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HPRA DRUG SAFETY NEWSLETTER

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In this Edition

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 Editions *23*, *27*, *35* and *63*).

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.

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HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

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 of post-paid reporting options available at www.hpra.ie.

Key Message

- 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 to 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.

* *Further details on bisphosphonates and denosumab authorised in Ireland are available at www.hpra.ie and www.ema.europa.eu*

Risk of severe allergic reactions with ambroxol and bromhexine-containing medicines considered small

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review of the safety of ambroxol and bromhexine-containing medicines*.

Ambroxol and bromhexine are indicated for mucolytic therapy in patients with respiratory conditions. Ambroxol lozenges are available for pain relief of sore throats. The majority of these medicines are available over-the-counter (OTC) in Ireland and are marketed as single ingredient products.

Ambroxol containing medicines authorised and marketed in Ireland include:

- Ambrobene 3mg/ml and 6mg/ml Oral Solution
- Lysopadol 20mg Lozenges

Bromhexine containing medicines authorised and marketed in Ireland include:

- Bisolvon 4mg/5ml Oral Solution

The review of these products was initiated following post-marketing reports of hypersensitivity reactions (including anaphylactic reactions) and accumulating evidence from case reports and literature demonstrating that ambroxol is potentially responsible for severe cutaneous adverse reactions (SCARs).

The review has concluded as follows:

- Severe hypersensitivity reactions have been reported in patients receiving ambroxol. These include:
  - Severe allergic reactions including anaphylactic reactions;
  - SCARs including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalised exanthematous pustulosis.

Advice to Healthcare Professionals

- Ambroxol and bromhexine are associated with a small increased risk of immediate and delayed hypersensitivity reactions, anaphylactic reactions including anaphylactic shock, angioedema, pruritus, rash and urticaria.
- There is a possibility of a risk of SCARs (including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalised exanthematous pustulosis) associated with ambroxol and bromhexine.
- If symptoms of allergy or SCARs occur, treatment with ambroxol or bromhexine should be immediately discontinued.

Key Message

- The PRAC considered that ambroxol and bromhexine are associated with a small increased risk of hypersensitivity reactions.
- The PRAC considered that there is a reasonable possibility of a risk of SCARs associated with ambroxol and bromhexine.
- The PRAC was of the view that the risk of SCARs should be addressed by its inclusion in the product information accompanied by a warning for patients and caregivers to recognise the prodromes of SCARs and to discontinue treatment immediately in the event of such signs.

* *Further details on ambroxol and bromhexine-containing products are available at www.hpra.ie*

New restriction for hydroxyzine-containing medicines to further minimise the known risk of QT prolongation

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recently completed a *review* of hydroxyzine-containing* medicines and has recommended new measures to further mitigate the previously known risk of QT prolongation and torsades de pointes.

Hydroxyzine-containing medicines currently authorised in Ireland include:

- Ucerax 25mg Film coated tablets;
- Ucerax 10mg/5ml Syrup.

Hydroxyzine has the potential to block hERG channels and other types of cardiac channels, resulting in a potential risk of QT interval prolongation and cardiac arrhythmia events. This potential risk was confirmed by clinical and post-marketing data. Most of the cases reviewed had other risk factors, e.g. electrolyte abnormalities or concomitant treatment that may have been contributory.

The review concluded that the potential risk of QT interval prolongation and torsades de pointes can be adequately minimised through measures targeting identified risk factors and restricting the use of hydroxyzine to the lowest effective dose for the shortest possible duration.

Hydroxyzine-containing medicines are now contraindicated in patients with acquired or congenital QT interval prolongation or with a known risk factor for QT prolongation and they are no longer recommended in elderly patients. In adults the maximum daily dose should be 100mg while in children weighing up to 40kg, the maximum daily dose should be 2mg/kg/day. There are already warnings in product information for patients and prescribers on the potential for such cardiac disorders and these warnings will now be strengthened, and along with the new restrictions, will aim to reduce exposure to the medicine, particularly in the most vulnerable groups.

Advice to Healthcare Professionals

- Hydroxyzine is now contraindicated in patients with known acquired or congenital QT interval prolongation or with a known risk factor for QT prolongation.
- Examples of risk factors for QT interval prolongation include cardiovascular disease, family history of sudden cardiac death, significant electrolyte imbalance (hypokalaemia, hypomagnesaemia), significant bradycardia, concomitant use with other drugs known to prolong QTc and/or induce torsades de pointes.
- Hydroxyzine-containing medicines are no longer recommended for use in elderly patients however if deemed necessary to use hydroxyzine in this patient group then the maximum daily dose is 50mg.
- Patients who are co-medicated with medicines that induce hypokalaemia and bradycardia should be treated with caution.
- The maximum recommended daily dose in adults is now 100mg (a reduction from 300mg daily).
- The maximum recommended daily dose in children (weighing up to 40 kg) is now 2mg/kg/day. Children over 40 kg should be given the adult dose.
- Hydroxyzine should be used at the lowest effective dose, for the shortest possible treatment duration.
- The product information (Summary of Product Characteristics (SmPC) and package leaflet (PL)) for hydroxyzine-containing medicines will be updated to include this information. A Direct Healthcare Professional Communication (DHPC) will also be circulated by the Marketing Authorisation Holder (MAH) to relevant healthcare professionals.

Key Message

- Hydroxyzine is contraindicated in patients with known QT interval prolongation or with a known risk factor for QT prolongation.
- Hydroxyzine is no longer recommended in elderly patients.
- The maximum daily dose in adults is 100mg and the maximum daily dose in children (weighing up to 40kg) is 2mg/kg/day. Hydroxyzine should be used at the lowest effective dose for the shortest possible duration.
- Patients treated with other hypokalaemia and bradycardia inducing medicines should be cautiously treated with hydroxyzine.
- The product information for hydroxyzine will be updated shortly.

* *Further details on hydroxyzine products are available at www.hpra.ie*

The Importance of Product Information for Medicines

The HPRA would like to remind healthcare professionals of the importance of regular review and monitoring of product information for medicines, to support awareness of relevant updates/changes which may affect prescribing, dispensing, administration or monitoring practices. It is also important that patients and care-givers, as appropriate are made aware of the information contained in the Package Leaflet (PL) and should be encouraged to read it prior to and during their treatment.

The product information is comprised of the Summary of Product Characteristics (SmPC) and the PL. These documents are issued when a medicine is first licensed for use and are reviewed and updated as necessary throughout the lifetime of a medicine, to reflect the current state of knowledge of the medicine and the risks associated with its use. The SmPC is mainly intended for use by healthcare professionals and SmPCs for all medicines currently authorised in Ireland are accessible on the HPRA website *(www.hpra.ie)* via the 'Find a Medicine' search function. The PL reflects the more comprehensive information described in the SmPC, but is required to be presented in an abbreviated and easy-to-read format for patients. PLs are also available on the HPRA website.

The SmPC provides the basis of information for healthcare professionals to use a medicine safely, effectively and in the most appropriate manner. It is also a legal document, agreed between the HPRA/EMA (European Medicines Agency) and the relevant pharmaceutical company.

The format and content of the SmPC is laid down in EU/national legislation and regulatory guidance documents. Use of a medicine outside the conditions/recommendations described in the SmPC falls under the responsibility of the healthcare professional.

It is important to note that the SmPC is not intended to provide general advice on the treatment of particular medical conditions. On the other hand, specific aspects of the treatment related to use of the medicine, or its effects may be mentioned. Similarly, general advice on administration procedures is not included, but any advice specific to the medicine concerned will be included, if appropriate.

The PL is drawn up in accordance with the SmPC and is subject to user-testing to ensure its ease of readability by patients/consumers. It plays an essential part in supporting the safe and appropriate use of a medicine by a patient. Consequently, it is important that a PL is provided each time a product is dispensed. Patients and care-givers should be encouraged to read the current version of the PL that accompanies their medicine(s) and to discuss any relevant concerns with a healthcare professional involved in their care.

Key Message

- Product Information (SmPC and PL) is available for all medicines currently authorised in Ireland from the HPRA/EMA websites (accessible from *www.hpra.ie*).
- The current versions of the product information should be consulted regularly to ensure medicines are used in the safest and most effective manner.
- Patients should be encouraged to read the PLs provided with their medicines and to discuss any concerns with a relevant healthcare professional.

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Eucardic (carvedilol)	Safety update regarding severe cutaneous adverse reactions (SCARs).
Gilenya (fingolimod)	First reported case of progressive multifocal leukoencephalopathy (PML) in an MS patient taking fingolimod without previous treatment by natalizumab or other immunosuppressive medicines.

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