AMGEN UK Limited
240 Cambridge Science Park
Milton Road
Cambridge
Cambridgeshire
CB4 0WD
Tel: +44(0)1223 420305
UK Freephone: 0800 243104
Fax: +44(0)1223 426314

26th August 2014

Denosumab 60mg (Prolia®): Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia

Dear Healthcare Professional,

Amgen Ltd. in agreement with the European Medicines Agency and the Medicines and Healthcare Products Regulatory Agency would like to inform you of updated information and recommendations to minimise the risk of osteonecrosis of the jaw (ONJ) and hypocalcaemia during treatment with Prolia.

Summary

Osteonecrosis of the jaw

- **Doctors should evaluate all patients for ONJ risk factors prior to treatment with Prolia**
- **A dental examination with appropriate preventive dentistry is recommended in patients with concomitant risk factors**
- **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 Prolia**

Hypocalcaemia

- **Hypocalcaemia is an identified risk in patients treated with Prolia, which increases with the degree of renal impairment.**
- **Pre-existing hypocalcaemia must be corrected prior to initiating therapy with Prolia**
- **Adequate intake of calcium and vitamin D is important in all patients, and especially important in patients with severe renal impairment**
- **Monitoring of calcium levels should be conducted:**
  - **prior to each dose of Prolia**
  - **within two weeks after the initial dose in patients predisposed to hypocalcaemia (e.g. patients with severe renal impairment, creatinine clearance <30 ml/min)**
  - **if suspected symptoms of hypocalcaemia occur or if otherwise indicated based on the clinical condition of the patient**
- **Tell patients to report symptoms of hypocalcaemia**

Further information

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.

ONJ has been reported rarely in clinical studies and in the post marketing setting in patients receiving Prolia (denosumab at dose 60 mg every 6 months for osteoporosis). ONJ has been reported commonly in patients with advanced cancer treated with denosumab at a dose of 120 mg administered monthly.

Known risk factors for ONJ include previous treatment with bisphosphonates, older age, poor oral hygiene, invasive dental procedures (e.g. tooth extractions, dental implants, oral surgery), co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection), smoking, a diagnosis of cancer with bone lesions, and concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck).

While on treatment, patients with risk factors should avoid invasive dental procedures if possible. For patients who develop ONJ while on Prolia therapy, doctors should develop a management plan for the individual patient in close collaboration with a dentist or oral surgeon with expertise in ONJ. Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated, where possible.

Hypocalcaemia, including severe symptomatic cases

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

In two phase 3 placebo-controlled clinical trials in postmenopausal women with osteoporosis, there were no reported cases of severe symptomatic hypocalcaemia.

In the post-marketing setting, rare cases of severe symptomatic hypocalcaemia have been reported. Renal insufficiency was described in the majority of these cases, with most cases occurring in the first weeks of initiating Prolia therapy but it can occur later.

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

Indication

Prolia is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia reduces the risk of vertebral, nonvertebral and hip fractures.
Prolia is also indicated the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia reduces the risk of vertebral fractures.

Call for reporting

Please continue to report suspected adverse reactions with any medicine or vaccine to the MHRA through the Yellow Card Scheme online at www.mhra.gov.uk/yellowcard. Please report

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼

It is easiest and quickest to report ADRs online via the Yellow Cards website: www.mhra.gov.uk/yellowcard. Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gsi.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- or by downloading and printing a form from the Yellow Card section of the MHRA website

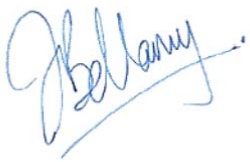
When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Reports can also be made to Amgen Europe B.V. by contacting Amgen UK/Ireland Drug Safety Department directly on 01223 436712.

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 01223 436441 or by email to gbinfoline@amgen.com.

Yours sincerely,



Dr Steven Bellamy MBChB
Medical Director, UK & Ireland

Prescribing information for Prolia can be accessed at http://www.medicines.org.uk/emc/medicine/23127 (Summary of Product Characteristics) and http://www.medicines.org.uk/emc/medicine/23128 (Package Leaflet)