20th March 2012

Circular No. P09/2012

Dear Healthcare Professional,

Re: European Medicines Agency confirms positive benefit-risk balance of Protelos/Osseor, but recommends new contraindications and revised warnings

In October 2011, the Medicines Authority had informed you in circular **P14/2011** of the start of a review of the Benefit-Risk ratio of Protelos and Osseor (strontium ranelate), by the European Medicines Agency (EMA). The review of Protelos and Osseor was started following the publication of a study in France identifying 199 severe adverse reactions reported with these medicines from January 2006 to March 2009. Around half of these were Venous Thrombo-Embolic events (VTE), and about a quarter were related to skin reactions.The EMA's Committee for Medicinal Products for Human Use (CHMP) has now finalised this review and recommended changes to prescribing advice to better manage risks associated with this treatment.

Protelos and Osseor are indicated for the treatment of osteoporosis in postmenopausal women to reduce the risk of broken bones in the hip and spine. VTE and severe skin reactions are known risks of these medicines and have been kept under close review by the CHMP. The risk of VTE was identified in clinical trials and the risk of severe skin reactions, such as DRESS (drug rash with eosinophilia and systemic symptoms), SJS (Stevens-Johnson syndrome) and TEN (toxic epidermal necrolysis) had been reported post marketing. Information on these risks had been included in the product information as warnings or listed as reported side effects.

The CHMP has reviewed all available data on the safety of Protelos and Osseor. The data show that the risk of VTE is higher in patients with a history of VTE, as well as in patients

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who are temporarily or permanently immobilised. The number of cases of VTE in elderly patients is also shown to be higher with Protelos and Osseor compared with placebo.

The data also show that the incidence rate of serious skin reactions such as DRESS, SJS and TEN is low and no possible mechanism of action has been identified so far. Since the best results for managing these conditions come from early diagnosis and immediate discontinuation of any suspect drug, it is very important that doctors and patients are alert to the time-to-onset and signs and symptoms of these conditions.

Advice for doctors and patients

- Doctors should not prescribe Protelos and Osseor to patients with current VTE or a history of VTE, as well as patients who are temporarily or permanently immobilised.
- Patients with current VTE or a history of VTE, and those who are temporarily or permanently immobilised are advised to discuss their treatment with their doctor at their next scheduled appointment.
- When treating patients over 80 years of age at risk of VTE, doctors should re-evaluate the need to continue treatment with Protelos or Osseor.
- Prescribers should make patients aware of the time-to-onset and likely signs and symptoms of severe skin reaction such as DRESS, SJS or TEN. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment and usually around 3-6 weeks for DRESS. Symptoms or signs of SJS or TEN include progressive skin rash, often with blisters or mucosal lesions; symptoms of DRESS include rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease).
- Patients should stop treatment immediately when symptoms of severe allergic reactions, including skin rash, occur. Treatment should not be re-started at any time in these patients.

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The Medicines Authority is in agreement with the full **press release** and **question-and-answer document** issued by the EMA, attached here for your perusal. Healthcare professionals are encouraged to maintain vigilance on these medicinal products. Suspected Adverse Drug Reactions may be reported using the Medicines Authority yellow card scheme or online at **http://www.medicinesauthority.gov.mt/pub/adr.doc** or to the marketing authorisation holder or their local representatives.

Healthcare professionals are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

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