularly those with a history of cardiovascular or cerebrovascular problems (problems with the blood supply to the brain), and those who are taking other medicines that lower the heart rate, the Committee concluded that Gilenya is not recommended in these patients. However, if treatment is nonetheless considered necessary, advice from a cardiologist should be sought and an extended monitoring, at least overnight, is recommended after the first dose.

The CHMP also noted that the maximum effect of Gilenya on decreasing the heart rate occurred within six hours after the first dose in most patients, and that this decrease in heart rate can be reversed, if necessary, by giving atropine or isoprenaline. Therefore, the Committee recommended that the product information be amended to further strengthen the warnings on the cardiovascular effects of the medicine and to ensure close monitoring of all patients, particularly during the six hours after the first dose. In addition, if patients develop any relevant heart problem during the six-hour monitoring, the monitoring should be extended at least overnight.

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/01/human_pha_detail_000050.jsp&mid=WC0b01ac058001d126&source=homeMedSearch&category=human

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefit-risk balance for Gilenya remains positive.

A communication will be distributed to doctors at national level to inform them of the changes to the use of Gilenya. The amended information to doctors and patients is detailed here.

What are the recommendations for patients?

- Patients are advised to report any symptoms that could suggest they have a heart problem (such as chest pain, nausea, palpitations, weakness or dizziness) to their doctor, as soon as possible.
- Patients who have any questions should speak to their doctor.

What are the recommendations for prescribers?

- Treatment with Gilenya is not recommended:
  - in patients with a history of cardiovascular or cerebrovascular disease. However, if treatment with Gilenya is considered necessary, advice from a cardiologist should be sought regarding the appropriate heart monitoring for these patients when starting treatment. Monitoring should be at least overnight;
  - in patients taking certain antiarrhythmic medicines (medicines used to restore normal cardiac rhythm);
  - in patients taking certain medicines that lower the heart rate. However, if treatment with Gilenya is considered necessary, advice from a cardiologist should be sought as to whether these patients should be switched to a different medicine that does not lower the heart rate, or whether they should be continuously monitored overnight by ECG after the first dose.
- When starting treatment with Gilenya, doctors should:
  - before the first dose, check the patient's blood pressure, heart rate, as well as their heart by ECG.
  - after the first dose, check the patient's blood pressure and heart rate every hour for six hours.
- Doctors are recommended to continuously monitor the patient's heart function by ECG for six hours after the first dose.
- Doctors are recommended to extend monitoring after the six-hour period if:
  - at the end of the six-hour period the heart rate is at its lowest since taking the first dose. In this case, the monitoring should be extended for at least two more hours and until the heart rate increases again;
  - patients develop any clinically relevant heart problem (such as bradycardia or atrioventricular block). If so, doctors are advised to extend the monitoring period at least overnight and until resolution.

A European Commission decision on this opinion will be issued in due course.