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Questions and answers

Withdrawal of the application for a change to the marketing authorisation for Xgeva (denosumab)

On 13 January 2017, Amgen Europe BV officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for Xgeva to be used to treat hypercalcaemia of malignancy (high levels of calcium in the blood caused by cancer).

What is Xgeva?

Xgeva is a medicine used to prevent bone complications in adults with a solid tumour that has spread to the bone. These complications include fractures (breaks in the bone), spinal compression (when the spinal cord is compressed by the bone), or complications requiring radiotherapy (treatment with radiation) or surgery.

Xgeva is also used to treat a type of bone cancer called giant cell tumour of bone in adults and adolescents whose bones have fully developed. It is used in patients who cannot be treated by surgery or in whom surgery would cause severe problems.

Xgeva has been authorised since July 2011. It contains the active substance denosumab and is available as a solution to be injected under the skin.

What was Xgeva expected to be used for?

Xgeva was also expected to be used to reduce hypercalcaemia of malignancy (high levels of calcium in the blood caused by cancer) that did not respond to previous treatment with medicines called bisphosphonates.

High calcium levels are a serious complication that can affect cancer patients in the last stages of their disease.

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How does Xgeva work?

The active substance in Xgeva, denosumab, is a monoclonal antibody, a protein that has been designed to recognise and attach to another protein called RANKL. RANKL is involved in activating osteoclasts, the cells in the body that are involved in breaking down bone tissue. By attaching to and blocking RANKL, denosumab reduces the formation and activity of the osteoclasts. This reduces the loss of bone, making fractures and other serious bone complications less likely to happen, and also lowers calcium levels in the blood.

What did the company present to support its application?

The company presented the results of a study involving 33 patients with hypercalcaemia. Xgeva was not compared with any other treatment in this study. The main measure of effectiveness was based on the number of patients who had a response to treatment, defined as having their blood calcium levels reduced to 2.9 mmol/l or lower within 10 days of the first dose.

How far into the evaluation was the application when it was withdrawn?

The application was withdrawn after the CHMP had evaluated the initial documentation provided by the company and formulated a list of questions. The company had not yet responded to the questions at the time of the withdrawal.

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 Xgeva could not have been approved for the treatment of hypercalcaemia caused by cancer and which did not respond to treatment with bisphosphonates.

The CHMP considered that there were several problems with the main study which did not allow the Committee to conclude on the effectiveness of Xgeva: the study did not compare Xgeva with any other treatments and only included a small number of patients; it was not certain whether the patients' condition had responded to bisphosphonates, as the patients' previous calcium levels were not available. Additionally, since patients were being treated with other hypercalcaemia treatments or had recently stopped treatment with bisphosphonates, it was not possible to determine the scale of the effect or whether the benefits observed in the study were due to Xgeva or were the effects of these other treatments.

Therefore, at the time of the withdrawal, the CHMP was of the opinion that the results of the study were not sufficient and concluded that the medicine could not have been approved based on the data presented by the company.

What were the reasons given by the company for withdrawing the application?

In its letter notifying the Agency of the withdrawal of application, the company stated that it was withdrawing the application because the CHMP considered the data provided insufficient to conclude that the benefits of Xgeva outweighed its risks in the treatment of hypercalcaemia caused by cancer.

The withdrawal letter is available here.

What consequences does this withdrawal have for patients in clinical trials or compassionate use programmes?

The company informed the CHMP that there are currently no ongoing clinical trials or compassionate use programmes with Xgeva.

What is happening with Xgeva for the prevention and treatment of other diseases?

There are no consequences for the use of Xgeva in its authorised indications.

The full European Public Assessment Report for Xgeva can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.