HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

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

Following a European-wide review of the latest safety data for Prolia, the product information for Prolia has been updated to include updated information and revised recommendations to minimise the risk of osteonecrosis of the jaw (ONJ) and hypocalcaemia during treatment.

ONJ is a condition in which the jawbone becomes necrotic, exposed and does not heal within eight weeks. It has been reported rarely in clinical studies and also in the post-marketing setting in patients treated with Prolia 60mg every six months for osteoporosis. ONJ has been reported commonly however in patients with advanced cancer treated with Xgeva at a dose of 120mg monthly. Known risk factors for ONJ include previous treatment with bisphosphonates, older age, poor oral hygiene, invasive dental procedures (tooth extractions, dental implants etc), co-morbid disorders (e.g. pre-existing dental disease, anaemia, etc), smoking and concomitant therapies (e.g. chemotherapy, corticosteroids, radiotherapy to head and neck).

Denosumab inhibits osteoclast bone resportion, thereby decreasing the release of calcium from bone into the blood stream. In the post-marketing setting, rare cases of severe symptomatic hypocalcaemia have been reported. The majority of cases occurred in the few weeks following initiation of treatment with Prolia and renal insufficiency was also described in the majority of cases. Severe symptomatic hypocalcaemia can manifest as QT interval prolongation, tetany, seizures and altered mental status. Additional symptoms of hypocalcaemia include muscle stiffness, twitching, spasms and muscle cramps. To minimise the risk of osteonecrosis of the jaw (ONJ) and hypocalcaemia during treatment with Prolia, healthcare professionals are reminded of the following recommendations:

Advice for Healthcare Professionals:
To minimise the risk of ONJ

- Prescribing 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 advised to maintain good oral hygiene practices, attend routine dental check-ups and immediately report any oral symptoms (such as pain or swelling) during treatment with Prolia.
- If a patient experiences ONJ while on Prolia therapy, a management plan for the individual patient should be developed in close collaboration with a dentist and/or oral surgeon with expertise in the area.
- Temporary interruption of treatment with Prolia should be considered until the condition resolves and contributing risk factors are mitigated, where possible.

To minimise the risk of hypocalcaemia

- Hypocalcaemia is a known 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.
- All patients taking Prolia should be encouraged to maintain an adequate intake of calcium and vitamin D. This is 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 <30ml/min).
  - If suspected symptoms of hypocalcaemia occur, or if otherwise indicated based on the clinical condition of the patient.
- Patients should be informed of the signs and symptoms of hypocalcaemia and advised to report any symptoms experienced.
- This information was highlighted in a Dear Healthcare Professional Communication (DHPC) circulated to relevant healthcare professionals in September 2014.

Key messages

- Prior to commencing treatment with Prolia, all patients should be evaluated for ONJ risk factors which include age, poor oral hygiene, co-morbid disorders and smoking. During treatment, patients should be encouraged to maintain good oral hygiene practices and report any oral symptoms experienced. If ONJ occurs, temporary interruption of treatment should be considered until the condition resolves.

- The risk of developing hypocalcaemia while being treated with Prolia increases with increasing degree of renal impairment. Any pre-existing hypocalcaemia must be corrected prior to initiating Prolia therapy and calcium levels should be monitored before each dose and for those patients predisposed to hypocalcaemia, within two weeks after the initial dose. Patients' should be informed of the signs and symptoms of hypocalcaemia and advised to report if any of these effects are experienced.

Further details of the product information for Prolia available at www.hpra.ie and www.ema.europa.eu/ema

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