EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 May 2013
EMA/PRAC/283429/2013

PRAC List of questions

To be addressed by the marketing authorisation holder for Protelos and Osseor

Review under Article 20 of Regulation (EC) No 726/2004, following the procedural steps laid out in Article 31 of Directive 2001/83/EC

Procedure number: Protelos EMEA/H/A20/1371/C/000560/0039
Osseor EMEA/H/A20/1371/C/000561/0034

INN: strontium ranelate

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Data submitted as part of the routine benefit-risk assessment within a periodic safety update report (PSUR), covering the period from 22 September 2011 to 21 September 2012, for Protelos/Osseor raised concern regarding cardiovascular safety beyond the already recognised risk for venous thromboembolism.

As a result of this assessment, an increased risk for serious cardiac disorders, including myocardial infarction has now been identified and risk minimisation measures specifically targeting the identified risk were recommended by the PRAC and the CHMP. The risk minimisation measures include reducing the target population by excluding patients with high risk for ischemic cardiac disorders, and restricting the indication to patients with severe osteoporosis, who are most likely to benefit from the treatment.

In view of this newly identified risk of serious cardiac disorders including myocardial infarction and the already recognised safety concerns such as serious skin disorders and venous thrombotic events (VTE), concerns have been raised over the overall balance of benefits and risks of medicinal products containing strontium ranelate, and their place in therapy. The CHMP recommended further wide-ranging evaluation of the benefits and risks of Protelos and Osseor. Therefore, the European Commission (EC) initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the EMA to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal products Protelos and Osseor.

The marketing authorisation holder (MAH) for Protelos and Osseor is requested to:

1. Provide a full benefit/risk assessment of strontium ranelate in the currently adopted indications in the EU, i.e. considering the newly defined target populations, including all restrictions in terms of contraindications and warnings. All identified and potential risks should be addressed, taking into account the demonstrated level of clinical efficacy.

2. Based on the PMO database, as well as for TROPOS separately, the following should be presented as absolute number of events / 1000 patient years for strontium ranelate and placebo treated patients:

    1. Numbers of deaths, serious adverse events, serious adverse events in each SOC;
    2. Numbers for specific harmful events (myocardial infarction, ischemic cardiac disorders, VTE);
    3. Numbers for beneficial events (non-vertebral, vertebral and hip fractures, respectively);
    4. Number of patients with adverse events leading to withdrawal;
    5. Provide relative risks and absolute risks with 95% confidence intervals for the above.

- The numbers from the same analyses (1-5) should be presented in this database for the restricted indication “severe osteoporosis in postmenopausal women” subgroup i.e. T score ≤ - 2.5 SD with 1 or more fragility fractures.

- The numbers from the same analyses (1-5) should be presented in this database in the subgroup excluding patients with all contraindications and warnings i.e. excluding patients with current or previous VTE, including deep vein thrombosis and pulmonary embolism, established, current or past history of, ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease and uncontrolled hypertension, hyperlipidaemia, diabetes mellitus and smoking.

- The numbers from the same analyses (1-5) should be presented in this database in the subgroup of patients with both severe osteoporosis and excluding patients with any condition included in present contraindications or warnings (see questions above).

- The numbers from the same analyses (1-5) should be presented in this database for patients below and above 75 years of age.

3. Provide a graphical presentation of the changes in effects (beneficial effects like prevention of non-vertebral, vertebral and hip fractures, respectively and harmful effects like myocardial infarction, VTE) across subgroups of osteoporosis severity, cardiovascular risk, and age in separate plots (For this purpose, L'Abbè plots where the control group risk is plotted versus the exposed group risk, are recommended).

4. Based on the clinical study-data requested above, discuss clinically feasible criteria for the identification of patients in whom benefit/risk is considered favourable.

5. The MAH should discuss, based on knowledge about similar risk factors for osteoporosis and for ischemic cardiac disorders as well as VTE, how realistic, in clinical practice, the current restrictions outlined in the summary of product characteristics are expected to be for minimising identified risks in the target populations.

6. The MAH should provide a detailed presentation of all serious skin reactions reported, in relation to an estimation of number of new patients initiating strontium ranelate treatment (post marketing data).

7. The MAH should discuss the possible mechanism for thromboembolic events including myocardial infarction, taking into account coagulation data from strontium ranelate studies as well as published information regarding the importance of various coagulation parameters for development of thromboembolic events.

8. Any new data, including the final study report of the Clinical Practice Research Datalink (CPRD) case control study should be submitted.

9. Based on the analyses and discussions provided in response to the questions listed above, the MAH is asked to address whether additional risk minimisation measures are warranted.