

## **Questions and answers on the review of bisphosphonates and the risk of osteonecrosis of the jaw**

The European Medicines Agency has completed a review on the risk of osteonecrosis (death of bone tissue) of the jaw associated with the use of bisphosphonates. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that there is an increased risk of osteonecrosis of the jaw in patients using these medicines. However, further studies should be carried out to better identify the factors that increase the risk and the measures needed to minimise it. The review was carried out under an 'Article 5(3)' procedure<sup>1</sup>.

### **What are bisphosphonates?**

Bisphosphonates are medicines that are used to treat and prevent bone disorders. They have been authorised in the European Union (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 European Union (EU) as tablets and as solutions for infusion (drip into a vein) under various trade names<sup>2</sup>.

### **Why were these medicines reviewed?**

In 2005, the CHMP's Pharmacovigilance Working Party concluded a review that showed an increased risk of osteonecrosis of the jaw in patients receiving bisphosphonates, particularly in cancer patients receiving intravenous forms (given into a vein). As a result, the prescribing information for all bisphosphonates was updated to include recommendations that patients have regular dental check-ups and avoid dental surgery whenever possible. However, a conclusive assessment of the risk was not possible because only limited data were available and there were no agreed criteria to define osteonecrosis of the jaw precisely.

Since then, more cases of osteonecrosis of the jaw have been reported, but with all forms of bisphosphonates (both tablets and infusions) and in patients with other diseases including osteoporosis. Consequently, in January 2009, the Danish medicines regulatory agency referred the matter to the CHMP to seek its scientific opinion on the association between the use of bisphosphonates and osteonecrosis of the jaw. In particular, the CHMP was asked to give its opinion on the following issues:

- the criteria that define osteonecrosis of the jaw related to bisphosphonates;
- how bisphosphonates may cause osteonecrosis of the jaw;
- whether the risk of osteonecrosis of the jaw is greater with some bisphosphonates or for some groups of patients;
- the measures that could be taken to minimise this risk.

<sup>1</sup> Article 5(3) of Regulation (EC) 726/2004, opinion on any scientific matter concerning the evaluation of medicinal products for human use.

<sup>2</sup> The centrally authorised bisphosphonates are Aclasta (zoledronic acid), Zometa (zoledronic acid), Bondenza (ibandronic acid), Bonviva (ibandronic acid), Bondronat (ibandronic acid), Adavance (alendronic acid and vitamin D3) and Fosavance (alendronic acid and vitamin D3).

### **Which data have the CHMP reviewed?**

The CHMP has reviewed all of the available data from the published literature and data provided by the companies that make bisphosphonates. It also looked at guidelines produced by learned societies. The Committee also took advice from a group of experts representing all areas of medicine where bisphosphonates are used, dentistry and bone surgery, and representatives of patients' organisations.

### **What are the conclusions of the CHMP?**

Based on the evaluation of the data and the scientific discussion within the Pharmacovigilance Working Party and the Committee, the CHMP concluded on the definition of osteonecrosis of the jaw related to bisphosphonates. This is defined as an area of exposed or dead bone in the jaw that has lasted for more than eight weeks, in a patient who has been exposed to a bisphosphonate and has not had radiation therapy on the jaw.

Regarding the mechanisms through which bisphosphonates may cause osteonecrosis of the jaw, the Committee noted that several mechanisms have been suggested in published literature. However, further studies are required and a suitable experimental model should be developed.

When looking at all cases of osteonecrosis of the jaw, the Committee noted that:

- the risk of osteonecrosis of the jaw is greater in cancer patients receiving intravenous bisphosphonates than in patients being treated for non-cancer indications, such as osteoporosis;
- the risk appears to be low in patients taking bisphosphonates by mouth.

Although the most important risk factors seem to be the potency of the bisphosphonate used, the dose and how it is given, the CHMP concluded that further research on risk factors is needed and that a European registry collecting information on cases of osteonecrosis of the jaw could be helpful.

Finally, the Committee concluded that further data are needed to determine the precise measures that could minimise the risk of osteonecrosis of the jaw, including looking at how intravenous bisphosphonates should be given (such as their dose, how often they are given and for how long), and looking into the risk of osteonecrosis of the jaw in patients taking bisphosphonates by mouth for long periods. The CHMP noted that other possible risk factors for developing osteonecrosis of the jaw should be considered, such as gender, genetic factors, smoking and other treatments or diseases that the patient has, as well as the type of cancer a patient has and how long they have had it. Finally, the Committee concluded that information on the known and potential risks of osteonecrosis of the jaw with bisphosphonates should be clearly communicated to healthcare professionals and to patients.

### **What are the recommendations for patients, dentists and prescribers?**

- Before taking any decisions concerning treatment with bisphosphonates, prescribers should take the risks and benefits for each individual patient into account.
- Prescribers should ensure that patients with cancer go to their dentist for a check-up and find out if they need any dental treatment before they start taking a bisphosphonate. They should also ensure that patients who do not have cancer go to their dentist for a check-up if their dental health is poor.
- During treatment with bisphosphonates, patients should maintain good oral hygiene, go for routine dental check-ups and report any symptoms in the mouth such as loose teeth, pain or swelling.
- Dentists should be aware of the risks in patients taking bisphosphonates and should keep dental treatment as conservative and preservative as possible.
- It is essential that prescribers, dentists and patients work together to manage the risk of osteonecrosis of the jaw.
- Patients who have any questions or concerns should speak to their doctor or dentist.

### **What will happen next?**

The CHMP opinion will be communicated to the Member States, so that they can take appropriate action at national level. For further information, see the scientific opinion adopted by the CHMP on 24 September 2009.

The European Medicines Agency, together with regulatory authorities in Member States, will keep this issue under close review.