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Questions and answers on the review of bisphosphonates and atypical stress fractures

Outcome of nine procedures under Article 20 of Regulation (EC) No 726/2004 and of one procedure under Article 31 of Directive 2001/83/EC as amended[1]

The European Medicines Agency has completed a review of bisphosphonate-containing medicines at the request of the United Kingdom and the European Commission, following reports of an increased risk of atypical stress fractures of the femur associated with these medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of bisphosphonates continue to outweigh their risks but that warnings of the risk of atypical femoral fractures should be added to the prescribing information for all bisphosphonate-containing medicines in the European Union (EU).

What are bisphosphonates?

Bisphosphonates are medicines that are used to treat and prevent bone disorders. They have been authorised in the EU since the early 1990s for hypercalcaemia (high levels of calcium in the blood) and the prevention of bone problems in patients with cancer. They have also been available since the mid 1990s for the treatment of osteoporosis (a disease that makes bones fragile) and Paget's disease (a disease involving bone growth that causes bone deformity). They work by stopping the action of the osteoclasts, the cells that are involved in breaking the bone down.

Bisphosphonates include alendronic acid, clodronic acid, etidronic acid, ibandronic acid, neridronic acid, pamidronic acid, risedronic acid, tiludronic acid and zoledronic acid. They are available in the EU as tablets and as solutions for infusion (drip into a vein) under various trade names and as generic medicines[2].

[1] Procedure numbers: EMEA/H/C/000595/A-20/0026, EMEA/H/C/000336/A-20/0036, EMEA/H/C/000101/A-20/0051, EMEA/H/C/000502/A-20/0025, EMEA/H/C/000501/A-20/0024, EMEA/H/C/000759/A-20/0012, EMEA/H/C/000619/A-20/0015, EMEA/H/C/001180/A-20/0005, EMEA/H/C/001195/A-20/0001 and EMEA/H/A-31/001279

[2] Bisphosphonates can be authorised nationally or centrally. The centrally authorised bisphosphonate-containing medicines concerned by these referrals are Aclasta and Zometa (zoledronic acid), Bondenza, Bonviva, Bondronat and Ibandronic acid Teva (ibandronic acid), and Adrovance and Fosavance (alendronic acid and vitamin D3).

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Why were bisphosphonates reviewed?

In 2008, the CHMP's Pharmacovigilance Working Party (PhVWP) noted that alendronic acid was associated with an increased risk of atypical fracture of the femur (thigh bone) that developed with low or no trauma. As a result, a warning was added to the product information of alendronic acid-containing medicines across Europe. The PhVWP also concluded at the time that it was not possible to rule out the possibility that the effect could be a class effect (an effect common to all bisphosphonates), and decided to keep the issue under close review.

In April 2010, the PhVWP noted that further data from both the published literature and post-marketing reports were now available that suggested that atypical stress fractures of the femur may be a class effect. The working party concluded that there was a need to conduct a further review to determine if any regulatory action was necessary.

Consequently, on 20 September 2010, the UK Medicines Regulatory Agency asked the CHMP to issue an opinion on bisphosphonate-containing medicines and atypical stress fractures and on whether the marketing authorisation for these medicines should be maintained, varied, suspended or withdrawn across the EU. At the same time, the European Commission requested the CHMP to carry out the same assessment for the centrally authorised medicines.

Which data has the CHMP reviewed?

The CHMP has reviewed all case reports of stress fractures in patients treated with bisphosphonates, relevant data from the published literature and data provided by the companies that make bisphosphonates. The Committee has also looked at epidemiological studies (studies of the causes and distribution of diseases in the population).

What are the conclusions of the CHMP?

The Committee noted that the number of reports of atypical fractures of the femur in users of bisphosphonates had increased since the 2008 review. The CHMP also noted that these fractures had a distinct pattern on X-rays and may be related to bisphosphonate use, especially during long-term use in osteoporosis. The Committee agreed that this could be related to the mode of action of bisphosphonates, which could lead to a delay in the repair of naturally occurring stress fractures although the exact mechanism is not known.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that atypical femoral fractures are likely to be a class effect of bisphosphonates but that such fractures occur only rarely and the benefits of bisphosphonate-containing medicines continue to outweigh their risks. However, the product information should be amended to add a warning concerning this risk, and, for bisphosphonates used in osteoporosis, to advise doctors to periodically review treatment, in particular after five or more years of treatment.

The full changes made to the information to doctors and patients are available on the Agency's website.

What are the recommendations for prescribers and patients?

- Doctors who prescribe bisphosphonate-containing medicines should be aware that atypical fractures may occur rarely in the femur (thigh bone), especially after long term use. If an atypical fracture is suspected in one leg then the other leg should also be examined.

- Doctors who are prescribing these medicines for the prevention or treatment of osteoporosis should regularly review the need for continued treatment, especially after five or more years of use.
- Patients who are taking bisphosphonate-containing medicines need to be aware of the risk of atypical fracture of the thigh bone. They should report to their doctor any pain, weakness or discomfort in the thigh or groin area, as this may be an indication of a possible fracture.
- Patients who have any questions should speak to their doctor or pharmacist.

The European Commission issued a decision on 13 July 2011.

The current European public assessment reports for the nine centrally authorised medicines containing bisphosphonates concerned by these referrals (Aclasta, Adrovance, Bondenza, Bondronat, Bonviva, Fosavance, Ibandronic acid Teva, Vantavo and Zometa) can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.