7 th June 2011

Circular No. P06/2011

Dear Healthcare Professional,

Re: European Medicines Agency finalises review of bisphosphonates and atypical stress fractures

Bisphosphonates have been authorised in the EU for hypercalcaemia and the prevention of bone problems in patients with cancer since the early 1990s. They have also been available since the mid 1990s for the treatment of osteoporosis and Paget's disease of the bone. 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 under various trade names and as generic medicines2.

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.

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The CHMP then reviewed all case reports of stress fractures in patients treated with bisphosphonates, epidemiological data, relevant data from the published literature and data provided by the companies producing bisphosphonates. 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.

Recommendations

- Doctors who prescribe bisphosphonate-containing medicines should be aware that atypical fractures may occur rarely in the femur, 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.

- Doctors who prescribe biphosphonates should ensure that their patients are 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.

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The Medicines Authority has participated in the discussions held at the EMA and is in agreement with the **question-and-answer** document issued by the EMA, attached here for your perusal.

Healthcare professionals are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis

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