European Medicines Agency

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QUESTIONS AND ANSWERS ON THE WITHDRAWAL OF THE MARKETING APPLICATION for MULTAQ

International Non-proprietary Name (INN): ***dronedarone***

This product was later resubmitted to the EMEA. See here for information on outcome of resubmission.

On 6 September 2006, sanofi-aventis officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for MULTAQ, for the treatment of atrial fibrillation and atrial flutter.

What is MULTAQ?
MULTAQ is a medicine that consists of tablets containing 400 mg of dronedarone.

What was MULTAQ expected to be used for?
MULTAQ was to be used to treat patients with atrial fibrillation or atrial flutter. Atrial fibrillation and atrial flutter are caused by problems in the conduction of electrical impulses in the upper chambers of the heart (atria). Both illnesses cause a rapid heart rate, but atrial fibrillation also makes the heart rhythm irregular.
Atrial fibrillation and flutter are very common conditions, particularly in people over 65 years of age. MULTAQ was expected to help patients maintain normal heart rhythm and to reduce the heart rate.

How is MULTAQ expected to work?
The active substance in MULTAQ, dronedarone, is an anti-arrhythmic agent. It is expected to correct altered heartbeat by affecting the electrical activity of the heart muscle. The medicine has a number of effects on the heart muscle, including reducing the flow of potassium ions (charged particles) out of the heart cells.

What documentation has the company presented to support its application to the CHMP?
The effects of MULTAQ were first tested in experimental models before being studied in humans. The company presented the results of two clinical trials comparing the effects of MULTAQ and placebo (a dummy treatment) on the maintenance of normal heart rhythm. The studies involved a total of 1,237 patients with an average age above 60 years. All of the patients had had atrial fibrillation or flutter at least once in the past three months but had a normal heart rhythm at the start of the study. The studies examined how long it took for atrial fibrillation or flutter to return.
The company also presented the results of a third study that compared the effects of MULTAQ and placebo on the heart rate in 174 patients who had had atrial fibrillation continuously for over six months. The study measured the change in heart rate between the start of the study and day 14 of treatment. The patients' heart rates were measured when they were resting.

How far into the evaluation was the application when it was withdrawn?
The application was at day 174 when the company withdrew. After the CHMP had assessed the responses from the company to a list of questions, there were still some unresolved issues outstanding.

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The CHMP normally takes up to 210 days to evaluate a new application. Based on the review of the initial documentation, the CHMP prepares a list of questions at day 120, which is sent to the company. Once the company has supplied responses to the questions, the CHMP reviews them and may, before giving an opinion, ask any remaining questions at day 180. Following a CHMP opinion, it usually takes around 2 months for the European Commission to grant a licence.

What was the recommendation of the CHMP at that time?
Based on the review of the data and the company's response to the CHMP's list of questions at the time of the withdrawal, the CHMP had concerns and was of the provisional opinion that MULTAQ could not be approved for the treatment of atrial fibrillation or atrial flutter.

What were the main concerns of the CHMP?
The CHMP was concerned that the studies presented by the company had not sufficiently shown that MULTAQ's effects on heart rate and rhythm would be beneficial to patients, since they had not compared MULTAQ to an existing medicine licensed for the same conditions. According to their guidelines for medicines used to correct heart rhythm, the CHMP would need to assess the results of a trial comparing MULTAQ to an existing medicine before it can be granted a licence.
The CHMP was also concerned that the levels of MULTAQ could be altered in patients taking some other medicines, including medicines used to treat the heart. In addition, MULTAQ can alter the levels of some other medicines. The CHMP also had concerns over a higher rate of side effects in patients taking MULTAQ than those taking placebo.
Therefore, at the time of the withdrawal, the CHMP's view was that further studies were needed to adequately assess the medicine's benefits and risks.

What were the reasons given by the company to withdraw the application?
The letter from the company notifying the EMEA of the withdrawal of the application is available here.

What are the consequences of the withdrawal for patients undergoing clinical trials with MULTAQ?
The Company has informed the CHMP that there are no consequences for patients currently included in clinical trials with MULTAQ. If you are in a clinical trial and need more information about your treatment, contact the doctor who is giving it to you.