

26<sup>th</sup> August 2014

**Denosumab 120mg (XGEVA® ▼) Updated information to minimize the risk of osteonecrosis of the jaw and hypocalcaemia**

Dear Healthcare Professional,

Amgen Ltd. would, in agreement with the European Medicines Agency and the Health Product Regulatory Authority, like to inform you of updated information and recommendations to minimize the risk of osteonecrosis of the jaw (ONJ) and hypocalcaemia during treatment with XGEVA.

**Summary**

**Osteonecrosis of the jaw**

- **ONJ is a common side effect in patients treated with XGEVA.**
- **Before starting XGEVA, a dental examination with appropriate preventive dentistry is recommended.**
- **Do not start XGEVA in patients with an active dental or jaw condition requiring surgery, or in patients who have not recovered following oral surgery.**
- **Tell patients receiving XGEVA to maintain good oral hygiene practices, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling during treatment with XGEVA.**

**Hypocalcaemia**

- **Hypocalcaemia  $\geq$  grade 3 is a common side effect of XGEVA. The risk increases with the degree of renal impairment.**
- **Pre-existing hypocalcaemia must be corrected prior to initiating therapy with XGEVA.**
- **Supplementation with calcium and vitamin D is required in all patients unless hypercalcaemia is present.**
- **Monitoring of calcium levels should be conducted:**
  - **prior to the initial dose of XGEVA**
  - **within two weeks after the initial dose**
  - **if suspected symptoms of hypocalcaemia occur**
- **Consider monitoring calcium levels more frequently during therapy in patients with risk factors for hypocalcaemia (e.g. patients with severe renal**

**impairment, creatinine clearance <30 ml/min), or if otherwise indicated based on the clinical condition of the patient.**

- **Tell patients to report symptoms of hypocalcaemia.**

### ***Further information***

XGEVA is indicated for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

### **Osteonecrosis of the jaw**

ONJ is a condition in which the jawbone becomes necrotic, exposed and does not heal within 8 weeks. The etiology of ONJ is not clear, but may be associated with inhibition of bone remodeling.

Known risk factors for ONJ include invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), poor oral hygiene or other pre-existing dental disease. Other risk factors for ONJ are advanced malignancies, infections, older age, concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors, radiotherapy to the head and neck), smoking and previous treatment with bisphosphonates. While on treatment, patients should avoid invasive dental procedures if possible.

In patients with risk factors for ONJ, an individual benefit-risk assessment should be performed before initiating therapy with XGEVA.

In clinical XGEVA trials, the incidence of ONJ was higher with longer duration of exposure. The patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment, 3.7% in the second year and 4.6% per year thereafter. Patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure were excluded from the clinical trials.

For patients who develop ONJ during treatment, doctors should create a management plan in close collaboration with a dentist or oral surgeon with ONJ expertise, and a temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Patients should be encouraged to maintain good oral hygiene practices, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling during treatment with XGEVA. Patients should also be advised to refer to the Patient Information Leaflet (PIL) for information on symptoms of ONJ.

### **Hypocalcaemia**

Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream.

Severe symptomatic hypocalcaemia (including fatal cases) has been reported in patients receiving treatment with XGEVA.

During clinical trials, severe hypocalcaemia (corrected serum calcium < 7 mg/dL or < 1.75 mmol/L) occurred in 3.1% of patients receiving treatment with XGEVA.

Most cases of severe symptomatic hypocalcaemia have occurred in the first weeks of initiating therapy. The risk of developing hypocalcaemia during XGEVA treatment is greater with increasing degree of renal impairment. In a clinical study in patients without advanced cancer, 19% of patients with severe renal impairment (creatinine clearance < 30 ml/min) and 63% of patients receiving dialysis developed hypocalcaemia despite calcium supplementation. The overall incidence of clinically significant hypocalcaemia was 9%.

Patients should be encouraged to report of symptoms indicative of hypocalcaemia. Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures, and altered mental status (including coma). Symptoms of hypocalcaemia in clinical studies included paresthesias or muscle stiffness, twitching, spasms and muscle cramps.

### **Call for reporting**

Suspected adverse reactions should be reported to the Health Products Regulatory Authority (HPRA) using a Yellow Card obtained either from the HPRA, or electronically via the online reporting system at [www.hpra.ie](http://www.hpra.ie). Adverse reactions can also be reported to the Health Products Regulatory Agency by calling on (01) 676 4971.

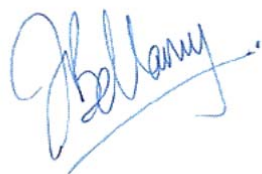
Reports can also be made to Amgen Europe B.V. by contacting Amgen UK/Ireland Drug Safety Department directly on 0044 1223 436712.

▼ This medicinal product is subject to additional monitoring.

### **Company contact point**

Should you have any questions or require additional information regarding the use of Prolia, please contact Amgen UK/Ireland Medical Information on 0044 1223 436441 or by email to [gbinfo@amgen.com](mailto:gbinfo@amgen.com).

Yours sincerely,



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Medical Director, UK & Ireland

**Prescribing information for XGEVA can be accessed at**  
<http://www.medicines.ie/medicine/15078/SPC/XGEVA/> (Summary of Product Characteristics) and <http://www.medicines.ie/medicine/15079/PIL/XGEVA/> (Package Leaflet)