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Questions and answers on the review of Multaq (dronedarone)

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

The European Medicines Agency has completed a review of the benefit-risk balance of Multaq following reports of severe liver injury and lung injury and the termination of a clinical trial due to severe cardiovascular events that occurred in some patients taking the medicine. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of Multaq continue to outweigh the risks for a limited population of patients with atrial fibrillation and has made recommendations to reduce the risk of adverse liver, lung and cardiovascular events.

What is Multaq?

Multaq is a medicine that contains the active substance dronedarone (400 mg). It was approved for use in adults with non-permanent atrial fibrillation or who have had atrial fibrillation in the past. Atrial fibrillation happens when the atria (the upper chambers of the heart) contract irregularly and rapidly. Multaq was used to prevent the fibrillation coming back or to lower the heart rate.

The active substance in Multaq, dronedarone, is an anti-arrhythmic medicine. It works mainly by blocking channels through which charged particles of potassium move in and out of the muscle cells causing the excessive electrical activity that leads to atrial fibrillation and rapid heart rate.

Multaq has been authorised in the European Union since 26 November 2009 and is marketed in 18 Member States[1] as well as Iceland and Norway.

Why was Multaq reviewed?

Following reports of two cases of serious liver injury leading to liver transplantation in patients taking Multaq, the Agency's Committee for Medicinal Products for Human Use (CHMP) recommended in January 2011 that warnings and precautions be introduced into the medicine's prescribing information to reduce the possible risk of severe liver complications. A review was then started to assess all

[1] Multaq is marketed in Austria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Ireland, Italy, Lithuania, Malta, Slovakia, Poland, Slovenia, Spain, Sweden and the United Kingdom.

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available data concerning the possible risks of liver injury associated with the use of Multaq and their impact on its benefit-risk balance.

During the review the Agency became aware of the termination of a clinical trial (PALLAS) investigating Multaq compared to placebo (a dummy treatment) in patients over 65 years of age with permanent atrial fibrillation and several risk factors. The trial was terminated, because of the occurrence of severe cardiovascular events (such as cardiovascular death or hospitalisation and stroke) in some patients taking Multaq. Although Multaq is not approved for use in patients with permanent atrial fibrillation, the Agency was concerned about the results of the PALLAS trial and extended the scope of the review to include the new data from the trial as well as other data that became available on the risk of damage to the lungs.

Which data has the CHMP reviewed?

The Committee reviewed all available data on Multaq. This included data from the clinical trials with Multaq including the results of the PALLAS study as well as information from the company's monitoring of the use of the medicine. The CHMP also consulted a group of experts in cardiovascular diseases and patient representatives.

What are the conclusions of the CHMP?

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that there was a risk of Multaq causing injury to the liver as well as the lung. The Committee also concluded that, although the population in the PALLAS trial (permanent atrial fibrillation with several risk factors) differs from the currently approved population (non-permanent atrial fibrillation), the cardiovascular findings from the study were significant and could be relevant for the currently approved population.

In order to ensure that the benefits of Multaq continue to outweigh its risks, the CHMP considered that restrictions and other measures were needed to minimize the risk of adverse liver, lung and cardiovascular events. The Committee is issuing a number of risk minimisation measures which include recommendations in the prescribing information on the use of Multaq.

The Committee has agreed with the company on a letter to be sent out shortly to prescribers in the EU explaining the changes to the prescribing information as well as educational material for prescribers.

The amended information to doctors and patients can be found here.

What are the recommendations for patients and prescribers?

- Multaq should only be prescribed if other antiarrhythmic medicines have been considered.
- Multaq should only be used for maintaining heart rhythm in patients with persistent and paroxysmal atrial fibrillation (types of non-permanent atrial fibrillation) and whose normal heart rhythm has been restored.
- Treatment with Multaq should only be started and monitored by a specialist.
- Prescribers should consider discontinuing Multaq if atrial fibrillation reoccurs.
- Switching treatment from amiodarone to Multaq should be done cautiously by a specialist.
- Multaq must not be given to patients with permanent atrial fibrillation.

- Multaq must not be given to patients with left ventricular systolic dysfunction (impairment affecting the left side of the heart) or patients who have had or have heart failure.
- Patients who have had previous liver or lung injury following treatment with amiodarone, another antiarrhythmic medicine, must not be given Multaq.
- Patients on Multaq should have their lung and liver function as well as their heart rhythm regularly monitored. Especially liver function should be monitored more closely during the first few weeks. Kidney function should also be monitored during the first week of treatment.
- Patients currently on Multaq are recommended to have their treatment evaluated by their doctor at their next scheduled appointment.
- Patients who have any questions should speak to their doctor or pharmacist.

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

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