HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Bisphosphonates and denosumab
Minimising the risk of osteonecrosis of the jaw (ONJ)

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has completed a periodic review of one of the bisphosphonate medicines, Aclasta (zoledronic acid). Bisphosphonates are used in the treatment of osteoporosis and are associated with a known, small risk of osteonecrosis of the jaw (ONJ). The HPRA has previously communicated on the risk of ONJ with these medicines and the steps to be taken by healthcare professionals and patients to reduce this risk (HPRA Drug Safety Newsletters 23rd edition, 27th edition, 35th edition and 63rd edition).

Following the routine periodic review for Aclasta, the PRAC has recommended a number of new measures, including an update to the product information and in particular the introduction of a patient reminder card, to reinforce the key risk minimisation messages for patients.

The card recommended by the PRAC will remind patients about:
- the benefit of treatment of osteoporosis;
- the risk of ONJ associated with treatment with Aclasta;
- the need to highlight any dental problems to their doctors/nurses before starting treatment;
- the need to ensure good dental hygiene during treatment;
- the need to inform their dentist of treatment with Aclasta and to contact the doctor and dentist if problems with the mouth or teeth occur during treatment. Patients may wish to show the reminder card to their dentist when discussing their dental treatment.

The product information (i.e. Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) will also include further information on how to minimise this risk.

The PRAC will consider similar revisions to the product information and the introduction of patient reminder cards for other intravenous bisphosphonates, used for osteoporosis or for preventing bone complications of cancers, as well as for denosumab which is also associated with a risk of ONJ. These will be considered during the upcoming and on-going periodic reviews, which are planned to take place over the course of 2015/2016.

The PRAC recommendations for Aclasta have been sent to EMA's Committee for Medicinal Products for Human Use (CHMP) for final opinion.

Advice to Healthcare Professionals

Before initiation of treatment / new treatment course

- The following factors should be considered when evaluating a patient's risk of developing ONJ
  - Route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy,
  - Potency of the medicinal product for inhibiting bone resorption (highly potent compounds are a higher risk),
  - Known risk factors for ONJ include previous treatment with bisphosphonates, older age, poor oral hygiene, history of dental disease, poorly fitting dentures, periodontal disease, invasive dental procedures (tooth extractions, dental implants etc.), co-morbid disorders (e.g. pre-existing dental disease, anaemia, infection, coagulopathies etc.), smoking and concomitant therapies (e.g. chemotherapy, corticosteroids, angiogenesis inhibitors and radiotherapy to head and neck).

- Ensure patients have a dental examination and an individual benefit-risk assessment before commencing treatment especially those with concomitant risk factors.

- Delay the start of treatment or a new course of treatment in patients with unhealed open soft tissue lesions in the mouth that may require oral or dental procedures.

During treatment

- Patients should maintain good oral hygiene practices throughout their treatment and maintain routine dental examinations.
- Patients should be advised to immediately report any oral symptoms (such as dental mobility, pain or swelling, non-healing of sores or discharge) during their treatment.
- Invasive dental procedures should be performed only after careful consideration and should be avoided in close proximity to administration of bisphosphonates or denosumab.
- If a patient experiences ONJ while on bisphosphonates or denosumab 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 should be considered until the condition resolves and contributing risk factors are mitigated, where possible.
- Please report any suspected cases of ONJ with bisphosphonates or denosumab to the HPRA via the online, downloadable or post-paid reporting options available at www.hpra.ie.

Key messages

- Patients should be evaluated for ONJ risk factors prior to commencing treatment with bisphosphonates or denosumab.
- Prior to commencing treatment, patients should visit their dentist for a dental examination and necessary dental surgical procedures should be completed prior starting treatment.
- During treatment, patients should maintain excellent dental hygiene and attend routine dental examinations.
- Patients should immediately report any oral symptoms experienced and healthcare professionals are requested to report any cases of suspected ONJ to the HPRA.
- The Product information (SmPC and PL) for Aclasta will be updated to reflect the additional risk minimisation measures.
- A patient reminder card will be available for Aclasta shortly to reinforce the key risk minimisation messages for patients in relation to ONJ.

**Bisphosphonates currently authorised in Ireland include Fosamax, Fosavance, Osteomel, Bonviva, Bonefos, Actonel, Zometa & Aclasta. Further details of their product information are available at www.hpra.ie and www.ema.europa.eu*

**Denusomab products currently authorised in Ireland include Prolia and Xgeva. Further details of their product information are available at www.hpra.ie and www.ema.europa.eu*

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