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18th August 2016

**Denosumab 60mg (Prolia®): Updated information to minimise the risk of osteonecrosis of the jaw, hypocalcaemia and atypical femoral fracture**

Dear Healthcare Professional,

Amgen Ltd. in agreement with the Saudi Food and Drug Authority would like to inform you of updated information and recommendations to minimize the risks of osteonecrosis of the jaw (ONJ), hypocalcaemia and atypical femoral fracture with Prolia.

Prolia is indicated for the treatment of osteoporosis in postmenopausal women 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.

***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**

- Prolia is contraindicated for use in patients with hypocalcaemia.
- Hypocalcemia is an identified risk in patients treated with Prolia, which increases with the degree of renal impairment.

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- Pre-existing hypocalcemia 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 or receiving dialysis)
  - 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

**Atypical Femoral Fracture**

- During Prolia treatment, patients should be advised to report new or unusual thigh, hip, or groin pain.
- Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture, and the contralateral femur should also be examined.

***Further information on the safety concern and the recommendations***

**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.

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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 hypocalcemia.

**Atypical femoral fracture**

Cases of atypical femoral fracture have been confirmed in patients receiving Prolia participating in the ongoing open-label extension study of the pivotal phase 3 fracture trial in postmenopausal osteoporosis (FREEDOM). These events have occurred very rarely (< 1/10,000) based on 31,266 subject-years exposed to Prolia in bone loss studies.

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Atypical femoral fractures are subtrochanteric or proximal diaphyseal fractures that occur with little to no trauma. Specific radiographic findings, including a simple transverse or oblique fracture with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft, characterize these events.[1] An increased risk of atypical femoral fractures has been reported with bisphosphonates, another class of anti-resorptive therapy for postmenopausal osteoporosis.[1,2] As a result, Amgen has proactively evaluated the potential for atypical femoral fractures in patients treated with Prolia in clinical trials and the post marketing setting.

During Prolia treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.

**The information in this letter has been approved by the Saudi Food and Drug Authority.**

***Call for reporting***

Any suspected adverse reactions should be reported immediately to Amgen local representative or to the National Pharmacovigilance and Drug Safety Centre.

Amgen Local Representative in Saudi Arabia is Cigalah Group, Mobile number: 00966539455825 or email: drug-safety@cigalah.com.sa

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***Company contact point***

Should you have any questions or require additional information regarding the use of Prolia®, please contact Amgen Medical Information on 00971 4 4396800 or by e-mail at meamedinfo@amgen.com

Sincerely,

P.P.

Nasser Alrajhi
Regulatory Affairs Senior Manager
Amgen Saudi Arabia

Dr Sibel Barti
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***Annexes***

References:

1. Shane E, Burr D, Ebeling PR, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society of Bone and Mineral Research. *J Bone Miner Res*. 2010;25:2267-2294.
2. Whitaker M, Guo J, Kehoe T, Benson G. Bisphosphonates for osteoporosis — where do we go from here? *N Engl J Med*. 2012;366:2048-2051

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