



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 March 2012
EMA/183047/2012
EMA/H/C/000560/A20/34
EMA/H/C/000561/A20/30

Questions and answers on the review of Protelos and Osseor (strontium ranelate)

Outcome of procedures under Article 20 of Regulation (EC) No 726/2004

On 15 March 2012, the European Medicines Agency completed a review of benefits and risks of Protelos and Osseor, following concerns over the risks of venous thromboembolism (VTE, formation of blood clots in the veins) and severe allergic skin reactions. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of Protelos and Osseor continue to outweigh their risks, but that these medicines should be contraindicated in patients with VTE or a history of VTE, as well as in patients who are temporarily or permanently immobilised. In addition, the Committee recommended an update of the warnings on the serious skin reactions seen with these medicines.

What are Protelos and Osseor?

Protelos and Osseor are medicines that contain the active substance strontium ranelate. They are used to treat osteoporosis (a disease that makes bones fragile) in women who have been through the menopause, to reduce the risk of broken bones in the spine and the hip. They are available as 2-g sachets containing granules that are made up into an oral suspension.

The active substance in Protelos and Osseor, strontium ranelate, acts on the bone structure. Once in the gut, strontium ranelate releases strontium, which is absorbed into the bone. Exactly how strontium works in osteoporosis is not fully understood, but it is known to stimulate bone formation and reduce bone breakdown.

Protelos and Osseor have been authorised in the EU since 21 September 2004 and are marketed in all EU Member States as well as Iceland.

The current European public assessment reports for these medicines can be found on the Agency's website: ema.europa.eu/Find_medicine/Human_medicines/European_public_assessment_reports.

Why were these medicines reviewed?

The risks of VTE and severe allergic skin reactions with Protelos and Osseor were already known and have been kept under close surveillance by the CHMP. The risk of VTE had been identified from clinical



studies at time of first authorisation, and a warning was included in the product information that these medicines should be used with caution in patients at increased risk of VTE, including patients with a history of VTE. In addition, cases of severe allergic skin reactions, such as life-threatening reactions called 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. In particular, for DRESS the warning advised patients to stop treatment immediately if allergic reactions including skin rash occur and to seek medical advice.

More recently, a study published in France identified 199 severe side effects with these medicines, of which around half were VTE events, and about a quarter related to skin problems. In light of these new data, the European Commission asked the CHMP to give its opinion on the measures necessary to ensure the safe and effective use of Protelos and Osseor, and on whether the marketing authorisations for these medicines should be maintained, varied, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The CHMP reviewed relevant information provided by the company on the effectiveness of Protelos and Osseor and on the risk of VTE and allergic skin reactions such as DRESS, SJS and TEN, including data from clinical and non-clinical studies, population-based studies and post-marketing surveillance.

What are the conclusions of the CHMP?

The CHMP concluded that data from clinical studies clearly demonstrate that Protelos and Osseor are effective in reducing the risk of broken bones in the spine and the hip in post-menopausal women with osteoporosis. Regarding the risk of VTE, results from population-based studies and post-marketing surveillance show that this risk is higher in patients with a history of VTE, as well as in patients who are temporarily or permanently immobilised. Therefore, the CHMP concluded that the current warning in the product information needs to be strengthened with wording clearly stating that Protelos and Osseor must not be used in these patients.

As the number of VTE cases in elderly patients (over 80 years of age) was shown to be higher with Protelos/Osseor in comparison with placebo, the CHMP also recommended that a warning should be included, with a recommendation for doctors to re-evaluate the need for continued treatment in patients over 80 years of age at risk of VTE.

Regarding the risk of severe allergic skin reactions, the CHMP concluded that these serious side effects should continue to be kept under close surveillance, and that the warnings section should be updated to include the signs and symptoms of DRESS, SJS and TEN, as well as their time-to-onset. Because the best results in managing these adverse reactions come from early diagnosis and discontinuation of treatment, patients should be advised to immediately stop treatment if they develop allergic reactions, and those who stop treatment should not re-start it at any time.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of Protelos and Osseor continue to outweigh their risks, but that changes should be made to the product information to ensure the safe use of these medicines. The full changes made to the information to doctors and patients can be found [here](#).

What are the recommendations for prescribers?

- Doctors should not prescribe Protelos and Osseor to patients with current VTE or a history of VTE, or to patients who are temporarily or permanently immobilised.

- Prescribers should advise patients at the time of prescribing on the likely signs and symptoms of severe skin reactions such as DRESS, SJS or TEN.
- Doctors should immediately discontinue Protelos and Osseor in patients who develop DRESS, SJS or TEN, and treatment should not be re-started at any time in these patients.
- 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.

What are the recommendations for patients?

- 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.
- Patients should stop treatment immediately and permanently if symptoms of severe allergic skin reactions occur. These include extended skin rashes, blisters, sores and flu-like symptoms.
- Patients who have any questions should speak to their doctor or pharmacist.

A European Commission decision on this opinion will be issued in due course.