European Medicines Agency

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QUESTIONS AND ANSWERS ON THE WITHDRAWAL OF THE APPLICATION FOR A CHANGE TO THE MARKETING AUTHORISATION
for
ZOMETA

International non-proprietary name (INN): ***zoledronic acid***

On 15 November 2007, Novartis Europharm Limited officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a new indication for Zometa, in the prevention of fracture and bone loss in postmenopausal women with early-stage breast cancer treated with aromatase inhibitors.

What is Zometa?
Zometa is a medicine containing the active substance zoledronic acid. It is available as a powder and solvent to be made up into a solution for infusion (drip into a vein), and as a concentrate for infusion. Zometa is already approved for use in the prevention of bone complications in patients with advanced cancer that affects the bone. This includes fractures (broken bones), spinal compression (pressure on the spinal cord), bone disorders needing radiotherapy or surgery, and hypercalcaemia (high levels of calcium in the blood). Zometa can also be used to treat the hypercalcaemia caused by tumours.

What was Zometa expected to be used for?
In the new indication, Zometa was expected to be used to prevent fractures and bone loss in postmenopausal women with early-stage breast cancer who were being treated with anticancer medicines called aromatase inhibitors. Aromatase inhibitors include anastrozole, letrozole and exemastane, and can cause bone loss and fractures as a side effect.

How is Zometa expected to work?
The active substance in Zometa, zoledronic acid, is a bisphosphonate. It stops the action of the osteoclasts, the cells in the body that are involved in breaking down the bone tissue. This leads to less bone loss. The reduction of bone loss helps to make bones less likely to break, which may be useful in preventing fractures.

What documentation did the company present to support its application to the CHMP?
The effectiveness of Zometa in preventing bone loss was studied in two main studies involving a total of 1,667 postmenopausal women treated for early-stage breast cancer with letrozole (an aromatase inhibitor). Both studies looked at the effects of starting Zometa at the same time as starting letrozole treatment, compared with the effects of waiting until there was significant bone loss or evidence of a fracture before starting Zometa. The main measure of effectiveness was the change in 'bone mineral density' (the amount of bone) in the spine, between the start of the study and one year later. Bone mineral density was measured using a special type of X-ray called 'dual energy X-ray absorptiometry' (DEXA).
The company also compared the results of these studies with results from studies of Aclasta, another medicine that also contains zoledronic acid, but which is used to prevent fractures in postmenopausal women with osteoporosis. This comparison was intended to provide information on the effect of zoledronic acid on bone fractures in women being treated with aromatase inhibitors.

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How far into the evaluation was the application when it was withdrawn?
The application was at day 90 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. The CHMP normally takes up to 90 days to adopt an opinion after it has received an application for a change to a marketing authorisation. Following the CHMP's opinion, it usually takes around six weeks for the European Commission to update the 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 list of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Zometa could not have been approved for the prevention of fractures and bone loss in women being treated with aromatase inhibitors.

What were the main concerns of the CHMP?
The CHMP had concerns over the way the two main studies were designed, since they did not look directly at bone fractures. Although Zometa seemed to reduce bone loss when it was started at the same time as letrozole, the CHMP was not convinced of the relevance of this finding in the absence of adequate information on fractures. This was not overcome by providing information on fractures from studies looking at Aclasta in the treatment of osteoporosis.
The CHMP was also concerned that there was insufficient information to show that the dose of Zometa used in the studies was the most appropriate for these patients.
Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Zometa 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 in clinical trials using Zometa?
The company informed the CHMP that this withdrawal does not have any effect on patients currently included in clinical trials with Zometa. If you are in a clinical trial and have any questions, contact your doctor.

What is happening for Zometa for the prevention of bone complications and hypercalcaemia?
There are no consequences on the use of Zometa in its approved indications, for which the balance of benefits and risks remains positive.