European Medicines Agency

London, 22 March 2007
Doc. Ref. EMEA/117441/2007

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

International non-proprietary name (INN): ***ruboxistaurin***

On 13 March 2007, Eli Lilly Nederland B.V. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for ARXXANT, for the treatment of diabetic retinopathy in adult patients with moderate to severe non-proliferative retinopathy.

What is ARXXANT?
ARXXANT is a medicine that contains the active substance ruboxistaurin (as 32 mg tablets).

What was ARXXANT expected to be used for?
ARXXANT was expected to be used to treat adult patients who have moderate to severe non-proliferative retinopathy as a complication of diabetes. Retinopathy is damage to the blood vessels within the retina, the light-sensitive surface at the back of the eye. This damage causes the blood vessels to leak fluid, leading to swelling in the retina. Retinopathy can eventually lead to a loss of vision and even blindness. 'Non-proliferative' means that the disease is an early stage, during which the patient may not notice any change in vision.

How is ARXXANT expected to work?
The active substance in ARXXANT, ruboxistaurin, blocks the activity of the enzyme protein kinase C (PKC) beta. This is a naturally-occurring enzyme that is responsible for regulating the activity of blood vessels in the retina. In patients with diabetes, high levels of glucose (sugar) in the blood may cause this enzyme to become overactivated, leading to damage to the blood vessels. By blocking PKC beta, ruboxistaurin is expected to prevent damage to the blood vessels and loss of vision.

What documentation did the company present to support its application to the CHMP?
The effects of ARXXANT were first tested in experimental models before being studied in humans. The company presented the results of one main study involving 685 patients with moderately severe to very severe non-proliferative diabetic retinopathy. The study compared the effects of ARXXANT and placebo (a dummy treatment) over three years. The main measure of effectiveness was the proportion of patients in each group who experienced a loss of vision at the end of the study. This was assessed by measuring the number of letters they could see on a standard vision chart: a fall of 15 letters or more over six months was considered to be a loss of vision.

How far into the evaluation was the application when it was withdrawn?
The application was at day 120 when the company withdrew. The CHMP had formulated a list of questions to be answered by the company, but the company had not yet responded to them.
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 the CHMP's opinion, it usually takes around two months for the European Commission to grant a licence.

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What was the recommendation of the CHMP at that time?
Based on the review of the data at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that ARXXANT could not have been approved for the treatment of diabetic retinopathy in adult patients with moderate to severe non-proliferative retinopathy.

What were the main concerns of the CHMP?
The CHMP was concerned that the effectiveness of ARXXANT had not been proven adequately in the clinical study. The committee also had concerns over the medicine's side effects, particularly disturbances of the heart rhythm.
Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of ARXXANT had not been sufficiently demonstrated and any benefits did not outweigh the identified 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 ARXXANT?
The company informed the CHMP that there are no consequences for patients currently included in clinical trials with ARXXANT.
If you are in a clinical trial and need more information about your treatment, contact the doctor who is giving it to you.