



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Further measures to minimise risk of osteonecrosis of the jaw with bisphosphonate medicine

Measures for other intravenous bisphosphonates and denosumab to be considered in upcoming reviews

The European Medicines Agency (EMA) has completed a periodic review¹ of Aclasta (zoledronic acid), one of the bisphosphonate medicines with a known risk of osteonecrosis of the jaw. The Agency concluded that the risk of osteonecrosis (or death of bone tissue) in the jaw remains very low, but has recommended a number of measures to minimise the risk, including an update to the product information and the introduction of a patient reminder card.

EMA is planning similar measures for other intravenous bisphosphonates and denosumab, used for osteoporosis or for preventing bone complications of cancers, as these are also associated with a risk of osteonecrosis of the jaw. Measures for these medicines will be considered during their [upcoming and ongoing periodic reviews](#), which are planned to take place over the course of 2015/2016.

EMA's Committee for Medicinal Products for Human Use (CHMP) has now adopted the recommendations for Aclasta, following a [review by the Pharmacovigilance Risk Assessment Committee \(PRAC\)](#).

The CHMP opinion will now be sent to the European Commission for a legally binding decision valid throughout the European Union (EU).

Information for patients

Aclasta is used to treat osteoporosis and bone loss. These conditions involve thinning and weakening of the bones and can cause bones to break more easily. A side effect called osteonecrosis of the jaw has been reported very rarely in patients treated with Aclasta. It is important that you continue your treatment as directed by your doctor.

It is also essential that you try to prevent osteonecrosis of the jaw developing as it can be painful and difficult to treat. In order to reduce your risk of osteonecrosis of the jaw, there are some precautions you should take.

- Before receiving treatment, tell your doctor, pharmacist or nurse if:

¹ Periodic safety update single assessment (PSUSA)



- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction;
 - you do not receive routine dental care or have not had a dental check-up for a long time;
 - you are a smoker (as this may increase the risk of dental problems);
 - you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders);
 - you are taking medicines called corticosteroids (such as prednisolone or dexamethasone);
 - you have cancer.
- Your doctor may ask you to undergo a dental examination before you start treatment with Aclasta.
 - You should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or are due to undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Aclasta.
 - Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

You will find the information above in the package leaflet that comes with your medicine. In addition, your doctor will provide you with a [patient reminder card](#). Please read the information in the card carefully and discuss any question you may have with your doctor.

Information for healthcare professionals

Osteonecrosis of the jaw is a known risk with bisphosphonate medicines and denosumab. In patients treated for osteoporosis, the risk is very small compared to patients treated with higher doses for cancer related conditions. The risk seems also to be greater when parenteral formulations are used.

During a periodic review of Aclasta, EMA recommended some measures to further minimise this risk with this medicine. EMA is planning similar recommendations for other parenteral formulations of bisphosphonate medicines and denosumab at their next periodic reviews over the course of 2015/2016.

Healthcare professionals should follow the following recommendations for Aclasta:

- Delay the start of treatment or a new course of treatment in patients with unhealed open soft tissue lesions in the mouth that may require dental or oral procedures.
- Ensure patients have a dental examination and an individual benefit-risk assessment before starting treatment in patients with concomitant risk factors.
- Consider the following when evaluating a patient's risk of developing osteonecrosis of the jaw:
 - Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
 - Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection) and smoking.

- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors and radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures and a history of dental disease, invasive dental procedures, e.g. tooth extractions.
- Encourage patients to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, non-healing of sores or discharge during treatment with zoledronic acid. While patients are on treatment, invasive dental procedures should be performed with caution and these procedures should be avoided close to their treatment.
- Managing patients who develop osteonecrosis of the jaw should involve close collaboration between the treating physician and a dentist or oral surgeon with expertise in osteonecrosis of the jaw. Consider interrupting treatment temporarily until the condition resolves and the contributing risk factors are mitigated, where possible.

The information above can be found in text proposed for the [updated summary of product characteristics \(SmPC\) for Aclasta](#) (part of the product information).

More about the medicine

Aclasta (zoledronic acid) is a bisphosphonate medicine used to treat osteoporosis (a disease that makes bones fragile) in women who have been through the menopause and in men. It is also used to treat Paget's disease of the bone in adults. This is a disease where the normal process of bone growth is changed.

Aclasta works by reducing the action of the osteoclasts, the cells that break down bone tissue. As a result, Aclasta leads to less bone loss in osteoporosis and less disease activity in Paget's disease.

More about the procedure

This review was conducted by EMA's Pharmacovigilance Risk Assessment Committee (PRAC) and is a type of review known as a periodic safety update single assessment (PSUSA).

During this type of review, the PRAC evaluates any new risks identified in order to determine whether the balance of benefits and risks of a medicine has changed and can make recommendations to better manage or minimise risks.

The PRAC's recommendations were sent to EMA's Committee for Medicinal Products for Human Use (CHMP), which has issued the Agency's final opinion. The CHMP opinion will now be sent to the European Commission for a legally binding decision valid throughout the EU.

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