EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Questions and answers on the review of calcitonin-containing medicines

Outcome of a procedure under Article 31 of Directive 2001/83/EC

On 19 July 2012, the European Medicines Agency completed a review of the benefits and risks of calcitonin-containing medicines, concluding that there was evidence of a small increased risk of cancer with long-term use of these medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that they should only be authorised for short-term use in Paget's disease, acute bone loss due to sudden immobilisation and hypercalcaemia caused by cancer. The Committee also concluded that the benefits of calcitonin-containing medicines did not outweigh their risks in the treatment of osteoporosis and that they should no longer be used for this condition.

After a re-examination, the Committee confirmed its recommendation on 15 November 2012.

What is calcitonin?

Calcitonin is a hormone that increases the amount of calcium in the bones and lowers the calcium level in the blood.

Calcitonin, manufactured in the laboratory, is used in medicines to treat or prevent conditions that involve the loss of calcium from the bones. It has been used in the EU for treating osteoporosis (a disease that makes bones fragile), Paget's disease (a bone disease that involves bone remodelling and can cause deformity), and hypercalcaemia (increased blood calcium) caused by cancer. It is also used to prevent acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures.

Calcitonin-containing medicines have been available in the EU as solutions for injection or infusion (drip into a vein) since 1973, and as a nasal spray since 1987. They are currently marketed in most EU countries.

Why were calcitonin-containing medicines reviewed?

This review was initiated following preliminary findings from two studies of an unlicensed oral calcitonin medicine, which pointed to a possible association with prostate cancer. These findings were made available to EU national authorities in November 2010.

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A possible association between calcitonin and prostate cancer was first investigated by the UK medicines regulatory agency in 2004, but a causal association could not be established with the evidence available at the time. The issue was also investigated in 2009 and 2010 by the EMA's Pharmacovigilance Working Party (PhVWP), but there was insufficient evidence at the time for any regulatory action.

Following the receipt of the data from the studies on the unlicensed oral medicine, the UK medicines agency asked the CHMP to carry out a full assessment of the benefit-risk balance of calcitonin-containing medicines and to issue an opinion on whether their marketing authorisations should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

In addition to the two studies of the unlicensed oral calcitonin medicine, the CHMP reviewed available data on the benefits and risks of calcitonin-containing medicines provided by the companies that market these medicines as well as data from the scientific literature and from third parties. The CHMP also reviewed post-marketing safety data, randomised controlled studies and experimental cancer studies.

What are the conclusions of the CHMP?

The CHMP noted that the available data suggest that a higher proportion of patients treated with calcitonin for long periods of time may develop cancer of various types, compared with patients taking placebo. Although the cancer rates reported in the studies were low, the increase in cancer rates seen with calcitonin varied between 0.7% in studies with the oral formulation to 2.4% in the studies with the nasal formulation. Taking into account the limited benefit of calcitonin when used to treat post-menopausal osteoporosis to reduce the risk of vertebral fractures, the CHMP concluded that the benefits of calcitonin did not outweigh the risks in this condition. As the nasal spray is only used in osteoporosis, the CHMP recommended that this formulation should no longer be used.

The benefit-risk balance remains positive only for the following uses: treatment of Paget's disease for patients who cannot be treated with alternative treatments, prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures, and the treatment of hypercalcaemia caused by cancer. However, the CHMP recommended that even for these uses calcitonin treatment should be given for the shortest possible time using the smallest effective dose. The Committee maintained its recommendations after re-examination.

The full changes made to the information to doctors and patients are detailed here.

What are the recommendations for patients?

- Calcitonin will no longer be used for the treatment of osteoporosis. Patients being treated for osteoporosis with calcitonin nasal sprays or other formulations are advised to speak to their doctor at a routine appointment, who will recommend suitable alternative treatment.
- Patients receiving injectable calcitonin who have any questions should speak to their doctor or pharmacist.

What are the recommendations for prescribers?

- Prescribers should note that calcitonin should no longer be used for the treatment of osteoporosis.

- Calcitonin will only be available as a solution for injection and infusion, and should only be used for:
  - prevention of acute bone loss due to sudden immobilisation, with a recommended treatment period of two weeks and a maximum treatment period of four weeks;
  - Paget's disease, restricted to patients who do not respond to alternative treatments or for whom such treatments are not suitable, and with treatment normally limited to three months (longer treatment and periodic retreatment may be considered taking into account the benefits and risks);
  - hypercalcaemia caused by cancer.
- Treatment with calcitonin should be limited to the shortest possible time using the smallest effective dose.

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