Direct Healthcare Communication

April 2013

Risk of Atypical Femoral Fracture with Prolia (denosumab)

Dear Healthcare Professional,

This letter is sent to inform you of the risk of atypical femoral fracture associated with the use of denosumab.

Summary of the issue

- Atypical femoral fractures have been reported rarely in patients with postmenopausal osteoporosis receiving Prolia (denosumab)

Recommendations for Health Care Professionals

- During Prolia (denosumab) 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 contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture.
- Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated. An individual assessment of the benefits and risks should be performed.

This letter is sent in agreement with the European Medicines Agency and the Medicines Authority.

Denosumab is also available as XGEVA, 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. The risk of AFF also exists for this product.

Further information on the safety concern

Prolia is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fractures and the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

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). The duration of Prolia exposure to time of atypical femoral fracture diagnosis was as early as 2½ years. These events have occurred rarely (≥ 1/10,000 to < 1/1,000) based on 8,928 subjects being exposed to Prolia in bone loss studies.

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] They may occur bilaterally. An increased risk of atypical femoral fractures has been reported with bisphosphonates, another class of antiresorptive therapy for postmenopausal osteoporosis.[1,2] As a result, Amgen has evaluated the potential for atypical femoral fractures in patients treated with Prolia in clinical trials and the postmarketing setting.

To communicate this important information, the warnings and description of undesirable effects in the product information will be updated to inform prescribers of the risk of atypical femoral fractures.

For more information regarding denosumab refer to the product details available on the EMA website: http://www.ema.europa.eu

Call for reporting

Any Adverse Drug Reactions and Medication Errors should be reported to:

Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or at: http://www.medicinesauthority.gov.mt/adrportal; Phone Number: +356 2343 9000

Or to:

Amgen Dompè S.p.A. (Italy), Via Tazzoli 6, 20154 Milano, E-mail: eu-it-farmacovigilanza@amgen.com, Phone number: +39 026241121, Fax Number: +39 02624112370

Contact details

Should you have any questions or require additional information regarding the use of Prolia please contact Amgen's local representative of Medical Information Department in Italy (Telephone number: +39 02 6241121).

Sincerely

Dr Antonio Baldassarre
Amgen Global Safety Sr. Manager

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